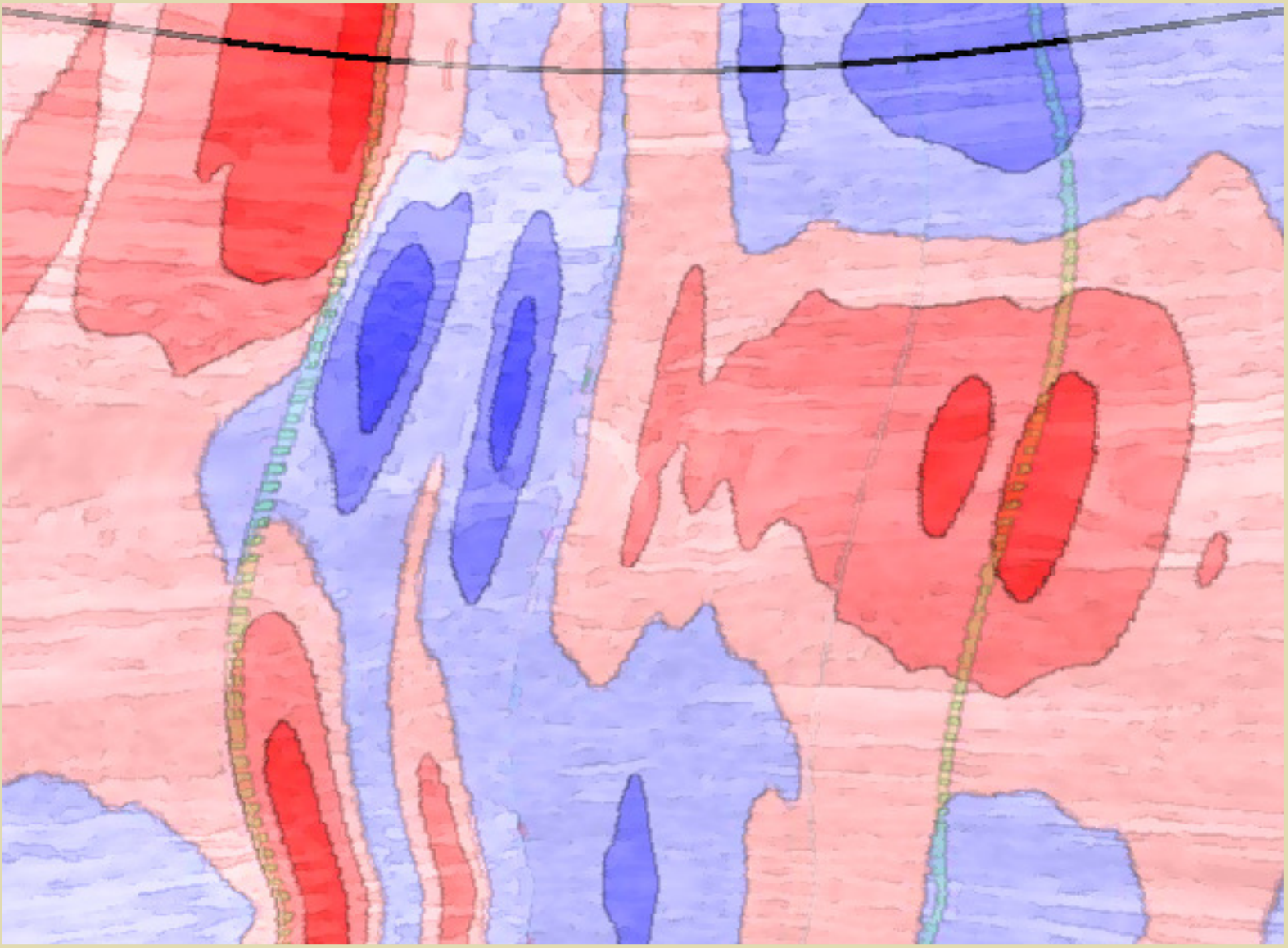

Rui Providência

NEW METHODS FOR THROMBOEMBOLIC RISK STRATIFICATION IN NON-VALVULAR ATRIAL FIBRILLATION

Tese de Doutoramento em Ciências da Saúde – Ramo de Medicina
Orientada por Professor Doutor Lino Gonçalves e Professora Doutora Maria João Ferreira
Apresentada à Faculdade de Medicina da Universidade de Coimbra

Setembro de 2014

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UNIVERSIDADE DE COIMBRA

New Methods for Thromboembolic Risk Stratification in Non-Valvular Atrial Fibrillation

Novos Métodos para a Estratificação de Risco da Fibrilhação Auricular Não-Valvular

Imagem da capa: *"Aurícula Fibrilhando"*

Autoria: Rui Providência

”In life, unlike chess, the game continues after checkmate.”

Isaac Asimov

Agradecimentos

Aos meus Orientadores, Professor Doutor Lino Gonçalves e Professora Doutora Maria João Ferreira, pelo apoio e valioso aconselhamento prestado nesta etapa.

A todos os Colaboradores nos trabalhos que constituem esta tese pelo seu contributo de valor inestimável.

À Carina, pela compreensão e aceitação da dedicação e do tempo necessário para a execução deste passo.

À minha Família, em especial ao meu avô João e todos aqueles que me antecederam, por me terem encaminhado e permitido a continuação deste trajeto.

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Abstract.

Introduction: Thromboembolic risk in patients with atrial fibrillation (AF) is highly variable and is currently assessed through the use of clinical risk schemes, the $CHADS_2$ and CHA_2DS_2-VASc scores, which perform only slightly better than chance.

Transesophageal echocardiogram (TEE) changes are associated with a very high thromboembolic risk and may be used for better understanding the thrombogenic process in this arrhythmia. There are two situations where thromboembolic risk is very acutely increased in patients with AF: cardioversion and catheter ablation.

Aims:

Goal I: To assess the impact of AF on cerebrovascular mortality at a national level through the review of the currently available evidence.

Goal II.A: To evaluate the role of echocardiographic parameters (left atrial – LA - area, volume and speckle-tracking derived strain and strain rate and left ventricle ejection fraction) in the prediction of LA thrombi and other markers of atrial stasis.

Goal II.B: To assess the possible contribution of biomarkers (troponin I, mean platelet volume - MPV, red cell distribution width - RDW, mean globular volume – MCV - and C reactive protein) in the understanding of the pathways involved LA stasis.

Goal II.C: To clarify the role of chronic kidney disease (CKD), assessed through the estimated glomerular filtration rate (eGFR), as a predictor of thrombogenesis and thromboembolic events. To clarify the benefit and safety of warfarin and the novel oral anticoagulants in patients with CKD and AF.

Goal III: To systematically revise all the published evidence concerning dabigatran in the setting of catheter ablation of AF, evaluating its efficacy and safety.

Goal IV: To derive the first scheme combining clinical and echocardiographic variables, alongside with biomarkers able to discriminate with high accuracy the presence of LA thrombi.

Results:

I. AF accounts for a relevant number of ischemic strokes in Portugal and its contribution should not be negleted since it seems not to be decreasing.

II.A. Adding LA area and left ventricular ejection fraction to the $CHADS_2$ and CHA_2DS_2-VASc scores significantly improved their discriminative capability for TEE findings: c-statistics of 0.62 and 0.63, respectively, increased to 0.73 and 0.74 (both $P<0.01$).

AF episode duration, peak negative strain rate and time-to-peak positive strain were independent predictors of LA appendage thrombi or sludge. The c-statistic for the estimated probabilities using this model was 0.89 (95%CI 0.81-0.96; $P<0.001$).

II.B. A direct relation between rising concentrations of troponin I and a higher prevalence of TEE stasis-related changes was found. Adding troponin I to $CHADS_2$ and CHA_2DS_2-VASc scores improved their predictive ability.

MCV and RDW were independent predictors of LA appendage thrombus and dense spontaneous echocardiographic contrast. MPV was an independent predictor of LA appendage thrombus and was incorporated in the predictive models of dense spontaneous echocardiographic contrast, low flow velocities and LA stasis, adding predictive value to clinical, echocardiographic and laboratory variables.

II.C. A higher prevalence of dense spontaneous echocardiographic contrast in patients with lower eGFR rate was observed. On multivariate analysis, a predictive value was found for eGFR, that was additive to that of clinical parameters from $CHADS_2$ and CHA_2DS_2-VASc.

The presence of CKD leads to increased risk of thromboembolism (HR = 1.46; 95%CI 1.20-1.76, $P=0.0001$), particularly in case of terminal CKD (HR = 1.83; 95%CI 1.56-2.14, $P<0.00001$). Warfarin decreased the incidence of thromboembolic events in patients with non-endstage CKD (HR = 0.39; 95%CI 0.18-0.86, $P<0.00001$), as well as among patients on dialysis (HR = 0.44; 95%CI 0.26-0.74, $P=0.002$). In addition, novel oral anticoagulants showed higher efficacy, compared to warfarin (HR = 0.77; 95%CI 0.64-0.93, $P=0.006$) and aspirin (HR = 0.32; 95%CI 0.19-0.55, $P<0.0001$) among non-endstage CKD.

III. In the setting of cateter ablation of AF, no significant differences were found between patients treated with dabigatran and warfarin regarding thromboembolic events and major bleeding. No difference was found between the 110mg bid and 150mg bid dabigatran dosages concerning these two endpoints.

IV. $CHADS_2$ and CHA_2DS_2-VASc had a modest performance in predicting TEE endpoints displaying a 0.62 c-statistic in average. Using CATES score (C-reactive protein, LA volume, Troponin I, Episode duration and Stroke or embolism) displayed a higher c-statistic: 0.82 for LA appendage thrombus. No patients with thrombus were observed in patients with CATES scores ranging from "0" to "2", which corresponded to 49.4% of the sample.

Conclusion:

We have identified new markers and pathways that seem to be involved in this thrombogenic process: clinical variables (CKD as assessed through the eGFR), biomarkers (MPV, MCV, RDW, troponin I and C-reactive protein) and echocardiographic parameters (LA size - area and volume - and deformation). These variables seem to independently increment the discriminative of the clinical variables currently used in risk scores ($CHADS_2$ and CHA_2DS_2-VASc). In the context of moderate CKD, the novel oral anticoagulants performed favourably, when compared with warfarin. However, in end-stage kidney disease, no data exists concerning the use of these agents. Also, our results seem to ease some of the concerns regarding the use of warfarin in these patients.

Despite not clarifying the best regimen for dabigatran in the setting of catheter ablation of AF, our meta-analysis confirms the efficacy and safety of this drug.

Using the new CATES scheme, a great amount of patients may eventually be spared TEE before cardioversion.

Resumo.

Introdução: O risco tromboembólico nos doentes com fibrilhação auricular (FA) é altamente variável, sendo avaliado através de classificações clínicas, os scores de $CHADS_2$ e CHA_2DS_2-VASc, que são algo aleatórias.

Existem alterações no ecocardiograma transesofágico (ETE) que estão associadas a um aumento do risco tromboembólico e podem ser utilizadas para o melhor conhecimento do processo trombogénico nesta arritmia. Existem dois contextos particulares nos quais o risco se encontra aumentado de forma aguda: a cardioversão e a ablação por cateter.

Objectivos:

Tarefa I. Avaliar o impacto da FA na mortalidade cerebrovascular a nível nacional através da revisão da evidência atualmente disponível.

Tarefa II.A. Avaliar o papel dos parâmetros ecocardiográficos (área e volume da aurícula esquerda - AE, *strain* e *strain rate* obtidos através de *speckle-tracking* e fração de ejeção do ventrículo esquerdo) na predição de trombos no apêndice AE e outros marcadores de estase auricular.

Tarefa II.B. Estimar qual o contributo dos biomarcadores (troponina I, volume plaquetar médio - VPM, índice de anisocitose eritrocitário - RDW, volume globular médio – VGM - e proteína C reativa) na compreensão das vias envolvidas na estase auricular.

Tarefa II.C. Clarificar o papel da insuficiência renal crónica (IRC), avaliada através da taxa de filtração glomerular estimada (TFG), como preditora de trombogénese e eventos tromboembólicos. Clarificar o benefício e segurança da varfarina e novos anticoagulantes orais nestes doentes.

Tarefa III. Reunir toda a evidência disponível relativa ao uso do dabigatran na ablação por cateter de FA, avaliando a sua segurança e eficácia.

Tarefa IV. Proceder à derivação da primeira classificação combinando elementos clínicos, ecocardiográficos e biomarcadores para a discriminação eficaz da presença de trombos AE.

Resultados:

I. A FA é responsável por uma percentagem importante dos acidentes vasculares cerebrais isquémicos em Portugal e o seu contributo não deve ser nelicenciado, dado que a sua prevalência irá aumentar.

II.A. A adição da área da AE e fração de ejeção do ventrículo esquerdo às classificações de $CHADS_2$ e CHA_2DS_2-VASc melhorou significativamente a sua capacidade discriminativa para achados no ETE: *c-statistics* de 0.62 e 0.63, respetivamente, passou a 0.73 e 0.74 (ambos *P* <0.01).

A duração do episódio de FA, o pico negativo de *strain rate* e o tempo para o pico de *strain* positivo da AE foram preditores independentes de trombo AE ou *sludge*. A área sob a curva da probabilidade estimada usando este modelo foi 0.89 (95%CI 0.81-0.96; *P* <0.001).

II.B. Encontrou-se uma relação direta entre concentrações crescentes de troponina I e prevalência de estase auricular. A adição da troponina I às classificações de $CHADS_2$ e CHA_2DS_2-VASc melhorou a sua capacidade de preditiva.

O VGM e o RDW foram preditores independentes de trombo no apêndice AE e autocontraste ecocardiográfico espontâneo denso. O VPM foi preditor independente de trombo no apêndice AE e foi incorporado em modelos preditivos de outras formas de estase AE, acrescentando valor preditivo a variáveis clínicas, ecocardiográficas e laboratoriais.

II.C. Encontrámos maior prevalência de autocontraste ecocardiográfico espontâneo denso nos doentes com menor TFG. Na análise multivariada foi descoberto um valor preditivo para a TFG, aditivo ao dos parâmetros clínicos das classificações de $CHADS_2$ e CHA_2DS_2-VASc.

A presença de IRC aumenta o risco tromboembólico (HR = 1.46; 95%CI 1.20-1.76, *P*=0.0001), principalmente nos estádios terminais (HR = 1.83; 95%CI 1.56-2.14, *P*<0.00001). A varfarina diminuiu a incidência de eventos tromboembólicos tanto em doentes com IRC moderada (HR = 0.39; 95%CI 0.18-0.86, *P*<0.00001), como na IRC dialítica (HR = 0.44; 95%CI 0.26-0.74, *P*=0.002). Os novos anticoagulantes orais mostraram maior eficácia comparativamente à

varfarina (HR = 0.77; 95%CI 0.64-0.93, *P*=0.006) e aspirina (HR = 0.32; 95%CI 0.19-0.55, *P*<0.0001) nos doentes com IRC moderada.

III. Não foram encontradas diferenças significativas entre dabigatran ou varfarina em contexto da ablação percutânea de FA em relação a eventos tromboembólicos e hemorragias major. Não foram também encontradas diferenças entre as dosagens de dabigatran 110mg bid e 150mg bid.

IV. As classificações de $CHADS_2$ e CHA_2DS_2-VASc mostraram uma capacidade modesta na predição de alterações da estase AE: *c-statistic* = 0.62, em média. Utilizando o esquema de CATES (proteína C reativa, volume AE, Troponina I, duração do Episódio de arritmia e *Stroke* ou embolia prévia) obteve-se um valor significativamente mais elevado da área debaixo da curva: 0.82 para a discriminação de trombo do apêndice AE. Nenhum doente com trombo apresentou valores de CATES entre "0" e "2", o que correspondeu a 49.4% da amostra.

Conclusões: Identificámos novos marcadores e vias envolvidas no processo de trombogénese na FA: variáveis clínicas (IRC), biomarcadores (VPM, VGM, RDW, troponina I e proteína C reativa) e ecocardiográficas (área e volume da AE e sua deformação). Estas variáveis parecem incrementar a capacidade discriminativa das variáveis clínicas atualmente incluídas nas classificações de $CHADS_2$ e CHA_2DS_2-VASc.

Na IRC moderada os novos anticoagulantes apresentaram um desempenho favorável relativamente à varfarina. Porém, na IRC terminal não existem dados relativamente a estes fármacos. Os nossos dados parecem refutar alguns dos receios relativos à utilização da varfarina em doentes dialisados.

Apesar de não termos esclarecido qual o melhor regime para o dabigatran em doentes submetidos a ablação por cateter, confirmámos a eficácia e segurança do fármaco.

De acordo com a classificação CATES, grande parte dos doentes poderão eventualmente ser dispensados da realização do ETE antes da cardioversão.

Introduction.

1. Historical Perspective

The use of the expression atrial fibrillation (AF) as a denomination for a heart condition dates from the beginning of the XXth century. However, the first description of the clinical entity was probably from the Yellow Emperor (Huang Ti) (a legendary emperor physician, one of China's first rulers who is thought to have ruled somewhere between 2697 and 2597 BC) in his Classic of Internal Medicine ("*Huang Ti Nei Ching Su Wen*"). In those days, the "irregular and tremulous pulse" was already associated with an adverse prognosis [1].

In 1628 William Harvey made the first direct observation of a fibrillating atrium ("an obscure movement, undulation/palpitation") in a dying animal heart [2]. Then, the first description of an auscultation of a patient with AF in context of mitral stenosis by Robert Adams was published in 1827 [1]. Decades later, in 1874 Vulpian observed the irregular atrial electrical activity in dog hearts, that he designated *"fremissement fibrillaire"* [3], and in 1876 Nothnagel referred the irregularity of the pulse, of what he called "*delirium cordis*" [4]. In 1903, Hering noticed that the condition might evolve into a permanent form ("*pulsus irregularis perpetuus*") [5] and in 1906 Einthoven published the first AF ECG [6]. MacKenzie described the loss of the "a" wave in the venous pulse of patients with "pulsus irregularis perpetuus". However, his first explanation for the phenomena was not the lack of organized atrial contractility, but rather an escape rhythm originating in the atrioventricular node and causing simultaneous atrial and ventricular contraction and therefore the loss of the "a wave" in the venous pulse [4, 7].

During that time, Cushny and Edmunds had been inducing fibrillation in the atria of dogs and noted an irregular pulse [8]. Later, Crushny persuaded MacKenzie that they might be investigating the same arrhythmia. However, the final connection between all these findings (irregular pulse, electrocardiographic and anatomic manifestations of AF) was made in 1909 by

Rothberger, Winterberg [9] and, some months later, Lewis [10], establishing AF as a clinical entity.

2. Atrial fibrillation in Portugal XXth Century and recent contributions

In the beggining of the XXth Century, after attending to the Medical Clinic of the Faculty of Medicine of the University of Berlim, a young Portuguese Doctor from the University of Coimbra published the first work on AF at a National level [7]. In Berlim, João Porto had the chance of collaborating with Professor Friederich Kraus and his Assistant Dr. Ernst Blumenfeldt, witnessing the "surprising results" of quinidine sulfat in a patient with AF who was successfully cardioverted to sinus rhythm. According to the Portuguese doctor, the enthusiasm and motivation for chosing the subject of AF for his thesis resulted in great part from this landmark experience.

The thesis was published in 1923 and entitled "Fibrilhação Auricular" (Figure 1). The first part was a review of semiological and pathogenic knowledge during those days, where most patients had the arrhythmia as a consequence of rheumatic fever [7]. However, the greatest emphasis of this publication was put in the treatment of the arrhythmia focusing on several of the available treatment options at the time: *digitalis purpurea* derivates ("foxglove"), strophantus and its pharmaceutical preparations, calcium salts, quinine and quinidine. The association with the Graves-Basedow syndrome was already known in those days and was also a part of the dissertation.

Later, in the year of 1949, João Porto was one of the founding members of the Portuguese Society of Cardiology.

Important contributions to the treatment and understanding of AF have been made in recent years by several Portuguese groups.

João Queirós e Melo, a Cardiac Surgeon from the group of Santa Cruz' Hospital, Carnaxide, developed a surgical technique for the treatment of this arrhythmia through the use of radiofrequency ablation for bilateral electrical disconnection of pulmonary veins from the left atrium [11]. This technique was further developed into a percutaneous approach by Pedro Adragão, an electrophysiologist of the same group, who wrote his PhD thesis on the subject [12].

The autonomic system is known to play a role in the development and sustaining of AF. This was the focus of Mário Oliveira's, an electrophysiologist from Santa Marta's Hospital, during his PhD, which combined clinical and basic research investigations providing further support to the association [13].

3. Epidemiological data and main concerns in patients with AF

AF is the most frequent sustained arrhythmia and its prevalence is likely to rise steeply in the next few decades [14]. The prevalence of AF is strongly related to age and gender. It is more frequent in males (1.1% males comparing with 0.8% women; $P < 0.001$) and doubles with each decade of age, occurring in 0.1% under the age of 55, approximately 5% in patients aged 60 to 69 years and 9.0% in those aged 80 years or older [15]. It is estimated that at least 25% of the world's population aged over 40 years of age will develop at least one AF episode during their lifetime [16]. Due to the increase in life expectancy and other risk factors associated with this arrhythmia, the number of patients with AF is even expected to rise. In 2000, approximately 5.1 millions patients with AF were estimated in the United States of America. The projected

numbers of persons with AF for 2050 are between 12.1 and 15.9 millions (if the incidence rate remains constant or increases, respectively) [17].

In 1992 AF accounted for 35% of arrhythmia-driven hospital admissions [18]. Despite being the most frequent cause of hospitalization of arrhythmia its prevalence is even growing progressively, with an approximate 60% increase in the last 10 to 20 years, independent of changes in known risk factors [19].

It is general opinion that this arrhythmia is broadly underdiagnosed due to the fact that it is most frequently asymptomatic. In patients with paroxysmal AF, asymptomatic events are approximately 12 fold more frequent [20]. In a recent epidemiologic national survey of 10,447 individuals assessed through a questionnaire and an electrocardiogram, the prevalence of this arrhythmia was 2.5% and 38.3% of these (100 out of the 261 with a final diagnosis of AF) did not know that they had the arrhythmia [21].

Data from the Framingham study has shown that the presence of AF was an independent risk factor for death, even after adjustment for the presence of structural heart disease and other comorbidities. AF was associated with an OR for death of 1.9 in females ($CI_{95\%}$ = 1.5-2.2) and 1.5 in males ($CI_{95\%}$ = 1.2-1.8) [22].

A recent analysis from 2 population-based cohorts, the *"Atherosclerosis Risk in Communities"* (ARIC) and the *"Cardiovascular Health Study"* (CHS), supports the findings from Framingham: the meta-analyzed HR of AF for sudden cardiac death was 2.47 ($CI_{95\%}$ = 1.95-3.13) [23]. This association has also been described for hypertensive patients, where the finding of new-onset AF was associated with a more than 3-fold increase in the risk of sudden cardiac death (HR = 3.13 and $CI_{95\%}$ = 1.87-5.24; $P < 0.001$) [24].

4. Stroke and thromboembolism

Besides increased mortality, the most feared complication of AF is stroke and thromboembolism.

The association of AF with systemic embolism in the context of rheumatic heart disease, namely mitral stenosis, has been known since the 50s [25]. However, the first solid evidence of the independent association of AF with stroke derives from the Framingham study in the 1970's, where a cohort of 5,184 men and women, aged 30 to 62, and free of stroke at entry, was followed for 24 years (109,051 person-years in subjects with no AF or rheumatic heart disease, 481 person-years in subjects with AF only and 154 person-years in subjects with rheumatic heart disease and AF). A 5.6 fold higher risk of stroke was found in patients with non-rheumatic AF than in controls. In patients with AF and rheumatic heart disease the risk was 17.6 fold higher [26].

According to data from the *"The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation"* (SPINAF) study, among the 516 evaluable patients (patients with non-rheumatic AF without previous stroke) undergoing a cerebral scan at baseline with the adequate window criteria, the prevalence of asymptomatic stroke in patients with AF was as high as 14.7% [27].

Among a sample of 2040 Framingham offspring free of clinical stroke, and undergoing volumetric brain magnetic resonance imaging, at least one silent cerebral infarction was found in 10.7%. AF was associated with a 2-fold increased risk of silent cerebral infarction (OR = 2.16; $CI_{95\%}$ = 1.07– 4.40) [28]. The association with AF was stronger than the one observed with the Framingham Stroke Risk Profile score (OR = 1.27; $CI_{95\%}$ = 1.10-1.46), stage I hypertension determined by JNC-7 criteria (OR = 1.56; $CI_{95\%}$ = 1.15-2.11), carotid stenosis >25% (OR = 1.62; $CI_{95\%}$ = 1.13-2.34), and increased carotid intimal-medial thickness above the lowest quintile (OR

= 1.65; $CI_{95\%}$ = 1.22-2.24). Only patients with an elevated plasma homocysteine in the highest quartile (OR, 2.23; CI, 1.42-3.51) displayed a similar risk.

It has been thought until recently, that about 15 to 20% of all ischemic strokes are associated with AF [29]. However, recent data showed a higher prevalence of this arrhythmia in patients admitted to stroke units with ischemic events. In a recent survey of patients admitted with ischemic stroke in a University Hospital, about 37.3% of these were cardioembolic, with 94.5% associated with AF [30]. Furthermore, a relevant number of cryptogenic strokes (i.e. with unknown cause) are now being associated with AF.

AF-related stroke is more severe [31], associated with higher incapacity (disabling in over 60% [32]) and higher mortality (overall one year mortality in AF-related stroke is estimated to be 50% [33]). This renders mandatory the treatment of high risk patients.

5. Risk stratification of stroke and thromboembolism

Thromboembolic risk in patients with AF is highly variable, ranging from 0% to 20% each year. Contrary to the initial belief, the risk of stroke is the same in AF patients regardless of whether they have paroxysmal or sustained AF [34]. Currently, thromboembolic risk is assessed through clinical risk classifications. The $CHADS_2$ score [35] was initially derived from a national registry of Medicare-aged patients with nonrheumatic AF and not prescribed warfarin at the time of hospital discharge. This scheme was based on a mix of risk factors from two other previously available risk classifications:

- SPAF (4 independent risk factors derived from data of the *"Stroke Prevention in Atrial Fibrillation"* trial patients' treated with aspirin): blood pressure higher > 160 mm Hg,

prior cerebral ischemia, recent heart failure – active in the last 100 days - or documented by echocardiography, or the combination of 75 years or older and being female.

- AFI (4 variables obtained from data of the *"Atrial Fibrillation Investigators"* pooled data concerning patients who did not receive anti-thrombotic therapy): age – a factor of 1.4 per decade, hypertension, prior stroke or transient ischemic attack and diabetes mellitus.

The $CHADS_2$ score was therefore composed by the following clinical variables: congestive heart failure ("C"), hypertension ("H"), age ≥ 75 years ("A", diabetes mellitus ("D") and stroke or transient ischemic attack ("S"). All these variables receive one point, except for "S" that is associated with twice the risk.

The refined Birmingham or NICE thromboembolic risk schema, widely known as CHA_2DS_2-VASc score [36] has been recently developed using data from the Euro Heart Survey on AF (1,577 patients without mitral stenosis of previous heart valve surgery who did not use either vitamin-K antagonists or heparin at discharge from the qualifying visit). Compared with the $CHADS_2$ risk score, it preserves all its variables with subtle changes: age ≥ 75 recieves 2 points and age 65 to 74 is already considered a risk factor with 1 point; female gender is assigned one point, but should only be considered in subjects over 65 [37]; peripheral vascular disease, previous acute myocardial infartion or the presence of aortic plaques, alltogheter defined as vascular disease (VASc) are assigned one point.

The obtained classification is associated with an annual risk of stroke and systemic embolism and these values provide the rational for deciding which patients will derive the most benefit from anticoagulation, antiplatelet agents of no prophylaxis at all. However, the observed discriminative capability for these scores is very modest, with c-statistics ranging from 0.54 to 0.65 [36]. A c-statistic value of 0.5 means that the model is no better than chance at making a

prediction. Conversely, a value of 1.0 indicates that the model perfectly identifies those at risk of events. Models are typically considered strong when the C-statistic is higher than 0.8.

Currently, according to the CHA_2DS_2-VASc scheme, more than 95% of patiens will have an indication for oral anticoagulation, resulting in extremely elevated numbers of patients worldwide under oral anticoagulation (and vulnerable to the concomitant bleeding risk), of whom, some would never experience events. Conversely, some high risk patients are misjudged to be at a lower risk level will be spared anticoagulant therapy and end up sustaining a stroke.

The HAS-BLED score designed for assessing bleeding risk in this population is an important piece in the decision process [38]. Patients are assessed based on the presence of hypertension (uncontrolled, > 160 mm Hg systolic), chronic kidney disease, abnormal liver function, stroke, bleeding history or predisposition (anemia), labile international normalized ratio (<60% of time in therapeutic range), elderly (> 65 years), Antiplatelet or non-steroidal anti-inflammatory drugs and alcohol. Each variable is assigned one factor and a score ≥ 3 should be interpreted with caution, requiring regular visits, as well as attempting to correct modifiable risk factors [37]. A high bleeding and thrombotic risk is frequently coexistent in patients with AF, this is illustrated by the fact that the HAS-BLED [38] shares risk factors with the $CHADS_2$ [35] and CHA_2DS_2-VASc [36] scores (Table I): stroke, hypertension and advanced age.

Recent data using biomarkers to improve their capacity (biomarker sub-analysis using troponin and NTproBNP in patients from the *"Randomized Evaluation of Long-Term Anticoagulation Therapy"* (RE-LY) [39] and *"Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation"* (ARISTOTLE) [40, 41] trials) or even adding echocardiographic parameters (being currently assessed in the ongoing echocardiographic sub-study from the *"Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In*

Myocardial Infarction" (ENGAGE AF-TIMI 48) trial [42]) are promising options in this field that may allow more appropriate tailoring of prophylactic treatment to the individual patient's needs.

6. Presence of left atrial stasis: a potential surrogate of increased thromboembolic risk

It is known that approximately 90% of thrombi in AF are formed in the left atrial appendage [43]. Spontaneous echocardiographic contrast (SEC), also known as "swirl" or "smoke", frequently coexists with these thrombi. Also, it is associated with low blood flow velocity [44]. These dynamic smoke-like echoes are thought to be composed either of aggregated activated platelets and leucocytes [45] or aggregates or of red blood cells that are interacting with plasma proteins [46, 47] and can be classified into 4 groups (1 to 4+), depending on the intensity, location and presence of the swirling movement [48].

Sludge is often difficult to differentiate from a thrombus and is a dynamic and gelatinous, but not solid or well-formed, echodensity present throughout the cardiac cycle. It is thought that along the continuum of thrombus formation, sludge represents a stage beyond SEC and thrombus (the hypothesized progression is: mild, moderate and severe SEC, sludge and thrombus). Also, it may have greater prognostic significance than SEC [49].

The presence of all these markers of left atrial stasis has been associated with stroke, thromboembolism and adverse prognosis for long [50-52]. Furthermore, the associated risk may be present even in the context of anticoagulation: a high likelihood of cerebral embolism (either clinically assessed or observed on magnetic resonance images) and/or death at medium-term despite anticoagulation in patients with AF and left atrial thrombi and grade 3 or 4+ SEC has been described [53, 54]. Also, left atrial appendage thrombus and dense SEC are

very powerful predictors of cardiovascular death independent of other known clinical risk factors [55].

Over time, changes may occur in the left atrium milieu, leading to a dynamic process: left atrial appendage thrombus may disappear either because of embolization or adequate anticoagulation; SEC develops or increases over time alongside with dilatation, fibrosis and progressive atrial dysfunction or stunning; left atrial appendage flow decreases with time as AF episode duration progresses or increases some weeks after an effective cardioversion. The perception of these facts is important, since it translantes in the following: one transesophageal echocardiogram examination is like a single photograph of the LA milieu and may not be fully representative of past and future changes at this level [56, 57]. Repeated transesophageal procedures may be needed in some patients.

We cannot yet truly explain why some patients are more prone to developing left atrial thrombi. The involved factors and pathways in thrombi formation are a vastly unexplored subject of the utmost importance. Improving our knowledge in this field might help us in developing new treatment strategies and more effective ways of identifying the different patient risk profiles in this disease. This is based on the assumption that individuals more prone to develop a thrombotic milieu in the left atrium or left atrial appendage are also the ones at higher risk of sustaining thromboembolic events.

Also, in order to find alternatives to transesophageal echocardiography, investigations have assessed the ability of $CHADS_2$ and CHA_2DS_2-VASc scores to discriminate the presence of left atrial stasis (LA appendage thrombus, SEC, sludge and low LA appendage flow velocities). However, these scores seem to show low to moderate abilities (AUC ranging from 0.6 to 0.7) in discriminating between the risk factors [58].

7. Thromboembolic prophylaxis in atrial fibrillation: different options

There is strong evidence that the use of anticoagulants is far better in the protection of patiens with AF from embolic events, than the use Antiplatelet agents. In a meta-analysis of 15 studies of patients with non-valvular AF, warfarin has shown to be superior to placebo and to antiplatelet agents in the prevention of stroke and systemic embolism: OR = 0.50 ($CI_{95\%}$ = 0.33-0.75) and OR = 0.29 ($CI_{95\%}$ = 0.08-1.07), respectively [59]. Warfarin was also associated with a 3-fold increase (OR = 3.01; $CI_{95\%}$ = 1.31-6.92) in major bleeding when compared with placebo. However, and contrary to what is currently thought by a large number of practitioners, warfarin does not increase the risk of major bleeding when compared with antiplatelet agents (OR = 1.07; 95% CI 0.85 to 1.34). This means that antiplatelet agents are as dangerous as warfarin but less effective, which is why their use is currently discouraged in this setting [37].

Despite this apparent benefit of warfarin for preventing thromboembolic events, the associated bleeding risk lead to a lower net clinical benefit, which reinforces the need of individual case analysis for therapy tailoring and decision-making.

Three novel anticoagulants (dabigatran, rivaroxaban and apixaban) have been recently proven to be advantageous compared with warfarin concerning stroke and thromboembolism prevention in phase 3 trials of non-valvular AF [60-62]. These drugs need no systematic assessment of systemic anticoagulation levels and have a safer interaction profile, both with food and with other drugs.

Despite some specific features of the individual drugs, when analyzed as a whole in the more than 50,000 patients of the phase III trials the advantages of the novel oral anticoagulants are present in almost all the assessed endpoints: decrease in mortality, decrease in stroke and

systemic embolism, decrease in haemorrhagic stroke and less gastrointestinal and intracranial bleeding [63-65].

Patients with a creatinine clearance of less than 30 ml/min are lacking evidence support towards the use of these agents, since they have been excluded from the trials [60-62].

Aspirin was also compared with one of these agents in the *"Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment"* (AVERROES) trial, and it was shown once again to be less effective and to have a similar bleeding risk [66].

According to the recent European Society of Cardiology update of the guidelines [37], oral anticoagulant therapy (either with vitamin-K antagonists or the novel oral anticoagulants) is recommended, unless contraindicated, in individuals with a CHA_2DS_2-VASc score of ≥ 2 (class of recommendation I and level of evidence A). In individuals with a CHA_2DS_2-VASc score of 1, the indication is weaker, but still sustained by strong evidence and an apparent benefit (class of recommendation IIa and level of evidence A). Using a novel oral anticoagulant, rather than a vitamin-K antagonist is recommended if a patient is unable or unwilling to comply with adjusted-dose vitamin-K antagonist (class of recommendation I and level of evidence B). However, using these agents for most patients with non-valvular AF rather than vitamin-K antagonists based on their net clinical benefit presents a weaker indication despite the strong evidence (class of recommendation IIa and level of evidence A). The use of Antiplatelet agents should only be considered if patients refuse the use of any oral anticoagulant, and in this case aspirin 75-100mg plus clopidogrel 75mg daily should be considered preferentially. In alternative, the less effective aspirin 75-325mg daily can be used (class of recommendation IIa and level of evidence B). Only individuals with a CHA_2DS_2-VASc score of 0 with lone AF can be spared thromboprophylaxis (class of recommendation I and level of evidence A).

The knowledge of the left atrial appendage as the place of formation of most thrombi in patients with AF has led to the development of strategies to target this structure that can benefit patients with a high thromboembolic risk, but a concomitant high bleeding risk that contraindicates anticoagulation. In the *"Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF"* (PROTECT-AF) trial, percutaneous left atrial appendage closure with the *Watchman*® device was non-inferior to warfarin as far as effectiveness is concerned (RR = 0.62 and $CI_{95\%}$ = 0.35-1.25) [67], which makes it a possible option for this specific subset of patients (class of recommendation IIb and level of evidence B) [37].

8. Cardioversion and Ablation: high thromboembolic risk scenarios

There are two specific moments where thromboembolic risk is significantly increased in the lifetime of patients with AF.

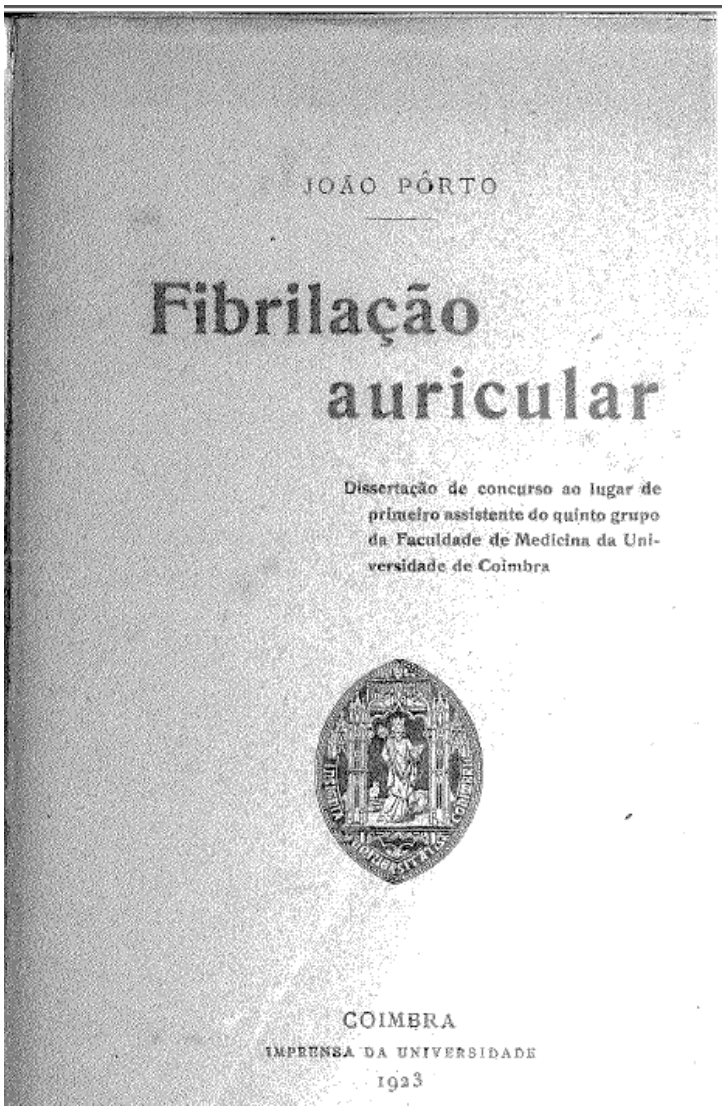
During cardioversion of AF (the procedure used for restoring sinus rhythm, either through pharmacologic agents, or by direct-current) the risk increases, not only due to the fact that existing thrombi in the left atria may be expelled with the recovery of organized left atrial contraction [68], but left atrial stunning is also known to develop after cardioversion [69]. This stunning phenomenon, results in compromised contraction of the atria walls, which leads to stasis and possibility of thrombus formation. Therefore, in all patients undergoing cardioversion of AF intra-cardiac thrombi must be excluded and effective anticoagulation should be continued for at least 3 to 4 weeks [37, 70]. Patients that present with episodes of AF lasting for less than 48 hours and those under effective anticoagulation during the previous month could be spared to the ruling out of intra-cardiac thrombi. In these patients, the presence of thrombi is highly unlikely (but still possible).

The original description of AF triggering by pulmonary ectopy by Haïssaguerre [71] led to the development of a novel treatment approach to patients with the arrhythmia: development of endocardial (or epicardial if through a surgical approach) lesions allowing the electrical disconnection of pulmonary veins. This has been referred as AF ablation. The development of lesions in the left atrium is known to be thrombogenic in the acute setting, placing these patients in an increased risk of stroke in the weeks after the procedure, which can be succefully tackled by anticoagulation [72]. Furthermore, thrombi in the left atrium must be ruled out before the procedure since, if present, they may dislodge with the manipulation of catheters [72]. According to the 2012 Consensus Statement on Catheter and Surgical Ablation of AF, a pre-procedure TEE is indicated to all patients with AF greater than 48 hours and without anticoagulation at a therapeutic level in the previous 3 weeks [73].

Table I – Putting thromboembolic risk stratification and bleeding risk assessment in perspective.

Thromboembolism				Bleeding	
C	"***C****ongestive Heart Failure*"	**C**	"**C**ongestive Heart Failure"	**H**	"**H**ypertension"
H	"**H**ypertension"	**H**	"**H**ypertension"	**A**	"**A**bnormal liver or renal function"
A	"**A**ge"	**A_2**	"**A**ge"	**S**	"**S**troke"
D	***D****iabetes mellitus*	**D**	***D****iabetes mellitus*	**B**	**"B**leeding history or predisposition"
S_2	"**S**troke or prior TIA"	**S_2**	"**S**troke or prior TIA"	**L**	**"L**abile INR"
		V A S c*	**VASc –V**ascular disease	**E**	**"E**lderly"
			* Female gender	**D**	"**D**rugs (Antiplatelet and NSAID) and/or alcohol"

Note: The presence of colours highlights existence of clinical variables that simultaneously signal thromboembolic and bleeding risk. **Legend:** TIA – transient ischemic attack; INR – international normalized ratio; NSAID – non-steroidal anti-inflammatory drugs.


JOÃO PÓRTO

Fibrilação auricular

Dissertação de concurso ao lugar de primeiro assistente do quinto grupo da Faculdade de Medicina da Universidade de Coimbra

COIMBRA
IMPRENSA DA UNIVERSIDADE
1923

Figure I – Thesis of Professor João Porto – published in 1923 (cover) [7].

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Aims.

Cerebrovascular disease is the main cause of mortality in Portugal. A big emphasis has been put on arterial hypertension which has led to recent changes in the presentation of this disease. The contribution of atrial fibrillation to the overall burden of cerebrovascular disease seems to be constantly overlooked in our country.

Goal I: To assess the impact of atrial fibrillation on cerebrovascular mortality at a national level through the review of the currently available evidence.

The currently used risk stratification schemes ($CHADS_2$ and CHA_2DS_2-VASc score) display only a low discriminative capability regarding the prediction of thromboembolic events in patients with non-valvular AF. This may arise from an insufficient knowledge of the pathways involved in thrombogenesis in this arrhythmia. These schemes use mostly clinical variables. We hypothesized that using biomarkers, echocardiographic parameters and other clinical parameters which still remain insufficiently explored may improve the discriminative capability of these models towards the prediction of thrombus and left atrial stasis and, consequently, thromboembolic events.

Goal II.A: To evaluate the role of echocardiographic parameters (left atrial area, volume and speckle-tracking derived strain and strain rate and left ventricle ejection fraction) in the prediction of left atrial thrombi and other markers of left atrial stasis, as assessed through transesophageal echocardiogram.

Goal II.B: To assess the possible role of biomarkers (cardiac troponin I, mean platelet volume, red cell distribution width, mean corpuscular volume and C reactive protein) in the prediction of left atrial stasis, as assessed through transesophageal echocardiogram.

Goal II.C: To clarify the role of chronic kidney disease, assessed through the estimated glomerular filtration rate as a predictor of thrombogenesis and thromboembolic events. A meta-analysis will be used for clinical endpoints and an echocardiographic study will be conducted to study the involvement of renal disease in the thrombogenic process.

Chronic kidney disease is a difficult treatment scenario in patients with atrial fibrillation. This is particularly due to the coexistence of increased thrombotic and bleeding risk. Also, concerns exist towards the efficacy of warfarin in the context of advanced dialytic kidney disease and regarding the efficacy and safety of the novel oral anticoagulants in moderate kidney disease.
To perform a meta-analysis to clarify the benefit and safety of warfarin and the novel oral anticoagulants in patients with chronic kidney disease and atrial fibrillation.

Despite the recommendations concerning the use of anticoagulation in the setting of catheter ablation of atrial fibrillation, there is still a gap in evidence concerning the use of the novel oral anticoagulants, namely dabigatran.

Goal III: To systematically revise all the published evidence concerning dabigatran in the setting of catheter ablation of atrial fibrillation, evaluating its efficacy and safety using a meta-analysis methodology.

Nowadays, transesophageal echocardiogram is still the most used and validated technique (gold-standard) for excluding the presence of thrombus in the left atrium and left atrial appendage. However, its semi-invasive nature poses some discomfort to the patients and this procedure is not totally devoid of risks.

Goal IV: To develop the first scheme combining clinical and echocardiographic variables, alongside with biomarkers, that can discriminate with a high accuracy the presence of left atrial thrombi, allowing some patients to be spared transesophageal echocardiography.

Material and Methods.

A. Original investigation studies

The population was composed of all consecutive patients undergoing transesophageal echocardiogram from April 2008 until the end of May 2013. Additional inclusion criteria: performance of a transthoracic echocardiogram, evaluation of laboratory data for any of the different sub-studies, in the previous 12 to 24 hours.

The possible indications for the performance of transesophageal echocardiogram were: direct-current cardioversion of atrial fibrillation, work-up of stroke (exclusion of cardioembolism), and structural or valvular evaluation.

The presence of any of the following was considered an exclusion criterion: presence of rheumatic heart disease, prosthetic heart valve or previous valve repair, moderate or severe aortic stenosis, acute coronary syndrome or infection at the time of transesophageal echocardiogram and absence of informed consent for inclusion in the study.

Clinical data (demographic, antropometric, risk factors and comorbidities and medication), as well laboratory and echocardiographic were assessed. $CHADS_2$ and CHA_2DS_2-VASc were estimated [1, 2]. Data was obtained from hospital registries (out-patient clinic, emergency department and hospitalization). The duration of the atrial fibrillation episode was estimated according to the patient's complains duration and previously known electrocardiogram. In patients with implantable cardiac devices (pacemakers and defibrillators), devices were interrogated for estimation of episode duration.

All echocardiographic procedures were performed in a General Electrics Vivid 7 using the following probes: 6T phased array multiplane for transesophageal (2.9 to 7.0 MHz) and a M4S for transthoracic (1.5 to 4.0MHz). Gain was adjusted for optimal evaluation of the presence of dense spontaneous echocardiographic contrast (neither excessive nor too low. Therefore, when the presence of autocontrast was suspected, gain was decreased in such a way to

confirm that even in that setting, autocontast remained detectable). The exams were performed by two cardiologists with accreditation in transthoracic and transesophageal echocardiogram by European Society of Cardiology. These were informed of the reason of the examination, but were blind to any other type of clinical or laboratory data.

Left atrial dimensions were estimated through the measurement of its area and volume, using the single-plane or bi-plane area-length method [3]. Left ventricle systolic function was qualitatively assessed and classified as normal, low, moderately or severely depressed, according to the measured left ventricle ejection fraction values with the Simpson method [3].

Images were acquired with > 50 frames per second for the evaluation of left atrial deformation in apical 4 chamber view [4]. Off-line analysis was performed through speckle tracking. 3 different cycles were assessed and the average values were kept. Peak values of positive and negative strain and strain rate were measured for each of the 6 studied segments. The time to peak-positive-strain was also measured and the standard deviation of the 6 segments was calculated.

On transesophageal echocardiogram left atrium and left atrial appendage were assessed in several tomographic planes, in order to detect the presence of thrombi or autocontrast. Spontaneous echocardiographic autocontrast was classified as 1 to 4+, according to the method proposed by Fatkin and colleagues [5]. Grade 3+ or 4+ were classified as dense spontaneous echocardiographic contrast. Flow velocities were measured by pulsed-wave Doppler, with the sample placed approximately 1 cm into the left atrial appendage. Maximum filling and emptying velocities were estimated as an average of 5 well-defined waves. Patients with a maximum velocity of ≤20cm/s were classified as having low flow velocities. Images were kept and transferred for off-line analysis in a workstation using the EchoPac Dimension PC version 108.1.4 software, by GE Health Care.

Venous blood samples were drawn from patients in the prespecified time-windows according to the performance of echocardiograms. Automatic counting of blood cells was performed

using the Cell-Dyn Sapphire Hematology Analyzer®, Abbot Diagnostics©. Troponin I was measured with the Ortho-Clinical Diagnostics VITROS® Troponin I ES Assay. C-reactive protein was measured with the CRP VITROS Chemistry Products assay and creatine with the CREA VITROS Chemistry Products assay. Estimated glomerular filtration rate was estimated using the Modified Diet in Renal Disease (MDRD) equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Urea levels were measured with the BUN/UREA VITROS Chemistry Products assay.

PASW Statistics version 18.0 was used for descriptive and inferential statistics: comparison of nominal values was done with the chi-square test and continuous variables were compared either with the t Student test or ANOVA, when appropriate, using the Levene test for assessing the homogeneity of variance; When appropriate, and the results of Kolmogorov-Smirnov supported this need, equivalent non-parametric tests were used.

Receiver-operator characteristic (ROC) curves were traced for the discrimination of events or transesophageal markers using the severall tested risk stratification schemes and variables. Data from these curves was also used for defining cutoff values (Youden index) for each parameter, when suitable data was not available in the literature. MedCalc 2.0 was used for comparison of ROC curves. Results with $P < 0.05$ were considered significant.

Univariate analysis through chi-square test was performed. Continuous variables were converted into categorical, when suitable. Backward stepwise logistic regression was performed using variables that were predictors on univariate analysis (likehood ratio; probability for stepwise = 0.1). The Hosmer-Lemeshow test was used for evaluating the goodness-of-fit of the obtained models.

The migration of patients classified of low, intermediate or high risk and its relation with the presence of markers of thromboembolic risk was evaluated through the Net reclassification improvement (NRI), method described by Pencina et al. [6]. A positive NRI translated a

successful reclassification into more appropriate categories and the amount of reclassification was illustrated by the extension NRI value, which represented a percentual value.

Crossed-tabulation was also performed to evaluate the presence of thromboembolic risk markers in each risk group and estimate the overall trend for the increase of its prevalence alongside with the risk estimated by the classification using the chi-squre for trend (Gamma).

B. Systematic Reviews and Meta-analysis

Two systematic reviews with meta-analysis have been performed based on the methods proposed by the Cochrane Colaboration [7]: one focusing on the use of dabigatran in patients undergoing catheter ablation of atrial fibrillation and the other aimed to elucidate the role of chronic kidney disease as a predictor of thromboembolic events in atrial fibrillation patients and the role of anticoagulation in this setting.

Data extraction and presentation followed the recommendations of the PRISMA group [8] and were pooled using random-effects, according to the Mantel-Haenszel model, through Review Manager (RevMan), Version 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Further details concerning these two investigations (search strategy on MEDLINE, EMBASE and COCHRANE, inclusion/exclusion criteria and methods) are provided in the respective articles.

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Goal I.

Atrial fibrillation and Cerebrovascular disease in Portugal: Impact in the XXIst century

I.

Cerebrovascular mortality in Portugal: Are we overemphasizing hypertension and neglecting atrial fibrillation?

Rui Providência, Lino Gonçalves, Maria Ferreira. Cerebrovascular mortality in Portugal: Are we overemphasizing hypertension and neglecting atrial fibrillation? Rev Port Cardiol 2013;32(11):905-13.
doi: 10.1016/j.repc.2013.04.010

Resumo:

As doenças cerebrovasculares têm sido desde há largos anos a principal causa de morte em Portugal. Apesar das intervenções que têm sido levadas a cabo a nível do tratamento da hipertensão e concomitante diminuição da mortalidade que lhe é atribuída, o gradual envelhecimento da população e aumento da prevalência de fibrilhação auricular têm evitado que o número de acidentes vasculares cerebrais atingisse os números desejáveis. Os autores fazem uma revisão do panorama nacional desta realidade e propõem um plano de intervenção.

Palavras-Chave: fibrilhação auricular; hipertensão auricular; acidente vascular cerebral; mortalidade cerebrovascular; Portugal.

Abstract:

Cerebrovascular disease has been the first cause of death in Portugal for a long time. Despite the interventions concerning the treatment of hypertension and the concomitant decrease in the associated mortality, the progressive aging of the population and increase in the prevalence of atrial fibrillation has prevented the number of strokes from reaching the desirable levels. The authors revise the evidence concerning national reality and propose a plan of intervention.

Keywords: atrial fibrillation; hypertension; stroke; cerebrovascular mortality; Portugal.

Introdução:

De acordo com o relatório da Direção Geral de Saúde de 2008, as doenças do aparelho circulatório continuam a ser a principal causa de mortalidade no nosso País [(1)], correspondendo a 32.3% dos óbitos. Trata-se de quase 40% mais do que a segunda causa de morte, ou seja, o conjunto de todas as doenças neoplásicas, responsável por 23.5%. Porém, contrariamente aos restantes países europeus, em que a maior fatia corresponde à cardiopatia isquémica, no nosso País as doenças cerebrovasculares são as principais responsáveis por esses números, contribuindo com 13.9% dos óbitos.

Desde há algumas décadas, tem sido dado especial ênfase ao diagnóstico e controlo da hipertensão arterial. Apesar de razoável sucesso, com melhoria dos nossos valores relativamente ao passado, continuamos longe da completa resolução da situação. Porém, fruto dessa circunstância e apesar das doenças cerebrovasculares continuarem a ser a principal causa de mortalidade, assistimos a uma mudança no padrão dos acidentes vasculares cerebrais (AVC) observados no território nacional, com um crescente reconhecimento da fibrilhação auricular (FA) como uma interveniente principal no processo. Esta é a arritmia cardíaca mantida mais prevalente [(2)], podendo ocorrer em até 25% da população acima dos 40 anos, durante o decurso da sua vida, e está associada a um aumento marcado da incidência de tromboembolismo cerebral e sistémico [(3)]. Além disso, os acidentes cerebrovasculares em doentes com FA têm maior mortalidade (50% ao final de um ano) [(4)] e são habitualmente extensos e incapacitantes [(5)]. Estudos recentes ao nível do nosso País mostram que a taxa de diagnóstico desta arritmia é francamente insatisfatória [(6)] e que mesmo quando na presença do diagnóstico, os doentes muito frequentemente não recebem o tratamento adequado [(7)].

O real conhecimento desta situação, assim como uma intervenção focada de toda a comunidade médica, incluindo cardiologistas, neurologistas, internistas e médicos de medicina

geral e familiar, bem como de todos os restantes profissionais de saúde, reveste-se da maior importância para travar o curso dos acontecimentos.

1) Hipertensão arterial em Portugal

a. Evolução do diagnóstico e controlo nos últimos anos

No *Estudo Epidemiológico de Prevalência da Síndrome Metabólica na População Portuguesa* (VALSIM), que decorreu entre Abril de 2006 e Novembro de 2007, com o apoio do Centro Nacional de Colecção de Dados em Cardiologia (CNCDC) da Sociedade Portuguesa de Cardiologia. Esse estudo, de carácter transversal, envolvenu 16.856 participantes acima dos 18 anos avaliados nos cuidados de saúde primários (envolvendo 719 Médicos de Família representativos de todas as regiões de Portugal), a prevalência de hipertensão arterial ajustada à idade e género foi 42.6% [(8)]. Além disso, e tendo em conta alguma variabilidade regional na prevalência e tratamento, verificou-se que em cerca de 10% dos indivíduos hipertensos não foi iniciada terapêutica farmacológica (esta cifra atingiu valores de mais de 50% nos indivíduos com menos de 30 anos) e que a percentagem de doentes sob monoterapia foi de 47.6%. Estes valores estão bastante acima da média europeia, demonstrando que a inércia terapêutica ainda é muito prevalente entre nós.

No estudo AMALIA *(um Estudo Epidemiológico de Avaliação do Risco de Doença Cardiovascular em Portugal)*, realizado através de entrevistas no domicílio a 38.893 indivíduos com idade igual ou superior a 40 anos, a prevalência de hipertensão auto-referida foi de apenas 23.5% [(9)]. Comparativamente ao estudo anterior, e apesar da ausência de faixas etárias jovens, os valores foram mais baixos, o que pode ser explicado pelo método utilizado (um questionário) e pelo muito frequente desconhecimento da presença desta alteração por parte da população.

Desta forma, estes números referem-se apenas aos indivíduos a quem já havia sido previamente detetada hipertensão arterial e o quiseram declarar, deixando de fora todos aqueles que apesar de hipertensos não o reportaram apesar de terem conhecimento de tal, ou que não o fizeram por desconhecimento e ausência de controlo tensional.

A questão do conhecimento da hipertensão foi analisada por *Pereira et al.* numa amostra de 2.310 portugueses com idade igual ou superior a 18 anos selecionados aleatoriamente na população do Porto entre 1999 e 2003. A prevalência de hipertensão arterial medida no domicílio dos participantes foi de 46.7% no sexo masculino e 42.7% no feminino [(10)]. O conhecimento prévio deste diagnóstico foi de apenas 41.3% nos homens e 58.9% nas mulheres. Concomitantemente, só 60.2% a 71.7% dos participantes que sabiam ser hipertensos se encontravam medicados e, destes, apenas 23.0% a 22.8% estavam controlados (referindo-se os primeiros valores ao sexo feminino e os últimos ao masculino).

O estudo *Prevalência, Conhecimento, Tratamento e Controlo da Hipertensão em Portugal* (PAP) incluiu 5.023 adultos, representativos de todo o território português, avaliados entre Março de 2003 e Fevereiro de 2004. Nele foram observados números semelhantes para a prevalência e conhecimento da hipertensão arterial. Porém, a prevalência de hipertensos tratados e controlados foi ainda mais baixa que no estudo previamente discutido: 39.0% e 11.2%, respetivamente [(11)].

Apesar de ainda apresentar números preocupantes, a evolução do panorama Nacional tem sido favorável. Uma revisão sistemática recentemente publicada mostra que a prevalência de hipertensão arterial em Portugal diminuiu nos adultos de meia (58.3% para 49.1% no sexo masculino e 51.5% para 42.3% no feminino) e terceira idades (96.4% para 74.5% no sexo masculino e 89.6% para 67.6% no feminino), no período de 1990 a 2005 [(12)]. A prevalência do auto-conhecimento aumentou 0.4% por ano, no mesmo período. Os valores médios de tensão arterial sistólica e diastólica registaram uma diminuição entre 1975 e 2005, sendo que nos

idosos do sexo masculino os valores de tensão arterial sistólica diminuíram em média 22 mmHg e no sexo feminino 32mmHg. Porém, os autores observam que apesar da evolução favorável, os valores do nosso país ainda se encontram acima da média dos países da Europa Ocidental.

b. A Problemática do Sal

Uma investigação de *Polónia e colaboradores* comprovou o elevado consumo de sal no nosso território. Nesta, foi avaliada a excreção de sódio na urina das 24 horas (sem alteração prévia do contexto dos hábitos alimentares habituais) em 426 participantes, com uma idade média de 50±22 anos, pertencentes a 4 grupos populacionais: estudantes universitários, operários fabris, familiares de doentes com eventos cerebrovasculares recentes e doentes hipertensos. O valor extrapolado de consumo médio diário de sal foi 12.3g/dia (não se encontrando diferenças significativas entre os 4 grupos estudados) [(13)], ou seja, o dobro do recomendado por organizações internacionais [(14)].

No seguimento deste trabalho, e dado que no tercil com maior consumo de sal se registava também maior consumo de pão, foi avaliado o conteúdo de sal na panificação portuguesa e comparado com a de outros 6 países. Detetou-se uma média de 19.2g de sal por Kg de pão, ou seja, 53% mais que no grupo de controlo. A partir de então foram tomadas uma série de medidas visando a educação da população de modo a frenar o consumo excessivo desta substância [(15, 16)]. Estabeleceram-se ainda contactos com os produtores alimentares, autoridades de saúde e governo. Em Março de 2009 foi aprovada no Parlamento Português uma lei definindo o limite máximo de 1.4g/100g para teor de sal adicionado ao pão após a sua confeção, bem como a necessidade de apresentar a quantidade relativa e absoluta de sal, por percentagem do produto e por porção/dose, na rotulagem de alimentos pré-embalados [(17)].

Outra possível fonte de sódio na dieta (apesar de o anião associado ao sódio neste caso ser o bicarbonato e não o cloro, o que parece estar associado a diferentes efeitos) seria em teoria a água gaseificada. Porém, um pequeno estudo com 17 participantes divididos por 2 grupos (*Água das Pedras* vs *Água Vitalis*) não cego e submetido a *cross-over* ao final de 7 semanas em cada braço terapêutico (com um intervalo de 6 semanas para *washout*), mostrou que o consumo diário de 500ml de *Água das Pedras* não tinha qualquer tipo de efeito na tensão arterial [(18)].

Face à sua recente implementação, ainda teremos que aguardar alguns anos de forma a poder observar o real efeito destas medidas para controlo do consumo de sal na prevalência de hipertensão arterial e número de AVC ocorridos no território.

2) Acidente vascular cerebral em Portugal: a recente mudança do panorama

A mortalidade por doença cerebrovascular tem vindo a diminuir nos últimos anos, muito provavelmente fruto do aumento do conhecimento e tratamento dos casos de hipertensão arterial, assim como da melhoria geral progressiva dos cuidados de Saúde. Os números relativos ao ano de 1996 mostram que 22.9% das mortes em indivíduos abaixo dos 65 anos tinham ocorrido devido a AVC [(19)]. Na estatística de 2008 [(1)], já englobando toda a população e não apenas os indivíduos com menos de 65 anos, os números rondaram os 13.9%. Apesar de não serem diretamente comparáveis, ilustram, de alguma forma, a diminuição que se tem vindo a verificar.

Paralelamente a essa diminuição, tem-se assistido a uma mudança no tipo de acidentes vasculares cerebrais que são admitidos nas Unidades de AVC. Num estudo retrospetivo

englobando todos os doentes internados nas enfermarias de um Hospital Universitário com o diagnóstico de AVC isquémico no primeiro trimestre de 2011, Cunha detetou que cerca de 37.3% (91) eram de etiologia cardioembólica, contrariamente aos cerca de 15 a 20% que se observavam no passado [20]. De entre estes, 94.5% (86) foram devidos a fibrilhação auricular (FA), sendo que em 83.7% (72) destes o diagnóstico de FA já era conhecido previamente e que em apenas 34.7% (25) se encontravam medicados com anticoagulantes.

Sabe-se que a FA aumenta de prevalência à medida que a idade avança [2]. Assim, o panorama Mundial relativamente a esta arritmia tem vindo gradualmente a mudar, fruto do progressivo aumento da esperança de vida. Uma análise recente das causas de morte em 187 países entre 1980 e 2010, parte do *Global Burden of Disease Study 2010*, mostrou um aumento de 233.9% na mortalidade atribuível à FA entre 1990 e 2010 [21].

Será lícito considerar que nos encontramos numa época de mudança de paradigma relativamente aos AVC, com diminuição daqueles que são atribuíveis à hipertensão não tratada ou descontrolada e aumento progressivo daqueles devidos ao embolismo cardíaco (Figura I).

3) Fibrilhação auricular em Portugal

a. Prevalência e Comorbilidades

A prevalência de FA (e flutter auricular) não era conhecida até à realização do estudo "*prevalência de Fibrilhação Auricular na população portuguesa com 40 ou Mais Anos*" (FAMA) [6]. Este estudo, englobando 10.447 participantes residentes nas várias regiões de Portugal

selecionados aleatoriamente e submetidos à realização de um electrocardiograma e questionário no seu domicílio, mostrou uma prevalência de 2.5% nesta faixa etária. Face à muito frequente coexistência de fibrilhação e flutter auricular e ausência de diferença no risco tromboembólico [22] ou na terapêutica preconizada para prevenção do mesmo, foram pesquisadas as duas patologias. Porém, o número detetado de casos de flutter foi muito reduzido (cerca de 12) e se removido da análise o valor estimado de prevalência cairia apenas 0.1%.

A variação de prevalência de FA de acordo com as faixas etárias reproduziu os valores encontrados noutras séries [2]. Antes dos 50 anos a prevalência foi de 0.2%, permanecendo nos 1.0% e 1.6% dos 50 aos 59 e 60 aos 69 anos, respetivamente. A partir dessa classe etária a prevalência subiu acentuadamente, atingindo os 6.6% dos 70 aos 79 anos e chegando aos 10.4% na classe seguinte. Apesar de não haver diferenças na prevalência entre ambos os sexos, a FA foi mais prevalente no sexo feminino acima dos 80 anos e mais prevalente no sexo masculino entre os 70 e os 79.

Este estudo permitiu também conhecer dados de capital importância relativamente às comorbilidades neste grupo de pacientes: a hipertensão arterial foi um preditor independente de FA e estava presente em 71.0% dos doentes com FA, comprovando a forte associação entre as duas entidades [23]. A prevalência de AVC nos indivíduos com FA, tal como esperado, foi superior, em cerca de 3 vezes, aos restantes indivíduos (14% vs 5%; $p < 0.001$) [6].

b. Profilaxia de tromboembolismo a nível Nacional

Da população de doentes com FA analisada no estudo FAMA, apenas 61.7% (161 dos 261) tinham diagnóstico previamente conhecido de FA. De entre aqueles com FA, e assumindo as

suas idades, presença de HTA, bem como a elevada prevalência de factores de risco, somos levados a pressupor que os scores de risco de $CHADS_2$ e CHA_2DS_2-VASc seriam, só por si, uma indicação para a anticoagulação oral. Porém, apenas 37.8% se encontravam anticoagulados, o que reflete a baixa intervenção a nível da profilaxia tromboembólica em doentes com FA a nível nacional. Desta forma, segundo os autores, *"uma explicação plausível para uma taxa tão alta de AVC poderia ser a existência na população portuguesa de uma presença elevada, diagnosticada ou não, de FA, com uma taxa reduzida de utilização de terapêutica anticoagulante"*.

Algumas destas noções obtidas no estudo FAMA foram validadas posteriormente, à escala da realidade hospitalar, numa investigação de doentes admitidos consecutivamente num Serviço de Medicina Interna de um Hospital Central, entre Outubro de 2006 a Outubro de 2007 com o diagnóstico de fibrilhação ou flutter auricular à data de alta [(7)].

Esta população, possuía uma idade idade média de 77±10 anos, o que só por si e mesmo na ausência de qualquer outro factor de risco do score de $CHADS_2$ ou CHA_2DS_2-VASc conferia uma indicação para anticoagulação oral. Aplicando a classificação presente nas Recomendações conjuntas de 2006 para o tratamento de doentes com FA do American College of Cardiology, American Heart Association e European Society of Cardiology [(24)], 126 (81.3%) dos doentes avaliados apresentavam risco elevado e os restantes 29 doentes risco moderado para tromboembolismo (presença de 1 factor de risco moderado, sendo que hoje em dia todos estes fazem parte ou do score de $CHADS_2$ [(25)] ou CHA_2DS_2-VASc [(26)]). Apesar da indicação para anticoagulação ter sido identificada em 70.6% dos doentes estratificados como possuindo risco elevado, só 51.6% destes foram medicados de tal forma.

Este estudo enfatiza que nessa altura, mesmo a nível hospitalar, a indicação para anticoagulação oral não era identificada em até 30% dos doentes com FA de alto risco

tromboembólico e que mesmo quando esta era identificada, quase metade não recebia o tratamento adequado.

4) Importância da adequada profilaxia do tromboembolismo em doentes com FA

a. Classificações de risco clínico e recomendações da Sociedade Europeia de Cardiologia e outros Grupos internacionais.

Está actualmente recomendado que a decisão relativa à realização ou não de profilaxia de tromboembolismo num dado paciente com FA se baseie em classificações clínicas, constituídas pela presença de factores de risco clínico, facilmente pesquisados numa breve anamnese. As classificações atualmente preconizadas a nível da Europa [27] e América do Norte [28] são o CHA_2DS_2VASc e o $CHADS_2$, respectivamente, e encontram-se ilustradas na Tabela I. A decisão de anticoagular, ou não, um paciente baseia-se no risco expectável de tromboembolismo que este apresenta (Tabela II).

Existe também uma classificação de risco hemorrágico, o HAS-BLED e que deve ser utilizada como um elemento moderador da decisão terapêutica [29]. Porém, dado de que o HAS-BLED partilha várias comorbilidades com as classificações de CHA_2DS_2-VASc e $CHADS_2$, é frequente que grande parte dos doentes de risco tromboembólico mais elevado tenha também um risco hemorrágico aumentado. Nesses casos deve ser selecionada uma opção de baixo risco hemorrágico como alguns dos novos anticoagulantes ou, eventualmente, o encerramento percutâneo do apêndice auricular esquerdo. Está hoje em dia demonstrado que a decisão de não anticoagular um doente, medicando-o em alternativa com um antiagregante face à crença

de menor risco hemorrágico por parte destes agentes, é errada, dado que a protecção de eventos tromboembólicos é muito menor (3 a 5 vezes) e o risco hemorrágico é sobreponível, tal como demonstrado com no estudo *Apixaban Versus Acetilsalicylic Acid to Prevent Stroke in Atrial Fibrillation* (AVERROES) [30] ou com os antagonistas da vitamina-K no *Birmingham Atrial Fibrillation Treatment of the Aged study* (BAFTA) [31].

b. Anticoagulantes

Existem desde há poucos anos 3 novas opções (dabigatran, rivaroxaban e apixaban) no campo dos anticoagulantes para a prevenção de tromboembolismo na FA não valvular que demonstraram algumas vantagens relativamente à varfarina. Dado não ser este o principal enfoque deste artigo, serão apenas muito breve e resumidamente mencionadas.

O facto de não necessitarem de controlo dos níveis terapêuticos através de análises sanguíneas e de terem um perfil de interações (farmacológicas e alimentares) muito mais favorável, foram as vantagens que motivaram bastante expectativa relativamente aos ensaios de fase 3 utilizando a varfarina como comparador [32-34].

Apesar de algumas particularidades observadas, específicas a um ou outro fármaco, quando analisamos em bloco os mais de 50.000 participantes nos ensaios com estes novos anticoagulantes são demonstradas vantagens relativamente à varfarina em quase todos os *endpoints* avaliados. Assim, nestas meta-análises [35-38] foi observada diminuição da mortalidade, diminuição de AVC ou embolismo sistémico, diminuição de AVC hemorrágico, menos hemorragias intracraneanas e hemorragias gastrointestinais.

c. Papel do encerramento percutâneo do apêndice auricular esquerdo

O facto de a maioria dos trombos na FA se formar no apêndice auricular esquerdo (pensa-se que tal ocorra em até cerca de 90% [39]) levou a que se equacionasse outro tipo de opções terapêuticas para travar o tromboembolismo. No estudo *the Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF* (PROTECT-AF), mostrou-se que o encerramento percutâneo do apêndice auricular esquerdo através do dispositivo *Watchman®* possuía um semelhante perfil de eficácia (ou seja, não inferioridade) quando comparado com a varfarina [40]. Desta forma, torna-se uma opção lícita a considerar como alternativa nos doentes que apresentam contraindicações à anticoagulação [27].

Em Portugal existem já alguns Centros a realizar este procedimento. *Faustino et al.* demonstraram a sua experiência inicial num pequeno grupo de 13 doentes com risco elevado de tromboembolismo ($CHADS_2$ 3.5±0.9 e CHA_2DS_2-VASc 5.5±1.0) onde se registou uma baixíssima taxa de complicações intra-procedimento (2 pequenas hemorragias e 1 hematoma resolvidos com tratamento conservador) [41]. Um dos doentes desenvolveu ainda 1 trombo numa das superfícies do disco controlado com um curto curso de terapêutica médica. Nenhum dos doentes apresentou fenómenos embólicos sistémicos ou AVC durante um período de 11±5meses, um valor bem abaixo do previsto de acordo com o score $CHADS_2$ da amostra (7.3±2.3%).

d. As decisões limite e receios não justificados na profilaxia tromboembólica

No estudo previamente discutido, da autoria de *Dores e colaboradores*, 19.0% dos doentes com indicação formal para anticoagulação oral por serem de alto risco não terão sido anticoagulados face à eventual presença de uma contraindicação formal: em 26% uma discrasia hemorrágica prévia, em 16% alcoolismo, em 16% doença renal e 13% por impossibilidade do controlo do INR) [(7)]. Nos restantes 29.4% não foi apresentada qualquer justificação para a ausência desse tratamento. Atendendo ao estado atual do conhecimento e terapêutica, no momento presente quase todos os doentes de alto risco podem ser efetivamente protegidos e as contraindicações contornadas, ou por utilização dos novos anticoagulantes orais (nos doentes em que havia dificuldade do controlo do INR) ou por encerramento percutâneo do apêndice auricular esquerdo (naqueles com risco hemorrágico demasiadamente elevado, contraindicado a anticoagulação). Relativamente à doença renal crónica, está actualmente demonstrado que é não só um factor de risco hemorrágico, mas também um factor de risco tromboembólico [(42-44)]. O benefício da anticoagulação com varfarina nestes doentes foi demonstrado num registo Dinarmarquês com centenas de milhar de doentes com FA. Nesse mesmo registo, a aspirina, frequentemente selecionada para este tipo de doentes mostrou-se ineficaz e com risco hemorrágico semelhante à varfarina. Nos ensaios com os novos anticoagulantes, foram estudados indivíduos até níveis de *clearance* de 25 a 30ml/min, pelo que neste caso, estes novos anticoagulantes também poderão ser considerados uma opção. Porém, abaixo desse nível, a varfarina é o único fármaco com evidência favorável a suportar a sua utilização [(42)].

Além da questão da insuficiência renal, existem ainda algumas situações de práticas comuns, mas que não são baseadas em qualquer tipo de evidência, podendo mesmo ser deletérios para o próprio doente. Pensa-se frequentemente que a aspirina é mais segura que os

anticoagulantes orais. Tanto no estudo AVERROES (apixabano vs aspirina) [30], como no registo Dinamarquês previamente referido e no BAFTA (varfarina vs aspirina) [31] se demonstrou que a incidência de hemorragias foi igual para os dois tratamentos, com menor eficácia da aspirina na prevenção de AVC e eventos embólicos.

Além deste motivo, a outra razão frequente que leva a que os anticoagulantes sejam frequentemente preteridos é o receio de complicações hemorrágicas face ao risco elevado de queda que existe nos idosos. Porém, está demonstrado que seriam necessárias 295 quedas para que fosse ultrapassado o benefício da anticoagulação num doente com score de $CHADS_2$ = 2 a 3 [45].

5. Importância da detecção precoce da FA

Face a toda a diversidade de opções terapêuticas que nos permitem abordar a quase totalidade dos pacientes, atendendo às suas especificidades, podemos afirmar que nos encontramo-nos numa época privilegiada para adequadamente proteger esta população.

Os autores do estudo FAMA, comentaram que face à "*elevada mortalidade por AVC em Portugal e assumindo-se que a FA está na base de 15% destes acidentes [3], considerou-se que o conhecimento da prevalência de FA nas diversas faixas etárias, poderia ser importante não só na melhoria do nível de controlo desta arritmia, como na prevenção dessas complicações vasculares.*" Se atendermos aos números mais recentes [20], a importância do conhecimento dos casos em risco e seu tratamento, reveste-se ainda de maior significado.

Assim, um dos grandes entraves para atingir tal objetivo, poderá mesmo ser o desconhecimento da presença do diagnóstico, que tal como ilustrado no estudo pré-citado é

bastante prevalente. Esta investigação demonstrou que o aumento da idade e do índice de massa corporal, hipertensão arterial e ausência de prática de exercício físico foram preditores independentes da presença desta arritmia. De destacar que além de terem maior prevalência de FA, os indivíduos mais idosos e hipertensos têm também um risco tromboembólico mais aumentado, sendo que são estes que têm ainda maior benefício do diagnóstico atempado [(6)].

Se atendermos ao facto de que esta arritmia é muito frequentemente assintomática e que muitas vezes a primeira apresentação é um AVC, a melhor maneira de não falhar o seu diagnóstico poderá ser a realização de rastreios sistemáticos. Seria importante que fossem universais a partir de certa idade, e que, face ao seu risco aumentado, em alguns grupos de risco fossem repetidos com alguma periodicidade. No Reino Unido estão atualmente em desenvolvimento programas deste tipo. Uma das hipóteses em estudo será a medição rotineira do pulso a nível do Médico Família nos utentes acima dos 65 anos e posterior realização electrocardiograma nos casos com pulso irregular [(46)]. A efectividade desta estratégia de rastreio encontra-se atualmente também em avaliação numa iniciativa em Espanha [(47)].

Porém, dado que no nosso País existe uma grande franja da população que não tem ou não recorre frequentemente ao Médico de Família, outras opções deverão ser consideradas para complementar essa lacuna: a realização de um rastreio global por ECG em idades chave (a cada 5 ou 10 anos a partir dos 65 anos) ou mesmo a instalação de sistemas automáticos de medicação da pulsação (e deteção de ritmos irregulares) em farmácias, instituições de saúde, ou locais de grandes concentrações humanas, como centros comerciais e estruturas desportivas. Num pequeno estudo Alemão, o electrocardiograma mostrou elevada capacidade diagnóstica, detetando FA previamente desconhecida em 7 de 132 participantes com média de idades 64 anos e possuindo algumas combinações de comorbilidades de risco (hipertensão, diabetes, etc) [(48)].

Em casos de elevada probabilidade de prevalência da arritmia poderão mesmo ser equacionados os sistemas de registo electrocardiográfico contínuo de 24 horas, ou mesmo por períodos mais prolongados.

Conclusões

A deteção e o controlo da hipertensão arterial têm sido e devem manter-se uma prioridade, pois os níveis alcançados não são ainda os ideais, encontrando-se mesmo algo abaixo da generalidade dos países da Europa.

Contrariamente, a fibrilhação auricular como causa de mortalidade cerebrovascular pode ter vindo a ser negligenciada no nosso País, contribuindo para a manutenção de uma elevada incidência da mortalidade de causa cerebrovascular.

Face ao esperado aumento da idade média da nossa população até 2025, será de esperar um aumento não só desta arritmia, mas também dos AVC que lhe poderão ser atribuídos. De forma a evitar que tal aconteça será importante traçar um plano de intervenção fortemente apoiado nas três seguintes linhas: deteção de casos assintomáticos, evicção da inércia terapêutica e aplicação das recomendações terapêuticas no que concerne à profilaxia tromboembólica nos doentes de risco (Figura II).

Figura I – Esquema ilustrativo da mudança do panorama relativo ao acidente vascular cerebral em Portugal nas últimas décadas.

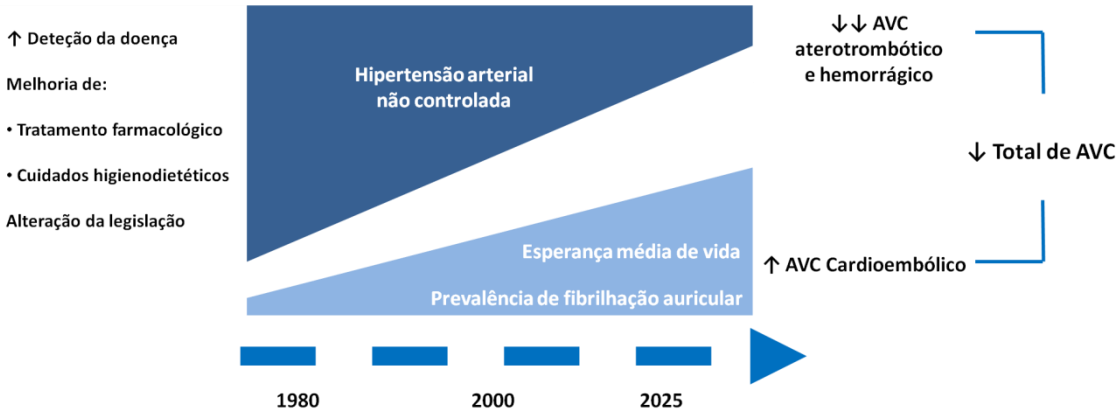

Figura II – Principais linhas orientadoras para o atingimento da diminuição da mortalidade cerebrovascular.

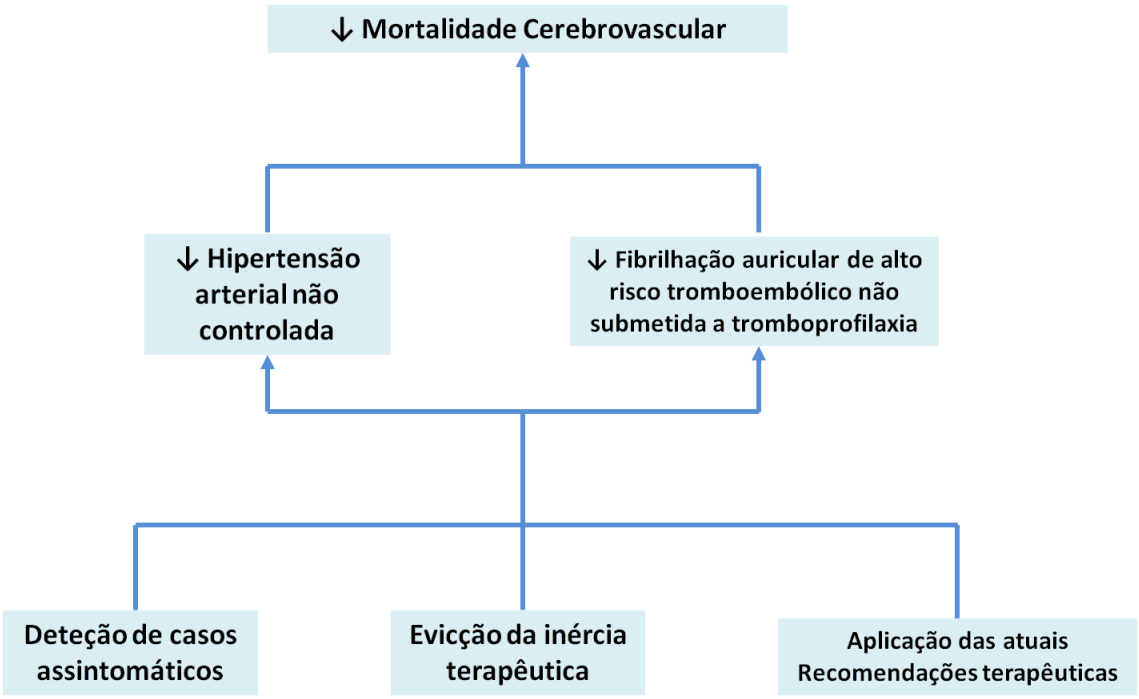

Tabela I – Composição das classificações de risco recomendadas pela *European Society of Cardiology* [27] e *American College of Cardiology/ American Heart Association / Heart Rhythm Society* [28] para a orientação da profilaxia de risco tromboembólico em doentes com fibrilhação auricular não-valvular.

C	"***C**ongestive Heart Failure*"	**C**	"**C**ongestive Heart Failure" – Insuficiência cardíaca congestiva ou fracção de ejecção do ventrículo esquerdo ≤ 40%
H	"**H**ypertension"	**H**	"**H**ypertension"
A	"**A**ge" – Idade ≥ 75 anos	**A_2**	"**A**ge" – Idade dos 65 aos 74 anos ou ≥ 75 anos
D	***D**iabetes mellitus*	**D**	***D**iabetes mellitus*
S_2	"**S**troke or prior TIA" – AVC ou AIT prévio	**S_2**	"**S**troke or prior TIA" – AVC ou AIT prévio
		V	**VASc –** doença **V**ascular – definida como tendo pelo menos um dos seguintes: enfarte agudo do miocárdio, doença arterial periférica e placas complexas na aorta
		A	
		S	
		c*	* o sexo feminino também é considerado um factor de risco nesta classificação

Nota: De acordo com as recomendações da *European Society of Cardiology*[27] a presença de um score de CHA_2DS_2-VASc de 2 é indicação para anticoagulação oral, salvo se contraindicado. Perante a presença de um score de 1 a anticoagulação oral deve ser considerada, de acordo com o risco de complicações hemorrágicas e preferência do doente. Se o score for de zero, não está recomendada qualquer terapêutica.

Nas recomendações do *American College of Cardiology/ American Heart Association / Heart Rhythm Society*[28] a interpretação em termos de pontuação é semelhante, embora baseada no mais conservador score de $CHADS_2$.

Como ressalva, reforçam-se ainda as duas seguintes noções: A decisão de anticoagular ou não um doente com FA não valvular baseia-se nestes scores e não no tipo de FA em questão (paroxística, persistente ou permanente). A profilaxia de tromboembolismo no flutter auricular deve ser realizada exatamente da mesma forma que na FA.

Tabela II – Risco anual estimado de AVC ou embolismo sistémico, na ausência de profilaxia de tromboembolismo, em indivíduos com fibrilhação auricular não valvular de acordo com as classificações de CHA_2DS_2-VASc e $CHADS_2$.

$CHADS_2$	**Risco anual Estimado [25]**	**CHA_2DS_2-VASc**	**Risco anual Estimado [26]**
0	1.9%	0	0
1	2.8%	1	0.7%
2	4.0%	2	1.9%
3	5.9%	3	4.7%
4	8.5%	4	2.3%
5	12.5%	5	3.9%
6	18.2%	6	4.5%
		7	10.1%
		8	14.2%
		9	100%*

N.B.: Taxas extraídas dos artigos originais de validação dos scores de $CHADS_2$ e CHA_2DS_2-VASc [25, 26]. Dado que se tratam de taxas anuais, sugere-se que seja tido em conta a esperança de vida do paciente em questão de forma a apurarmos qual o risco de vir a padecer de um evento se não tratado.

* Face ao reduzido de participantes no estudo de derivação com um score de 9, não foi possível estabelecer um valor fidedigno para o risco expectável neste grupo.

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Goal II.

New Advances in Non-valvular Atrial Fibrillation Thrombogenesis and Risk Stratification

Goal II.A

Advances in Echocardiography

II.A.1

Possible Refinement of Clinical Thromboembolism Assessment in Patients with Atrial Fibrillation Using Echocardiographic Parameters.

Rui Providência, Ana Botelho, Joana Trigo, Nuno Quintal, José Nascimento, Paula Mota, António Leitão-Marques. Possible Refinement of Clinical Thromboembolism Assessment in Patients with Atrial Fibrillation Using Echocardiographic Parameters. Europace. 2012;14(1):36-45. doi: 10.1093/europace/eur272

Abstract:

Aim: Some transesophageal echocardiogram (TEE) findings are associated with an increased risk of stroke in patients with atrial fibrillation (AF). This study was designed to evaluate and compare the accuracy of $CHADS_2$ and CHA_2DS_2-VASc in the prediction of these findings and test the additive value of transthoracic echocardiogram (TTE) derived parameters as a possible refinement for these classifications.

Methods: Cross-Sectional study of 405 consecutive patients who underwent TTE and TEE evaluation during AF. Stroke risk assessment was performed using the $CHADS_2$ and CHA_2DS_2-VASc scores, alone and alongside with the addition of two TTE derived parameters (left atrium area and left ventricle global systolic function). Comparisons regarding the presence of left atrial appendage thrombi (LAA T), dense spontaneous echo contrast (SEC) and LAA low flow velocities (LFV) were performed using ROC curves.

Results: In low-risk patients, as assessed through the CHA_2DS_2-VASc score and $CHADS_2$ and CHA_2DS_2-VASc scores plus echo parameters, no high-risk features were found on TEE. In subjects classified as low-risk using $CHADS_2$, this figure rose to 10%. No significant differences were found between $CHADS_2$ and CHA_2DS_2-VASc in the prediction of LAA T, dense SEC and LAA LFV. The addition of TTE derived parameters to the previous clinical risk scores resulted in improved prediction of the TEE endpoints.

Conclusion: These findings suggest that the use of TTE derived parameters may be a valuable way of refining the available clinical risk schemes for the detection of surrogate markers of stroke. Follow-up studies using clinical endpoints will be necessary to confirm this hypothesis.

Keywords: Atrial fibrillation; Stroke; Risk stratification; $CHADS_2$ score; CHA_2DS_2-VASc score; Echocardiography;

Introduction:

The occurrence of stroke is one of the most feared complications resulting from atrial fibrillation (AF). Clinical and echocardiographic risk factors related to an increased risk of stroke have been identified. Risk classification schemes like $CHADS_2$ [(1)] and CHA_2DS_2-VASc [(2)] have been proposed and are used in daily clinical practice [(3)]. The $CHADS_2$ score is based on clinical data from history taking, namely the presence of congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus and previous stroke or transient ischemic attack (TIA). CHA_2DS_2-VASc score was recently developed aiming to refine risk stratification for predicting stroke and thromboembolism in AF. Major improvements were assigning 2 points to definitive risk factors (previous stroke, TIA or thromboembolism, and age ≥ 75 years) and 1 point to combination risk factors (heart failure or moderate to severe cardiac dysfunction, hypertension, diabetes mellitus, vascular disease, female gender and age 65 to 74 years).

The presence of thrombi (T) in the left atrial appendage (LAA) [(4)], spontaneous echo contrast (SEC) [(4-6)] and low LAA velocities (≤20cm/s) [(4)] have been previously identified as independent predictors of stroke and thromboembolism on transesophageal echocardiogram (TEE): relative risk (RR) 2.5 p = 0.04; RR 3.7 p <0.001; RR 1.7 p = 0.008. The presence of at least one of the three previous TEE changes has been designated by left atrial abnormality (LA ABN) and is associated with a risk of stroke of 7.8% a year [(6)]. Based on that premise, these parameters can be used as surrogate markers of an increased stroke risk [(3, 7)]. Comparative studies of $CHADS_2$ and CHA_2DS_2-VASc for stroke risk prediction have been conducted [(2, 8-9)], but data regarding comparison of these risk classification schemes in the detection of TEE AF-related risk factors is lacking.

In recent meta-analysis addressing risk stratification of patients with AF, the presence of moderate to severe LV dysfunction was the only independent predictor for stroke on multivariate analysis using two-dimensional transthoracic echocardiography (TTE) [(10-15)]. A

dilated left atrium (LA) has been identified as a marker of increased stroke risk in one observational study [16]. More recently, left atrial size has been associated to cardiovascular events in hypertensive patients [17]. Studies assessing this matter have been focused on diameter [12, 17]. The measurement of LA area on TTE apical 4 chamber view is an easy, fast and reproducible method that can more reliably provide a real estimation of LA dimensions.

The incorporation of TTE derived parameters instead of those obtained through TEE, seems to be a plausible possibility for the refinement of the already available clinical risk scores. Even though the NICE guidelines state that echocardiography may help refine clinical risk stratification [7], TTE derived parameters (most frequently moderate to severe cardiac dysfunction [2, 18] play only a minor role in risk classification schemes. The use parameters derived from transthoracic echocardiography (degree of LV systolic compromise and LA area assessed through TTE apical 4 chamber view) in combination with clinical variables for the detection of surrogate transesophageal endpoints of an increased stroke risk in patients with AF, has not been tested before.

Purpose:

This study had two main objectives: First, to evaluate and compare the accuracy of $CHADS_2$ and CHA_2DS_2-VASc in the detection of surrogate transesophageal echocardiogram markers of an increased risk of stroke (LAA T, low LAA velocities, dense SEC and LA ABN). Second, to evaluate the possible role of transthoracic echocardiogram derived parameters in the refinement of the previously available classifications.

Methods:

Cross-sectional study of 405 consecutive patients undergoing transthoracic and transesophageal echocardiogram during an AF episode (ECG monitoring was performed during the examinations) and enrolled during a 24 months period. TTE and TEE were sequentially performed, with no relevant time difference (less than 5 minutes) between them. 16 patients were excluded from analysis due to the presence of mitral valve stenosis and 13 due to prosthetic heart valve. Out of the remaining 376, 352 patients (93.6%) performed echocardiogram as part of standard evaluation before DC current cardioversion. The remaining patients presented different indications: assessment of mitral valve disease in 10 (2.7%) and 14 (3.7%) as part of routine stroke evaluation. All patients provided informed consent for echocardiographic evaluation.

Average age of the overall group was 68.6±10.0 and 35.9% (n=135) were females. Age differences between males and females were not found (♀ 69.5±10.8 vs ♂ 68.8±9.5; p=0.530). Baseline overall group characterization with demographic, anthropometric, clinical, laboratory and echocardiographic data, alongside with information on medication is provided on table I. This data was retrieved from clinical records (outpatient clinic evaluations, emergency department and hospital ward admissions) where discharge primary and secondary diagnoses are recorded according to the ICD-10 (international classification of diseases, 10^{th} revision). AF was diagnosed using ECG and endocardial electrograms, when available. Episode duration was estimated according to the patients' complaints and previously available clinical records and ECG. In patients with pacemakers and implantable cardioverter defibrillators device interrogation was used in order to estimate the duration of the episode. $CHADS_2$ and CHA_2DS_2-VASc score were calculated for all participants.

A GE Vivid 7 echocardiograph was used with the following probes: 6T phased array multiplane transesophageal probe (2.9 to 7.0 MHz) and M4S (1.5 to 4,0MHz). Gain was adjusted for optimal analysis of LA and LAA SEC (neither excessive, neither too low). Examinations were performed by three certified transesophageal echocardiographers and reviewed by two investigators.

Left atrium (LA) area was measured using planimetry in TTE apical 4-chamber view at end-ventricular systole according to the international recommendations, excluding the confluences of the pulmonary veins, LAA and mitral valve leaflets [19, 20]. Left ventricle (LV) systolic function was qualitatively assessed and classified as normal, mildly, moderately or severely depressed. In patients with depressed LV systolic function, LV ejection fraction was estimated using the modified Simpson's rule.

The LA and LAA were imaged in different tomographic planes on TEE to detect the presence of LAA T and SEC. SEC was classified according to the classification (1 to 4+) proposed by *Fatkin et al* [21]. Grade 3+ or 4+ was defined as dense SEC. LAA flow velocities were assessed with a pulsed Doppler sample placed approximately 1 cm from the entry of the LAA into the body of the LA. Maximum emptying and filling velocities were estimated from an average of 5 well defined emptying and filling waves. Patients with maximum emptying and filling velocity ≤20cm/s were classified as having low flow velocities (LFV). Patients having either LAA T, LAA LFV or dense SEC were designated as having LA ABN [6].

The saved 2D images were transferred for off-line analysis using the commercially available software EchoPac Dimension PC version 108.1.4, GE Health Care.

Lab tests were performed in the preceding 24 hour interval for patients undergoing TEE in the emergency department and were available (within a 1 month interval, preceding the echo examination) for participants undergoing elective TEE (Table I).

Comparisons were performed between $CHADS_2$ and CHA_2DS_2-VASc score for the prediction of TEE changes using ROC curve analysis: LAA T, LAA LFV, dense SEC and LA ABN. The addition of transthoracic echocardiogram parameters (Echo Parameters) to $CHADS_2$ and CHA_2DS_2-VASc score, and the use of these Echo Parameters alone for the prediction of these TEE markers was also tested.

The utilized Echo Parameters were derived from TTE: LA area and LV systolic function. Cut-off points were defined according to ROC curves and guidelines [19, 20]. ROC curves were traced for the prediction of TEE endpoints using LA area and LA area corrected by body surface area in order to assess the need to adjust this measurement to patient size. Patients with mildly abnormal LV systolic function (ejection fraction 45 to 54%) were assigned 1 point and those with moderately or severely depressed LV systolic function (ejection fraction ≤ 44%) received 2 points; LA area between 24 and 32.5cm^2 was assigned with 1 point and over 32.5cm^2 was given 2 points.

SPSS for Windows version 16.0 was used for descriptive and inferential statistical analysis: comparison of nominal variables with *chi-square* test and *t student* test was used for comparison of continuous variables; *Levene* test was used in order to check the homogeneity of variance; equivalent non-parametric tests were used when appropriate. The overall tendency of increasing event rates with increasing risk score was tested using chi-square for trend (gamma). ROC curves were traced for the prediction of LAA T, dense SEC, low LAA velocities and LA ABN using the four risk classification schemes. MedCalc for Windows version 9.2.0.1 was used for comparison of ROC curves. Results with $p < 0.05$ were regarded as significant.

Results:

A high prevalence of hypertension (84.3%), diabetes mellitus (21.3%) and previous stroke or transient ischemic attack (13.6%) was found in this population. Moreover, 59.3% had a previous history of congestive heart failure and 19.7% had been implanted with a pacemaker or an implantable cardioverter defibrillator. Regarding medication, most patients (68.4%) were on angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, 41.0% were on statin treatment, 38.8% on oral anticoagulants and 44.9% on antiplatelet agents.

Average risk scores for thromboembolic events were: $CHADS_2$ 2.21±1.18 and CHA_2DS_2-VASc 3.89±1.71. A LAA T was found in 9.8% (37/376), dense SEC in 22.1% (83/376) and LAA LFV in 13.7% (39 out of 284). LA ABN was present in 99 patients (26.3%). The evaluation of Echo Parameters was possible in 334 patients (88.8%) and LAA flow velocities were measured in 284 patients (75.5%). In the remaining patients echocardiographic data was classified as unsuitable for accurate assessment of LAA flow velocities or measurement of LA area.

Among patients performing TTE plus TEE as part of recent stroke evaluation, a trend for a higher prevalence of dense SEC was found when compared to the remaining patients (those undergoing echocardiographic evaluation for other reasons): 42.9% (6/14) vs 21.3% (77/362); OR 2.78 $CI_{95\%}$ 0.94-8.24; p=0.056. No significant differences were found for the remaining TEE endpoints: LAA T 21.4% (3/14) vs 9.4% (34/362); p=0.138; LAA LFV 20% (1/5) vs 13.6% (38/279); p=0.681; LA ABN 42.9% (6/14) vs 25.7% (93/362); p=0.152.

Table II illustrates the number of patients and prevalence of TEE endpoints (LAA T, Dense SEC, LAA LFV and LA ABN) in the different classifications, for each score value.

Comparison of statistical measures of performance between risk stratification schemes using different cut-off values for positive tests (score ≥ 1 in the first row and score ≥ 2 in the second

one) is shown on Table III. The following statistical measures of performance are presented: Sensitivity - number of true positives (TP) divided by the sum of TP plus false negatives (FN); Specificity - number of true negatives (TN) divided by the sum of TN plus false positives (FP); Positive predictive value - number of TP divided by the sum of TP plus FP; Negative predictive value - number of TN divided by the sum of FN plus TN.

I. Comparison of $CHADS_2$ vs CHA_2DS_2-VASc

No significant differences were found between $CHADS_2$ and CHA_2DS_2-VASc in the prediction of LAA T (AUC 0.62; $CI_{95\%}$ 0.57-0.67 vs 0.63; $CI_{95\%}$ 0.58-0.68; p = 0.752), dense SEC (AUC 0.60; $CI_{95\%}$ 0.55-0.65 vs 0.60; $CI_{95\%}$ 0.55-0.65; p = 0.745), LAA LFV (AUC 0.54; $CI_{95\%}$ 0.48-0.60 vs 0.56; $CI_{95\%}$ 0.50-0.62; p = 0.412) and LA ABN (AUC 0.60; $CI_{95\%}$ 0.55-0.65 vs 0.61; $CI_{95\%}$ 0.56-0.66; p = 0.678) (Figure 1).

Using the $CHADS_2$ classification, 24/376 (6.4%) patients were classified as low risk ($CHADS_2 = 0$), 79/376 (21.0%) as intermediate risk ($CHADS_2 = 1$) and the remaining 273/376 (72.6%) as high risk ($CHADS_2 \geq 2$) (Table II). Some patients classified as low risk presented TEE markers of increased stroke risk (Negative Predictive Value of 90 to 95.8%).

According to CHA_2DS_2-VASc scoring (Table II), 11 patients (2.9%) were classified as low-risk (CHA_2DS_2-VASc = 0), 20 (5.3%) were placed in the intermediate risk group and the remaining 345 (91.8%) in the higher risk group. No patients in the low risk group had LAA T, dense SEC, LAA LFV and LA ABN: 100% negative predictive value for the exclusion of echocardiographic changes.

Comparing subjects in the upper tertile of risk, those with $CHADS_2 \geq 3$ (50 out of 146; 34.2%) had a similar prevalence of LA ABN when compared to those with CHA_2DS_2-VASc ≥ 5 (48 out of 135; 35.6%).

The overall tendency for increasing of these changes with increasing $CHADS_2$ risk score can be observed in Table II. Chi-square for trend revealed similar findings for CHA_2DS_2-VASc.

II. $CHADS_2$ and CHA_2DS_2-VASc plus Transthoracic Echocardiogram Parameters

Adding Echo Parameters (LA area and LV global systolic function, according to the previously defined criteria) to $CHADS_2$ and CHA_2DS_2-VASc scores resulted in an improvement of AUC for the prediction of the different endpoints.

$CHADS_2$ score plus Echo Parameters displayed a 0.73 AUC ($CI_{95\%}$ 0.68-0.78; p=0.003 vs $CHADS_2$) regarding LAA T; AUC 0.72 ($CI_{95\%}$ 0.67-0.77; p<0.001 vs $CHADS_2$) for dense SEC; AUC 0.65 ($CI_{95\%}$ 0.59-0.71; p=0.007 vs $CHADS_2$) for LAA LFV; AUC 0.71 ($CI_{95\%}$ 0.66-0.76; p<0.001 vs $CHADS_2$) for LA ABN.

CHA_2DS_2-VASc score plus Echo Parameters had a 0.74 AUC ($CI_{95\%}$ 0.69-0.78; p=0.005 vs CHA_2DS_2-VASc score) regarding LAA T; AUC 0.71 ($CI_{95\%}$ 0.66-0.76; p<0.001 vs CHA_2DS_2-VASc score) for dense SEC; AUC 0.66 ($CI_{95\%}$ 0.60-0.72; p=0.010 vs CHA_2DS_2-VASc score) for LAA LFV; AUC 0.71 ($CI_{95\%}$ 0.66-0.76; p<0.001 vs CHA_2DS_2-VASc score) for LA ABN.

Comparison between $CHADS_2$ and CHA_2DS_2-VASc score both with the addition of Echo Parameters revealed no significant differences for the prediction of LAA T (p=0.778), dense SEC (p=0.796), LAA LFV (p=0.734) and LA ABN (p=0.905).

Using the $CHADS_2$ score plus Echo Parameters, 11 out of the 334 (3.3%) patients were classified as low risk (score = 0), 34 (10.2%) as intermediate (score = 1) and the remaining 289 (86.5%) as high risk (score ≥ 2). Being placed in the low risk group of $CHADS_2$ score plus Echo Parameters had 100% negative predictive value (NPV) for the exclusion of all TEE endpoints.

Using the CHA_2DS_2-VASc score plus Echo Parameters, 6 subjects (1.8%) were classified as low risk, 10 (3.0%) as intermediate risk and the remaining 318 (95.2%) were categorized as high risk. In patients classified as low or intermediate risk according to CHA_2DS_2-VASc score plus Echo Parameters, no TEE changes were found (100% NPV). Even in high-risk patients classified with a score of 2, changes were present in only 5%.

Comparing subjects in the upper tertile of risk, those with $CHADS_2$ plus Echo Parameters ≥ 4 (69 out of 167; 41.3%) had a similar prevalence of LA ABN when compared to those with CHA_2DS_2-VASc plus Echo Parameters ≥ 6 (64 out of 153; 41.8%). These prevalences were higher than those found in $CHADS_2$ and CHA_2DS_2-VASc without Echo Parameters.

A strong relationship between increasing $CHADS_2$ score plus Echo Parameters values and the prevalence of TEE changes is shown on Table II. Similar results were found with the CHA_2DS_2-VASc score plus Echo Parameters values.

LA area divided by BSA yielded only slight but not significant improvement in the prediction of LAA T (AUC 0.66 vs 0.67; p = 0.64), dense SEC (AUC 0.67 vs 0.70; p = 0.17) and LAA LFV (AUC 0.70 vs 0.73; p = 0.37), when compared to non adjusted LA area.

III. Usefulness of Transthoracic Echocardiogram Parameters Alone

The following ROC AUC values were found using the Echo Parameters alone (p value represents the difference from AUC = 0.5): LAA T AUC 0.75 ($CI_{95\%}$ 0.70-0.79; p = 0.0001), dense SEC AUC 0.75 ($CI_{95\%}$ 0.70-0.79; p = 0.0001), LAA LFV AUC 0.69 ($CI_{95\%}$ 0.63-0.74; p = 0.0002) and LA ABN AUC 0.73 ($CI_{95\%}$ 0.68-0.78; p = 0.0001). Echo-score was superior to $CHADS_2$ in the detection of dense SEC (p=0.001), LAA LFV (p=0.035) and LA ABN (p=0.002). Regarding LAA T, only a trend (p=0.081) in favor of Echo Parameters was found. In comparison with CHA_2DS_2-VASc, superiority was found regarding detection of dense SEC (p=0.004) and LA ABN (p=0.006). A trend for superiority was found regarding LAA LFV (p=0.086) and no differences were found in LAA T (p=0.124) prediction.

No differences were found in AUC when comparing Echo Parameters with $CHADS_2$ score plus Echo Parameters and CHA_2DS_2-VASc score plus Echo Parameters regarding the LAA T (p=0.762 vs $CHADS_2$ plus Echo Parameters and p=0.898 vs CHA_2DS_2-VASc plus Echo Parameters), dense SEC (p=0.283 vs $CHADS_2$ plus Echo Parameters and p=0.312 vs CHA_2DS_2-VASc plus Echo Parameters), LAA LFV (p=0.418 vs $CHADS_2$ score plus Echo Parameters and p=0.616 vs CHA_2DS_2-VASc plus Echo Parameters) and LA ABN (p=0.373 vs $CHADS_2$ plus Echo Parameters and p=0.430 vs CHA_2DS_2-VASc plus Echo Parameters).

According to the Echo Parameters (Table II), 88 out of the 334 (26.4%) patients were classified as low risk (score = 0), 117 (35.0%) as intermediate (score = 1) and the remaining 129 (38.6%) as high risk (score ≥ 2).

In the low risk group, no subjects had LAA T (100% NPV), but the negative predictive value for dense SEC, LAA LFV and LA ABN was inferior and ranged from 94.3% to 97.5%. The prevalence

of TEE changes in the upper tertile of risk with Echo Parameters alone ≥ 2 (58 out of 129; 33.3%) was lower than the one observed with the combined scores.

A higher prevalence of changes was progressively found with increasing score values of Echo Parameters, displaying a very strong relationship in chi-square for trend (Table II). When used alone, Echo Parameters displayed higher specificity values when compared to the remaining scores at the expense of a lower sensitivity (Table III).

Discussion:

The presence of a left atrial thrombus, left atrial appendage low flow velocities (≤20cm/s) and dense spontaneous echo contrast are strong independent predictors of an increased risk of stroke in subjects with AF [3-6].

It has been demonstrated that CHA_2DS_2-VASc provides improvement in predictive value for thromboembolic events over $CHADS_2$, with very low event rates in low-risk subjects [2, 9]. This has led to the proposal that the low-risk group should receive no anticoagulant treatment or aspirine, as an alternative [3]. Our investigation demonstrated that this also applies to TEE surrogate markers of thromboembolic events: Unlike what was found in the low-risk subjects (score=0) of $CHADS_2$, none of the patients in the low-risk group of CHA_2DS_2-VASc had LAA T, dense SEC, LAA LFV or LA ABN. These findings support previous research and demonstrate the CHA_2DS_2-VASc superior capability to identify patients at truly low risk of thromboembolic events when compared to $CHADS_2$ score.

LA SEC has been previously reported to be associated with LA enlargement [22, 23]. An association between compromised LAA and LA function parameters and LV systolic

dysfunction is also known [24-28]. A low prevalence of LAA T (3%) and dense SEC (8%) in patients with AF and a low $CHADS_2$ score (0 or 1) has been previously described by *Kleemann* et al [29]. Independent predictors for the presence of these findings were LV ejection fraction <40% and LA dimension > or = 50mm. *Puwanant et al* have described absence of TEE changes (LAA T, SEC and sludge) in patients with $CHADS_2$ = 0 and 2% in those with $CHADS_2$ = 1. These changes were significantly associated with LV ejection fraction < 35% and history of congestive heart failure in a multivariate model [30]. Despite a lower prevalence of TEE changes than we have observed in our sample, these findings support a possible role for echocardiographic derived parameters (LV systolic function and LA dimensions) in the refinement of clinical risk stratification schemes.

The addition of Echo Parameters to $CHADS_2$ and CHA_2DS_2-VASc has resulted in an improvement in risk stratification of these transesophageal markers: higher negative predictive value for TEE changes in for lower score values and higher positive predictive value in higher scores.

Comparing these 3 types of risk stratification (clinical, echocardiographic and combined), we observed that echocardiographic parameters alone were more specific but displayed lower sensitivity when compared with the remaining schemes. This high specificity was responsible for the higher AUC vales observed with Echo Parameters alone. Still, this score seemed unbalanced, due to lower sensitivity, when compared with the combined scores.

Almost one third of ischemic strokes in AF patients are non-embolic (due to atherosclerosis and cerebrovascular disease) [31, 32]. In risk classification schemes using only echocardiographic parameters, those patients might be undetected. Nevertheless, in models combining clinical risk stratification and echo parameters, under-detection would be less likely, assuming the higher accuracy of clinical risk factors (namely hypertension and diabetes mellitus) for detecting these subjects [33].

Unlike other reports [9] very few patients were classified as low risk in our population. This can be explained by the fact that these were patients with a high prevalence of comorbidities (hypertension, diabetes mellitus and congestive heart failure) and ongoing close follow up in our hospital's outpatient cardiology clinic. The increased prevalence of medication with renin-angiotensin system inhibitors and statins alongside with the very low prevalence of patients with no anti-thrombotic treatment at all, when compared to other surveys/registries [9] also reflects the increased patient severity and the careful follow-up that was provided to this high risk population. The high percentage of patients with cardiac devices in this cohort can be explained by the high activity in our centre (third at national level in pacemaker implants) and the fact that AF is a very frequent diagnosis in these subjects. Since a rhythm control strategy is very frequently chosen for these patients, this may have resulted in a referral bias.

Study Limitations and Future Directions:

It is known that LA dilatation occurs spatially in an asymmetric way in different planes, thus left atrial antero-posterior diameter in M-mode is not an accurate way of assessing LA dimensions. The measurement of left atrium area using planimetry in apical 4 chamber view is a method that can already provide further and more consistent information regarding size and is used as part of the formula to calculate LA volume. Additionally, LA volume is consensually used as the gold standard to evaluate LA size and known to be a stronger prognostic marker of cardiovascular disease than LA diameter [19], and can be used in a much precise risk stratification model. Still, in this paper, we have chosen to use LA area, since it is a reliable, simple and fast to perform technique allowing some degree of simplification and widespread use.

We think that the use of LA area adjusted for body surface area (BSA) might have slightly improved the accuracy of the combination of risk scores with echocardiographic parameters. However, this would have made calculations a much more time-consuming task, with no significant impact on its clinical accuracy (like illustrated in the results II section) and less appealing for daily clinical practice.

We recognize the fact of some patients being under oral anticoagulation may have had some impact in the study's results. Still, we wanted to have a population that could be representative of the subjects observed in our everyday practice. The impact of anti-thrombotic treatment and other factors in LA ABN can be assessed in Table I.

Even though TEE parameters are helpful for risk stratification, it is known that this examination is unsuitable for routine evaluation in AF patients. Therefore, we reinforce that this population had other indications for undergoing TEE (see Methods section). Even though SEC was qualitatively assessed, it followed the objective criteria defined by *Fatkin et al* [(21)]. In a not negligible number of patients echocardiographic data was classified as unsuitable for accurate assessment of LAA flow velocities. We do not think that this had any real impact, since the observed results are similar to what was found with the other TEE endpoints. Regarding LA area this has happened only in a minority of patients.

The value of a risk schema is based on widespread applicability. Therefore this type of stratification methods using clinical and transthoracic echocardiogram parameters is based in the assumption that, like in our country, all physicians may request a routine transthoracic echocardiogram for patients with AF.

Conclusion:

Based on the assumption that the presence of dense spontaneous echo contrast, left atrial appendage thrombi and low flow velocities predicts a high risk of a future thromboembolic event, this study seems to confirm the increased sensitivity of CHA_2DS_2-VASc risk classification over $CHADS_2$ in the detection of low risk individuals for AF related-stroke.

The use of transthoracic echocardiogram derived parameters in combination with the $CHADS_2$ and CHA_2DS_2-VASc scores seemed to improve the way these scores risk stratified this cohort of AF patients. This seems to suggest that echocardiography (namely through the assessment of left ventricle systolic function and left atrium area measurement) may be a valuable tool for the refinement of the available clinical risk schemes. Still, we reinforce that this hypothesis is based on surrogate TEE endpoints and needs to be clinically validated. A possible association between LA dimensions (namely LA area and volume) and clinical thromboembolism needs to be further clarified, since most previous studies have focused in LA diameter, an outdated method for this type of assessment. Follow-up studies having stroke and other clinical thromboembolic events as an endpoint will be necessary to confirm the accuracy and advantages of risk classification schemes combining clinical and TTE derived parameters.

Table I – Population baseline characteristics and sub-analysis according to presence of LA ABN.

Parameter	Overall group (n=376)	Without LA ABN (n=277)	With LA ABN (n=99)	P (between patients with and without LA ABN)
Demographics				
♀	35.9%(135)	35.7%(99)	36.4%(36)	0.912
Age	69.0±10.0	68.5±10.4	70.6±8.4	0.051
Age 65 to 75 years	41.0%(154)	38.6%(107)	47.5%(47)	0.124
Age ≥ 75 years	30.9%(116)	31.8%(88)	28.3%(28)	0.519
Body Mass Index (Kg/m^2)	28.7±5.2	28.9±5.5	28.1±4.2	0.305
Clinical Data				
Congestive heart failure	59.3%(223)	55.6%(154)	69.7%(69)	0.014
Hypertension	84.3%(317)	83.4%(231)	86.9%(86)	0.415
Diabetes mellitus	21.3%(80)	19.1%(53)	27.3%(27)	0.089
Stroke or TIA	13.6%(51)	11.9%(33)	21.2%(21)	0.025
Vascular disease*	61.2%(230)	56.7%(157)	73.4%(73)	0.003
Est. AF duration ≤ 48h	5.6%(21)	5.8%(16)	5.1%(5)	0.829
Est. AF duration < 1 week	19.7%(74)	22.7%(63)	11.1%(11)	0.017
Est. AF duration < 1 month	35.1%(132)	37.2%(103)	29.3%(29)	0.216
Est. AF duration > 6 months	38.0%(143)	34.3%(95)	48.5%(48)	0.005
Est. AF duration > 1 year	28.2%(106)	24.5%(68)	38.4%(38)	0.004
Pacemaker or ICD	19.7%(74)	19.5%(54)	20.2%(20)	0.891
Echocardiographic characterization				
Protuberant aortic plaque in TEE	22.1%(83)	18.8%(52)	31.3%(31)	0.008
LV telediastolic diameter (mm)	54.5±9.5	54.6±9.8	54.4±8.9	0.899
LA M-mode (mm)	46.4±8.3	45.9±8.4	47.8±7.9	0.077
LA area (cm^2)	27.7±7.5	26.8±7.6	30.0±6.9	<0.001
LV ejection fraction ≥ 55%	72.1%(271)	80.9%(224)	47.5%(47)	<0.001
Native mitral regurgitation ≥ III/IV	27.4%(103)	28.5%(79)	24.2%(24)	0.622
Moderate to Severe Aortic Stenosis	2.7%(10)	2.2%(6)	4.1%(4)	0.320
Hypertrophic cardiomyopathy	2.1%(8)	1.4%(4)	4.0%(4)	0.124
Medication				
Oral anticoagulants	38.8%(146)	37.5%(104)	42.4%(42)	0.329
Antiplatelet agents	44.9%(169)	44.8%(124)	45.5%(45)	0.919
1 to 3 admin. of enoxaparine before TEE	38.0%(143)	39.4%(109)	34.3%(34)	0.366
No anti-thrombotic treatment	8.2%(31)	9.4%(26)	5.1%(5)	0.178
ACE-i/ARB-II	68.4%(257)	68.6%(190)	67.7%(67)	0.935
Statin	41.0%(154)	37.9%(105)	49.5%(49)	0.036
Laboratory assessment				
Hemoglobin (g/dL)	14.3±7.5	14.5±8.7	13.7±1.6	0.422
Platelets (10^3/uL)	222.3±87.6	224.2±95.9	217.2±60.3	0.515
INR	1.5±0.8	1.5±0.8	1.5±0.7	0.435
INR ≥ 2.0	22.6%(85)	23.8%(66)	19.2%(19)	0.314
Creatinine (umol/L)	112.3±84.1	112.6±86.4	111.5±77.7	0.910
CRP (mg/dL)	1.6±2.9	1.6±3.0	1.8±2.6	0.732

Legend: ABN – abnormality; TIA – transient ischemic attack; Est. – estimated; ICD – implantable cardioverter-defibrilator; AF – atrial fibrillation; TEE – tranesophageal echocardiogram; LA – left atrium; LV – left ventricle; Admin. – administrations; ACE-i angiotensin converting enzyme inhibitor; ARB-II – angiotensin II receptor blocker ; INR – international normalized ratio; CRP – C reactive protein;

* vascular disease is defined as having at least one of the following: myocardial infarctions, peripheral artery disease and complex aortic plaque.

Table II – Echocardiographic surrogate markers for increased risk of stroke according to the $CHADS_2$, CHA_2DS_2-VASc, CHADS-Echo and Echo-score risk classification schemes.

$CHADS_2$ Score					
Score	No.	**LAA T**	**Dense SEC**	**LAA LFV**	**LA ABN**
0	24 (6.4%)*	1 (4.2%)**	1 (4.2%)**	2 (10.0%)**	2 (8.3%)**
1	79 (21.0%)	5 (6.3%)	15 (19.0%)	8 (13.6%)	17 (21.5%)
2	127 (33.8%)	11 (8.7%)	25 (19.7%)	11 (11.1%)	30 (23.6%)
3	100 (26.6%)	10 (10.0%)	27 (27.0%)	13 (18.3%)	33 (33.0%)
4	34 (12.3%)	9 (26.5%)	12 (35.3%)	5 (18.5%)	14 (41.2%)
5	9 (2.4%)	1 (11.1%)	2 (22.2%)	0	2 (22.2%)
6	3 (0.8%)	0	1 (33.3%)	0	1 (33.3%)
Total:	376	37	83	39	99
Gamma (Chi-Square for trend)		0.31	0.25	0.10	0.26
P		0.018	0.004	0.408	0.002

CHA_2DS_2-VASc Score					
Score	**No.**	**LAA T**	**Dense SEC**	**LAA LFV**	**LA ABN**
0	11 (2.9%)	0	0	0	0
1	20 (5.3%)	1 (5.0%)	1 (5.0%)	1 (6.3%)	1 (5.0%)
2	51 (13.6%)	3 (5.9%)	9 (17.6%)	3 (7.9%)	11 (21.6%)
3	61 (16.2%)	5 (8.2%)	13 (21.3%)	8 (18.2%)	15 (24.6%)
4	98 (26.1%)	7 (7.1%)	19 (19.4%)	11 (13.9%)	24 (24.5%)
5	70 (18.6%)	11 (15.7%)	24 (34.3%)	10 (18.9%)	28 (40.0%)
6	45 (12.0%)	7 (15.6%)	11 (24.4%)	4 (13.3%)	14 (31.1%)
7	16 (4.3%)	2 (12.5%)	5 (31.3%)	2 (16.7%)	5 (31.3%)
8	2 (0.5%)	1 (50.0%)	1 (50.0%)	0	1 (50.0%)
9	2 (0.5%)	0	0	0	0
Total	376	37	83	39	99
Gamma (Chi-Square for trend)		0.31	0.25	0.15	0.26
P		0.009	0.002	0.165	0.001

$CHADS_2$ Score plus Echo Parameters					
Score	No.	**LAA T**	**Dense SEC**	**LAA LFV**	**LA ABN**
0	11 (3.3%)	0	0	0	0
1	34 (10.2%)	0	1 (2.9%)	1 (3.6%)	2 (5.9%)
2	53 (15.9%)	3 (5.7%)	7 (13.2%)	5 (10.6%)	9 (17.0%)
3	69 (20.7%)	3 (4.3%)	9 (13.0%)	5 (8.6%)	12 (17.4%)
4	70 (21.0%)	6 (8.6%)	21 (30.0%)	13 (23.2%)	25 (35.7%)
5	50 (15.0%)	10 (20.0%)	18 (36.0%)	7 (21.2%)	20 (40.0%)
6	24 (7.2%)	3 (12.5%)	6 (25.0%)	6 (30.0%)	10 (41.7%)
7	15 (4.5%)	6 (40.0%)	10 (66.7%)	1 (11.1%)	10 (66.7%)
8	7 (2.1%)	1 (14.3%)	3 (42.9%)	0	3 (42.9%)
9	1 (0.3%)	0	1 (100%)	0	1 (100%)
Total:	334	32	76	38	92
Gamma (Chi-Square for trend)		0.53	0.51	0.36	0.49
P		<0.001	<0.001	0.001	<0.001

CHA_2DS_2-VASc Score plus Echo Parameters					
Score	**No.**	**LAA T**	**Dense SEC**	**LAA LFV**	**LA ABN**
0	6 (1.8%)	0	0	0	0
1	10 (3.0%)	0	0	0	0
2	20 (6.0%)	0	1 (5.0%)	0	1 (5.0%)
3	31 (9.3%)	1 (3.2%)	3 (9.7%)	2 (7.7%)	5 (16.1%)
4	54 (16.2%)	2 (3.7%)	6 (11.1%)	5 (10.9%)	8 (14.8%)
5	60 (18.0%)	4 (6.7%)	12 (20.0%)	6 (12.0%)	14 (23.3%)
6	54 (16.2%)	5 (9.3%)	15 (27.8%)	11 (25.6%)	19 (35.2%)
7	49 (14.7%)	9 (18.4%)	19 (38.8%)	7 (20.0%)	21 (42.9%)
8	30 (9.0%)	5 (16.7%)	7 (23.3%)	6 (27.3%)	11 (36.7%)
9	13 (3.9%)	5 (38.5%)	10 (76.9%)	1 (12.5%)	10 (76.9%)
10	4 (1.2%)	1 (25.0%)	2 (50.0%)	0	2 (50.0%)
11	3 (0.9%)	0	1 (33.3%)	0	1 (33.3%)
Total:	334	32	76	38	92
Gamma (Chi-Square for trend)		0.54	0.49	0.37	0.48
P		<0.001	<0.001	0.001	<0.001

Score	Echocardiographic Parameters No.	LAA T	Dense SEC	LAA LFV	LA ABN
0	88 (26.3%)	0	3 (3.4%)	2 (2.5%)	5 (5.7%)
1	117 (35.0%)	8 (6.8%)	22 (18.8%)	15 (15.2%)	29 (24.8%)
2	72 (21.6%)	12 (16.7%)	21 (29.2%)	12 (24.0%)	25 (34.7%)
3	35 (10.5%)	8 (22.9%)	19 (54.3%)	6 (27.3%)	20 (57.1%)
4	22 (6.6%)	4 (18.2%)	11 (50.0%)	3 (20.0%)	13 (59.1%)
Total:	334	32	76	38	92
Gamma (Chi-square for trend)		0.61	0.62	0.49	0.59
P		<0.001	<0.001	<0.001	<0.001

Legend: LAA T – left atrial appendage thrombus; SEC – spontaneous echocardiographic contrast; LFV – low flow velocities (≤20cm/s); LA ABN – left atrial abnormality, defined as the presence of any of the previous echocardiographic changes.
* Represents the percentage of the total population classified within a certain value, for each score. ** This percentage represents the number of patients with TEE endpoints (LAA T, Dense SEC, LAA LFV and LA ABN) among all the patients classified with the same score value.

Table III – Comparative analysis of $CHADS_2$ and CHA_2DS_2-Vasc scores, with and without Echo Parameters, for the detection of transesophageal markers of an increased risk of stroke using statistical measures of performance.

	$CHADS_2$	CHA_2DS_2-Vasc	$CHADS_2$ +Echo Param	CHA_2DS_2-Vasc +Echo Param	Echo Param
Positive Test ≥ 1	**LAA T**	**LAAT**	**LAAT**	**LAAT**	**LAAT**
	NPV 95.8%	NPV 100%	NPV 100%	NPV 100%	NPV 100%
	Sens 97.3%	Sens 100.0%	Sens 100.0%	Sens 100.0%	Sens 100%
	Spec 6.8%	Spec 3.2%	Spec 3.6%	Spec 2.0%	Spec 29.1%
	PPV 10.2%	PPV 10.1%	PPV 9.9%	PPV 9.8%	PPV 13.0%
	Dense SEC	**Dense SEC**	**Dense SEC**	**Dense SEC**	**Dense SEC**
	NPV 95.8%	NPV 100%	NPV 100%	NPV 100%	NPV 96.6%
	Sens 98.8%	Sens 100%	Sens 100%	Sens 100%	Sens 96.1%
	Spec 7.8%	Spec 3.8%	Spec 4.3%	Spec 2.3%	Spec 32.9%
	PPV 23.3%	PPV 22.7%	PPV 23.5%	PPV 23.2%	PPV 29.7%
	LAA LFV	**LAA LFV**	**LAA LFV**	**LAA LFV**	**LAA LFV**
	NPV 90.0%	NPV 100%	NPV 100%	NPV 100%	NPV 97.5%
	Sens 94.9%	Sens 100.0%	Sens 100.0%	Sens 100%	Sens 94.7%
	Spec 7.3%	Spec 3.7%	Spec 4.4%	Spec 2.6%	Spec 33.9%
	PPV 14.0%	PPV 14.2%	PPV 14.9%	PPV 14.7%	PPV 19.4%
	LA ABN	**LA ABN**	**LA ABN**	**LA ABN**	**LA ABN**
	NPV 91.7%	NPV 100%	NPV 100%	NPV 100%	NPV 94.3%
	Sens 98.0%	Sens 100%	Sens 100%	Sens 100%	Sens 94.6%
	Spec 7.9%	Spec 4.0%	Spec 4.5%	Spec 2.5%	Spec 34.3%
	PPV 27.6%	PPV 27.1%	PPV 28.5%	PPV 28.0%	PPV 35.4%
Positive Test ≥ 2	**LAA T**	**LAA T**	**LAA T**	**LAA T**	**LAA T**
	Sens 83.8%	Sens 97.3%	Sens 100%	Sens 100%	Sens 75.0%
	Spec 28.6%	Spec 8.8%	Spec 14.9%	Spec 5.3%	Spec 65.2%
	PPV 11.4%	PPV 10.4%	PPV 11.1%	PPV 10.1%	PPV 18.6%
	Dense SEC	**Dense SEC**	**Dense SEC**	**Dense SEC**	**Dense SEC**
	Sens 80.7%	Sens 98.8%	Sens 98.7%	Sens 100%	Sens 67.1%
	Spec 29.7%	Spec 10.2%	Spec 17.1%	Spec 6.2%	Spec 69.8%
	PPV 24.5%	PPV 23.8%	PPV 26.0%	PPV 23.9%	PPV 39.5%
	LAA LFV	**LAA LFV**	**LAA LFV**	**LAA LFV**	**LAA LFV**
	Sens 74.4%	Sens 97.4%	Sens 97.4%	Sens 100%	Sens 55.3%
	Spec 28.2%	Spec 9.8%	Spec 16.3%	Spec 6.2%	Spec 70.9%
	PPV 14.1%	PPV 14.7%	PPV 16.3%	PPV 15.1%	PPV 24.1%
	LA ABN	**LA ABN**	**LA ABN**	**LA ABN**	**LA ABN**
	Sens 80.8%	Sens 99.0%	Sens 97.8%	Sens 100%	Sens 63.0%
	Spec 30.3%	Spec 10.8%	Spec 17.8%	Spec 6.6%	Spec 70.7%
	PPV 29.3%	PPV 28.4%	PPV 31.1%	PPV 28.9%	PPV 45.0%

Legend: LAA T – left atrial appendage thrombus; SEC – spontaneous echo contrast; LAA LFV – left atrial appendage low flow velocities (≤20cm/s); LA ABN – left atrial abnormality; NPV – negative predictive value; Sens - sensitivity; Spec – specificity; PPV – positive predictive value.

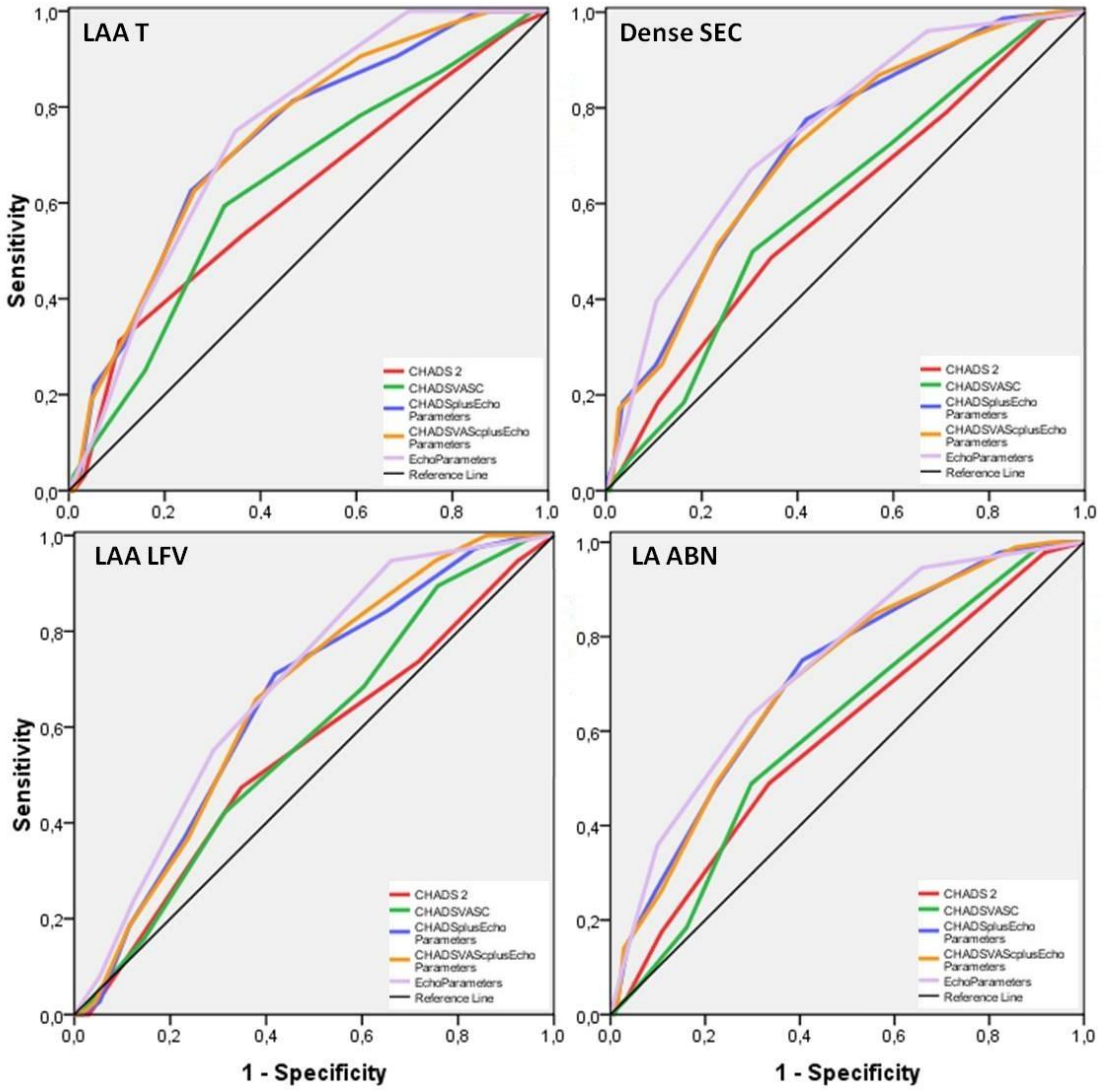

Figure 1 – ROC-curve comparison of the 2 risk classification schemes with and without transthoracic echocardiogram parameters and echocardiographic parameters alone. **LAA T** – Left atrial appendage thrombus: AUC $CHADS_2$ 0.62, AUC CHA_2DS_2-VASc 0.63, AUC $CHADS_2$ plus Echo Parameters 0.73, AUC CHA_2DS_2-VASc 0.74 and AUC Echo Parameters 0.75; **Dense SEC** - Dense spontaneous echocontrast: AUC $CHADS_2$ 0.60, AUC CHA_2DS_2-VASc 0.60, AUC $CHADS_2$ plus Echo Parameters 0.72, AUC CHA_2DS_2-VASc plus Echo Parameters 0.71 and AUC Echo Parameters 0.75; **LAA LFV** - Left atrial appendage low flow velocities (≤20cm/s): AUC $CHADS_2$ 0.54, AUC CHA_2DS_2-VASc 0.56, AUC $CHADS_2$ plus Echo Parameters 0.65, AUC CHA_2DS_2-VASc plus Echo Parameters 0.66 and AUC Echo Parameters 0.69; **LA ABN** – Left atrial abnormality: AUC $CHADS_2$ 0.58, AUC CHA_2DS_2-VASc 0.60, AUC $CHADS_2$ plus Echo Parameters 0.68, AUC CHA_2DS_2-VASc plus Echo Parameters 0.71 and AUC Echo Parameters 0.73.

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II.A.2

Evaluation of Left Atrial Deformation to Predict Left Atrial Stasis in Patients with Non-Valvular Atrial Fibrillation – a Pilot-study.

Rui Providência, Ana Faustino, Maria João Ferreira, Lino Gonçalves, Joana Trigo, Ana Botelho, Serge Boveda. Evaluation of left atrial deformation to predict left atrial stasis in patients with non-valvular atrial fibrillation – a Pilot-study. Cardiovascular Ultrasound 2013;11:44. doi: 10.1186/1476-7120-11-44.

Abstract

Background: Speckle tracking-derived strain and strain rate are recently available parameters to assess left atrial (LA) deformation. We hypothesized that such new parameters could be of interest to evaluate the risk of LA stasis among patients with atrial fibrillation (AF).

Methods: Single-centre study enrolling all patients with non-valvular AF lasting longer than 48 hours for whom no therapeutic anticoagulation was given in the preceding 3 weeks and who were assessed through transesophageal and transthoracic echocardiogram during a 6 month time interval. LA deformation was assessed by transthoracic echocardiogram through speckle tracking analysis, whereas LA stasis parameters were sought on transesophageal echocardiogram.

Results: Among the 82 assessed patients, LA appendage thrombi or sludge were found in 16 (19.5%). A moderate positive correlation was found between peak positive strain rate and maximum emptying velocity (r= 0.589;*P* <0.001) and peak positive strain rate and maximum filling velocity of the LA appendage (r= 0.651;*P* <0.001). Peak negative strain rate was also found to be associated with both maximum emptying velocity (r= -0.513;*P* <0.001) and maximum filling velocity of the LAA (r= -0.552; *P* <0.001). AF duration, peak negative strain rate and time-to-peak positive strain were independent predictors of LAA thrombi or sludge on multivariate analysis logistic regression. The area under the curve for the estimated probabilities using the obtained logistic regression model was 0.89 (95%CI 0.81-0.96; *P* <0.001).

Conclusion: Our findings suggest that LA mechanical dysfunction assessed through speckle tracking may be of interest to predict LA stasis in the setting of AF.

Keywords: speckle tracking; strain; strain rate; left atrium; left atrial appendage; non-valvular atrial fibrillation; stasis; thrombus; sludge.

Background

Non-valvular atrial fibrillation (AF) is associated with stroke and peripheral embolism of cardiac origin [1] and over 90% of thrombi are thought to originate in the left atrial appendage (LAA) [2].

Transesophageal echocardiogram is the gold-standard for the detection of thrombi in the LAA [3] and its use before cardioversion and catheter ablation of AF has grown in recent years [4]. This is a semi-invasive technique that despite a very low incidence of complications carries risks over transthoracic imaging [5].

Transthoracic echocardiography is now a highly versatile technique that provides solid structural and functional information about the atria. Its potential role in the risk stratification of AF and prediction of left atrial stasis has been overlooked [3]. Speckle tracking is an imaging technique that provides accurate and angle-independent information regarding left atrial deformation and motion [6]. Echocardiographic parameters assessing structure, like left atrial size, are known to impact on the presence of left atrial stasis (thrombi or sludge, dense spontaneous echocardiographic contrast and low flow velocities in the LAA) [7].

We hypothesized that speckle tracking derived strain and strain rate could be of interest to evaluate the risk of LA stasis among patients with atrial fibrillation (AF).

Methods

I. Patient selection

All patients during a 6 month time interval undergoing transthoracic and transesophageal echocardiogram were assessed for the presence of criteria allowing admission into the study. Patients with an AF episode lasting for longer than 48 hours and without effective

anticoagulation in the preceding 3 weeks were considered eligible for the study except if any of the following exclusion criteria were met: lack of adequate endocardial border definition of the left atrium, presence of prosthetic heart valve or previous valve repair, significant aortic or mitral valve disease (any degree of aortic/mitral valve stenosis or mitral/aortic regurgitation > II/IV) and previous closure of the LAA.

This study was conducted with the approval of our Institution's Ethics Committee. All subjects provided their informed consent to undergo the necessary investigations and to allow the usage of their data for research purposes, preserving their anonymity.

Preliminary transthoracic echocardiography was performed using standard views (GE Vivid 7 echocardiograph with a M4S probe). The frame rate was set > 60 frames per second. Since all patients were in AF at the time of procedure, all measurements were obtained from an average of 3 cycles. Left atrium volume was measured using the bi-plane area length method. Left ventricle ejection fraction was calculated with the Simpson method. The ratio between indexed left atrial volume and left ventricle ejection fraction, which has shown to be highly accurate at excluding the presence of an LAA thrombus in patients with AF who are candidates for AF catheter ablation or cardioversion [7], was calculated.

Pulsed-wave Doppler at the tips of the mitral valve was used for measuring early diastolic filling velocity (E). The early diastolic tissue velocity (E') was measured with tissue Doppler imaging of the lateral mitral annulus. E/E' ratio was calculated. Mitral regurgitation was semi-quantitatively assessed by color Doppler across mitral valve and graded as none/trace (0), mild (I/IV) and moderate (II/IV). Individuals with moderately severe (III/IV) and severe (IV/IV) mitral regurgitation were excluded from analysis.

Global longitudinal strain and strain rate of the left ventricle were assessed as previously described by other authors [8, 9].

II. Assessment of left atrial deformation by transthoracic echocardiogram

Transthoracic images were processed for assessing left atrial deformation through speckle tracking imaging using the GE Health Care EchoPac Dimension software, PC version 108.1.4 (featuring a software for speckle-tracking of the left ventricle) by two cardiologists who were blinded for the transesophageal echocardiogram results and clinical information of the patients.

The left atrium endocardial surface was manually traced using a point-and-click approach in apical four-chamber view, which allowed the automatic definition of a region of interest. This was manually adjusted, if necessary, to better suit the atrium anatomy. The cardiac cycle was demarcated by indicating QRS onset. The region of interest was divided into 6 segments by the software (Figure 1) and the resulting tracking quality for each segment was scored as either acceptable or non-acceptable. Segments classified as “non-acceptable” were rejected by the software and excluded from the analysis. In subjects with adequate image quality, a total of 6 segments were analyzed. Longitudinal strain and strain rate curves for each segment were analyzed and the following parameters collected (Figure 2): peak positive and peak negative strain, peak positive and peak negative strain rate and time to peak-positive strain. Peak-to-peak strain and strain rate were also calculated (i.e., peak positive – peak negative strain and peak positive – peak negative strain rate). These parameters referred to data from the whole cardiac cycle based on the assumption that since the left atrium was fibrillating during the entire cardiac cycle duration, there was no strong rationale for its division in different phases of atrial function (just like there would be no sense in assessing the different phases of ventricular function in a fibrillating ventricle). An average of the 6 segments in three

consecutive heart cycles was estimated, except for time-to-peak positive strain, where standard deviation was calculated for three cycles also.

III. Assessment of left atrial stasis by transesophageal echocardiogram

Transesophageal echocardiogram was performed without anaesthesia or sedation using a 6T phased array multiplane transesophageal probe (frequency 7.0 MHz). The left atrium and LAA were imaged in different tomographic planes to detect the presence of LAA thrombus and spontaneous echocardiographic contrast, which was graded according to the classification (1 to 4+) proposed by *Fatkin et al.* [10]. When dense spontaneous echocardiographic contrast (grade 3+ or 4+) was present and organized into a dynamic and gelatinous, but not solid or well-formed, echodensity present throughout the cardiac cycle, sludge was reported [11].

LAA flow velocities were assessed with a pulsed Doppler sample placed 1 cm from the entry of the LAA into the body of the left atrium. Emptying and filling velocities were estimated from an average of five well-defined emptying and filling waves.

Patients were divided into 2 groups, according to the type of findings on transesophageal echocardiogram: group I, with LAA thrombus or sludge and group II, without any of these changes.

IV. Statistical analysis

Comparisons were performed between the two patient groups. Chi-square was used for nominal variables and Student's t-test was used for comparison of continuous variables, where appropriate; the Levene's test was used in order to check the homogeneity of variance;

equivalent non-parametric tests were used when Kolmogorov-Smirnov was in favor of absence of normal distribution. Pearson's r correlation coefficient was used for quantifying the degree of association between two quantitative variables. Results with $p < 0.05$ were regarded as significant.

Univariate analysis was performed using the chi-square test. Predictors from univariate analysis were used for obtaining logistic regression models (using the backward stepwise method likelihood ratio; probability for stepwise = 0.10) that could predict the presence of left atrial thrombi or sludge. Continuous variables which statistically differed between group I and II (or presented a non-significant trend: $P<0.1$) were converted into qualitative variables and then used in the logistic regression analysis. Cut-off values were obtained through receiver operating characteristic (ROC) curves which allowed us to define the optimal cutoff point, which was the value combining the higher value of specificity plus sensitivity (Youden index). The Hosmer-Lemeshow summary statistic was used to assess the goodness-of-fit of the models. The coefficients from the obtained model (beta values from the incorporated variables and constant) were used for estimating the probability of event in each patient. Then, the discriminative capability of the obtained probabilities was also assessed through a ROC curve.

PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis.

Inter-observer variability was assessed using Bland-Altman plots with data from the first 7 included patients in the study (average for each of the 6 segments shown), that were separately assessed by the two operators. MedCalc for Windows version 9.2.0.1 was used.

Results

During the pre-specified inclusion period, 133 patients were assessed during an AF episode of longer than 48 hour duration and with no effective anticoagulation in the preceding 3 weeks. Of these, the following were excluded from analysis due to the presence of exclusion criteria: inappropriate endocardial border definition of the left atrium (n=11), previous closure of the LAA (n=3), valve repair or presence of prosthetic heart valve (n=10) and significant valvular disease (n=27).

Out of the remaining 82 patients, most were male (65.9%) and the average $CHADS_2$ and CHA_2DS_2-VASc scores were 2.0±1.1 and 3.2±1.6, respectively. Information on demographics, clinical data and anti-thrombotic medication are provided on Table I.

I. Echocardiographic findings

Thrombus or sludge in the left atrium or LAA was found in 16 patients (19.5%) (group I). No differences were found for baseline variables when comparing these patients with the remaining (group II), except for the estimated AF duration, which was more often longer than 1 month in group I.

As regards standard transthoracic echocardiographic parameters, no differences were found between the two groups (Table II). Also, no significant differences were found regarding left ventricular longitudinal strain and strain rate. On transesophageal echocardiogram lower flow velocities in the LAA and a higher prevalence of dense spontaneous echocardiographic contrast were observed in group I.

II. LA deformation in patients with LA thrombus or sludge

Adequate tracking of all 6 segments was possible in most patients (n=58; 70.7%). The segments which were more frequently excluded from analysis were Seg_6 (in 18 patients; 22.0%) and $Seg_1$1 (in 7 patients; 8.5%). In all the remaining segments, a satisfactory definition of the endocardial borders and tracking was possible (97.6% Seg_2 2; 93.9% Seg_3; 96.3% Seg_4; 96.3% Seg_5).

Bland-Altman analysis for inter-observer variability of speckle-tracking derived data is shown in Figure 3. Small differences were observed overall for PPS (-0.3%; 95%CI -5.2;4.6), PNS (0.5%; 95%CI -3.5;4.5), PPSR (-0.02 s^{-1}; 95%CI -0.54;0.51) , PNSR (0.06 s^{-1}; 95%CI -0.35;0.48) and TPPS (6.7 ms; 95%CI -93.2;106.6).

Lower values of peak positive and peak negative strain rate, as well as a lower peak-to-peak strain rate, were observed in group I patients. Patients with sludge or thrombi had a trend for higher indexed left atrial volume and left atrial dyssynchrony, as assessed through the standard deviation of time to peak positive strain (Table II).

III. Predictors of LA stasis

A moderate positive correlation was found between peak positive strain rate and maximum emptying velocity ($r= 0.589$; $P < 0.001$) and peak positive strain rate and maximum filling velocity of the LAA ($r = 0.651$; $p< 0.001$). Peak negative strain rate was also found to be associated both with maximum emptying velocity ($r = -0.513$; $p< 0.001$) and maximum filling velocity of the LAA ($r = -0.552$; $p< 0.001$). No significant correlation was observed between peak negative strain and LAA flow velocities and only a trend for a very slight association was

observed between peak positive strain and both LAA maximum emptying velocity (r = 0.231; p = 0.066) and LAA maximum filling velocity (r = 0.222; p = 0.078).

On univariate analysis, body mass index, AF episode duration, indexed left atrial volume, peak positive strain rate, peak negative strain rate, peak-to-peak strain rate and time to peak positive strain were predictors of thrombus or sludge on transesophageal echocardiogram. However, only AF duration, peak negative strain rate and time-to-peak positive strain remained significant on multivariate analysis (Table III). The area under the curve for the estimated probabilities using the obtained logistic regression model was 0.89 (95%CI 0.81-0.96; P<0.001). The same logistic regression model also displayed a high discriminative capability for the prediction of dense spontaneous echocardiographic contrast: c-statistic = 0.81; 95%CI 0.71-0.91; P<0.001).

Discussion

Our data suggest that left atrial mechanical dysfunction, as assessed through peak negative longitudinal left atrial strain rate and time-to-peak positive strain, are associated with the presence of LAA thrombus or sludge. These findings are important not only due to their possible application in the selection of patients for transesophageal echocardiogram before catheter ablation or cardioversion of AF, but also for risk stratification of AF. These parameters may relate to prognosis and clinical endpoints, since LAA thrombus [12, 13], sludge [11, 14], spontaneous echocardiographic contrast [12, 15, 16] and low flow velocities in the LAA [11, 12] have been associated with a worse outcome in patients with AF.

The described association may be explained by the following: higher left atrial dyssynchrony and lower deformation (compromised contraction and relaxation) may predispose to stasis (as shown by the correlation with flow velocities in the LAA) and subsequently to increasing

severity of spontaneous echocardiographic contrast, sludge and thrombus formation. Furthermore, it has been suggested that left atrial wall fibrosis, assessed through delayed enhancement magnetic resonance imaging is inversely related to the strain and strain rate derived from vector velocity imaging echocardiography [17]. Therefore, alongside with fibrosis, loss of left atrial endocardium integrity may occur, which may partially account for the increased pro-thrombotic profile in the atrial milieu in patients with compromised left atrial mechanical function.

The average strain and strain rate values in our population of patients with AF may be considered low compared to the standard values proposed by Cameli et al [18, 19]. However, despite the different methodology, they are in the range of what has been found in previous descriptions of strain and strain rate in patients with AF [19, 20].

In our sample, left atrial size (indexed left atrial volume) was not an independent predictor of left atrial stasis, after adjustment to other echocardiographic parameters and AF episode duration. This may mean that previously described associations between atrial size [21, 22] and transesophageal echocardiogram changes may be due to the mechanical function alterations that occur in the dilated atrium, rather than to atrial size alone. Furthermore, this may also explain why, unlike left ventricle ejection fraction, left atrial size has failed to consistently associate with thromboembolism in non-valvular AF [23] and is not used alongside other validated clinical variables in risk stratification [24].

Previous investigations support the assessment of left atrial strain and strain rate in patients with AF, with promising results [17, 25, 26] concerning its association with fibrosis and thromboembolism, which suggest a possible role as a predictor of poorer cardiovascular outcomes and risk of stroke. A case-control study has found that patients with permanent AF and a history of stroke have lower peak positive longitudinal left atrial strain during atrial filling and peak strain rate in the reservoir phase (measured through speckle tracking) when compared to matched controls with no history of stroke [26]. In a cross-sectional study of

patients with AF, global longitudinal left atrial strain (assessed through speckle tracking) was lower in patients with a higher thromboembolic risk ($CHADS_2$ score ≥ 2) [27]. A recent case-control study composed of patients with AF and a low-risk $CHADS_2$ score (≤ 1 assessed prior to cerebrovascular events) suggested that reduced peak negative left atrial strain might identify those at risk for stroke [25].

Besides this preliminary clinical evidence, data concerning a possible association between left atrial strain and strain rate with left atrial stasis are scarce. A study using tissue Doppler imaging has shown a moderately strong positive association (r=0.73; p=0.007) between mean left atrial systolic strain and LAA appendage emptying velocities [28], contrary to what we found in our sample. *Leong et al*. have found that speckle tracking derived parameters are more rapidly measured and more accurate than tissue Doppler for the discrimination of the presence of moderate-severe left atrial spontaneous echocardiographic contrast [29]. Patients with AF are also known to present higher degrees of left atrial dyssynchrony [30]. However, to the best of our knowledge, its association with the presence of left atrial stasis had not yet been demonstrated.

Unlike previous studies, our investigation includes only patients that were assessed during an AF episode. Using speckle tracking for the quantification of left atrial deformation and dyssynchrony we have provided the first evidence towards the association of these novel parameters with the presence of LAA thrombus or sludge. However, one point of our investigation must be highlighted: due to its cross-sectional design, we can only conclude towards an association of compromised left atrial deformation with left atrial stasis. Therefore, since no follow-up was performed, no causal association between left atrial dysfunction and thrombus or sludge formation can be inferred.

Most data of a possible association between compromised left atrial deformation and a pro-thrombotic state in AF are based on strain. Some reasons may explain why in our sample the

association was found for strain rate: Unlike other studies where most patients were assessed in sinus rhythm (e.g. ±60% in Azemi et al [25]), all patients in our study were in AF at the time of the exam. Also, our left atrial strain rate was slightly higher than in other studies (i.e. Saha et al. [27]), which may probably be due to the different method used for its measurement (peak positive and peak negative strain rate in a fibrillating left atrium), rather than peak systolic or end systolic strain rate, which may be difficult to ascertain when no systole or diastole can be clearly identified. From a pathophysiologic point of view, there may be a rationale for an association of left atrial strain rate rather than strain with atrial stasis, since probably the speed at which deformation occurs may be more strongly related to stasis than the overall amount of deformation. Additionally, left atrial strain is included as a predictor, as far as time to peak positive strain (traducing atrial dyssynchrony) is concerned. Lastly, the presence of a small sample with only 16 patients with left atrial appendage thrombus or sludge may lack the sufficient statistical power for revealing an association with left atrial strain, mainly since the degree of the association seemed to be smaller than what was verified for strain rate.

Limitations

Comparison of groups with a discrepancy in size may be associated with some issues. First, a small group of patients may be more prone to being affected by the presence of outliers and therefore, the average value of some variables may not be truly representative. However, in this sample of patients, standard deviations of the assessed echocardiographic variables were smaller in the group of patients with thrombi or sludge, which render the chance of selection bias or outliers less likely. Second, small samples may sometimes lack statistical power to demonstrate the presence of smaller significant statistical differences. For example, patients with thrombus or sludge display lower absolute values of left atrial strain, which fail to achieve statistical significance possibly due to insufficient power of the sample.

Our data were obtained using software that was designed for the assessment of the left ventricle, but still allowed the automatic definition of a region of interest and tracking of speckles in the left atrium. We do not know if using dedicated software to the left atrium would have changed our observations. However, we think it would likely improve the quality of tracking (namely in S_6) and the total percentage of patients where tracking in the 6 apical 4-chamber segments was achieved.

Due to deficient endocardial border definition of the left atrium in 2-chamber view in a significant number of patients, we have chosen not to evaluate these segments. We acknowledge that having a global evaluation of the left atrium, ideally with 3D echocardiography, may provide more accurate and precise data. However, this could lead to a more complex and time-consuming procedure.

Conclusions

Left atrial mechanical dysfunction assessed through speckle tracking seems to be associated with a higher prevalence of the different markers of left atrial stasis. These findings suggest a possible application of this technique in the selection of patients with AF for transesophageal echocardiogram. Moreover, there may be a rational for assessing left atrial deformation in the context of risk stratification of AF, but this should be further explored in future trials.

Abbreviations

AF – atrial fibrillation; LA – left atrial; LAA – left atrial appendage; E - early diastolic filling velocity E' - early diastolic tissue velocity.

Competing interests: none

Sources of funding: none

Author's contributions: RP designed the study, performed the analysis of data along side with AF and wrote the first draft of the manuscript. MJF, LG and SBo discussed and revised the study design. Data was acquired by AF, JT and AB. All authors actively revised the first draft of the paper, providing suggestions and corrections. Input from reviewers was used for preparing a new version of the paper, which was prepared and revised by all authors. SBa provided all the necessary English language support for the preparation of the final version. All authors read, revised, accepted the final version of the manuscript and confirm the accuracy or integrity of data.

Acknowledgements: none

Table I – Clinical data of the study sample.

	Overall (n=82)	Group 1 (n=16) LAAT or sludge	Group 2 (n=66) No changes	p
Demographics				
Age	68.1±10.6	70.7±8.0	67.4±11.1	0.516
Female Gender	34.1% (28)	25% (4)	36.4% (24)	0.390
Body Mass Index (Kg/m^2)	28.3±4.1	26.6±2.8	28.7±4.3	0.100
Clinical Data				
AF episode duration > 1 month	61.0% (50)	93.8% (15)	53.0% (35)	0.003
$CHADS_2$	2.0±1.1	2.3±1.4	1.9±1.1	0.418
CHA_2DS_2-VASc	3.2±1.6	3.7±1.6	3.1±1.6	0.247
Congestive heart failure	43.9% (36)	50% (8)	42.4% (28)	0.584
Hypertension	80.5% (66)	93.8% (15)	77.3% (51)	0.136
Diabetes mellitus	18.3% (15)	31.3% (5)	15.2% (10)	0.135
Previous stroke or TIA	13.4% (11)	18.8% (3)	12.1% (8)	0.485
Vascular disease	15.9% (13)	25.0% (4)	13.6% (9)	0.264
Anti-thrombotic medication				
Aspirin	22.8% (18)	37.5% (6)	19.0% (12)	0.116
Clopidogrel	12.7% (10)	25.0% (4)	9.5% (6)	0.096
Warfarin	29.1% (23)	37.5% (6)	27.0% (17)	0.408
INR in patients treated with warfarin	2.4±1.0	2.8±1.6	2.2±0.6	0.394
Dabigatran or Rivaroxaban*	15.2% (12)	18.8% (3)	14.3% (9)	0.657
Enoxaparin	35.4% (29)	25.0% (4)	37.9% (25)	0.334
Enoxaparin dosage (mg/Kg bid)	0.9±0.2	1.0±0	0.9±0.2	0.288

Legend: LAAT – left atrial appendage thrombus; AF – atrial fibrillation; TIA – transient ischemic attack; INR – international normalized ratio.

* all patients were treated with dabigatran 110mg bid except for two: one patient with rivaroxaban 20mg id and another one with dabigatran 150mg bid in group 2.

Table II – Echocardiographic data of the study sample.

	Overall (n=82)	Group 1 (n=16) LAAT or sludge	Group 2 (n=66) No changes	P
Standard transthoracic echocardiogram data				
Indexed LA volume (mL/m^2)	47.0±13.1	52.3±13.2	45.8±12.9	0.072
LVEF (%)	51.2±12.7	49.3±15.6	51.7±12.0	0.734
Indexed LA volume / LVEF (mL/m^2/%)	1.01±0.55	1.24±0.74	0.96±0.49	0.153
Mitral regurgitation II/IV	18.3% (15)	12.5% (2)	19.7% (13)	0.504
E (cm/s)	97.8±22.7	99.8±20.0	97.2±23.5	0.695
E' (cm/s)	11.4±2.4	11.6±2.5	10.5±1.9	0.113
E / E' ratio	9.0±3.2	9.8±2.6	8.8±3.3	0.268
Speckle tracking derived parameters				
Av. peak positive LA strain (%)	11.6±5.2	10.9±3.5	11.8±5.5	0.433
Av. peak negative LA strain (%)	-4.0±2.2	-3.5±2.4	-4.1±2.1	0.122
Av. peak-to-peak LA strain (%)	15.5±5.0	14.4±3.6	15.8±5.3	0.312
Av. peak positive LA strain rate (s^{-1})	1.20±0.32	1.00±0.27	1.25±0.32	0.003
Av. peak negative LA strain rate (s^{-1})	-1.37±0.42	-1.07±0.22	-1.45±0.42	<0.001
Av. peak-to-peak LA strain rate (s^{-1})	2.6±0.7	2.1±0.4	2.7±0.7	<0.001
SD time-to-peak positive LA strain (ms)	97.2±47.1	110.4±37.4	94.0±48.9	0.097
LV global longitudinal systolic strain (%)	-12.6±5.2	-12.3±2.9	-12.6±5.6	0.853
LV global longitudinal systolic strain rate (s^{-1})	-0.84±0.22	-0.82±0.17	-0.85±0.23	0.617
Transesophageal echocardiogram data				
LAA maximum emptying flow velocity (cm/s)	26.8±11.9	16.3±4.2	29.2±11.8	<0.001
LAA maximum filling flow velocity (cm/s)	33.8±14.2	23.2±8.4	36.2±14.2	0.001
Dense spontaneous auto-contrast (≥III/IV)	32.9% (27)	100% (16)	16.7% (11)	<0.001

Legend: LAAT – left atrial appendage thrombus; LA – left atrial; LV – left ventricle; LVEF – left ventricle ejection fraction; LAA – left atrial appendage; E – early diastolic filling velocity; E' - early diastolic tissue velocity in the lateral mitral annulus; Av. – average; SD – standard deviation.

Table III – Univariate and multivariate analysis predictors of left atrial thrombus or sludge

	Univariate analysis			Multivariate analysis				
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**	**Wald**	**Hosmer-Lemshow**
BMI ≥ 26.9 kg/m^2	0.3	0.1-1.0	0.049	-	-	-	-	
AF episode duration ≥ 1 month	13.3	1.7-106.5	0.003	13.3	1.5-119.6	0.021	5.3	
Indexed LAV≥45.2mL/m^2	3.4	1.0-11.6	0.044	-	-	-	-	
Av. peak positive strain rate ≤ 1.01 (s^{-1})	6.3	1.9-20.9	0.001	-	-	-	-	$\chi^2 = 1.054$
Av. Peak negative strain rate ≥ -1.33 (s^{-1})	21.7	2.7-173.9	<0.001	21.5	2.5-186.1	0.005	7.7	df = 6
Av. Peak-to-peak strain rate ≤ 2.02 (s^{-1})	12.1	3.5-42.3	<0.001	-	-	-	-	P=0.983
SD time-to-peak positive strain ≥ 101.3ms	3.6	1.1-11.6	0.026	3.8	0.9-15.1	0.062	3.5	
				Constant 0.01	-	0.002	16.2	

Legend: BMI – body mass index; LAV – left atrial volume; Av. Average; SD – standard deviation.

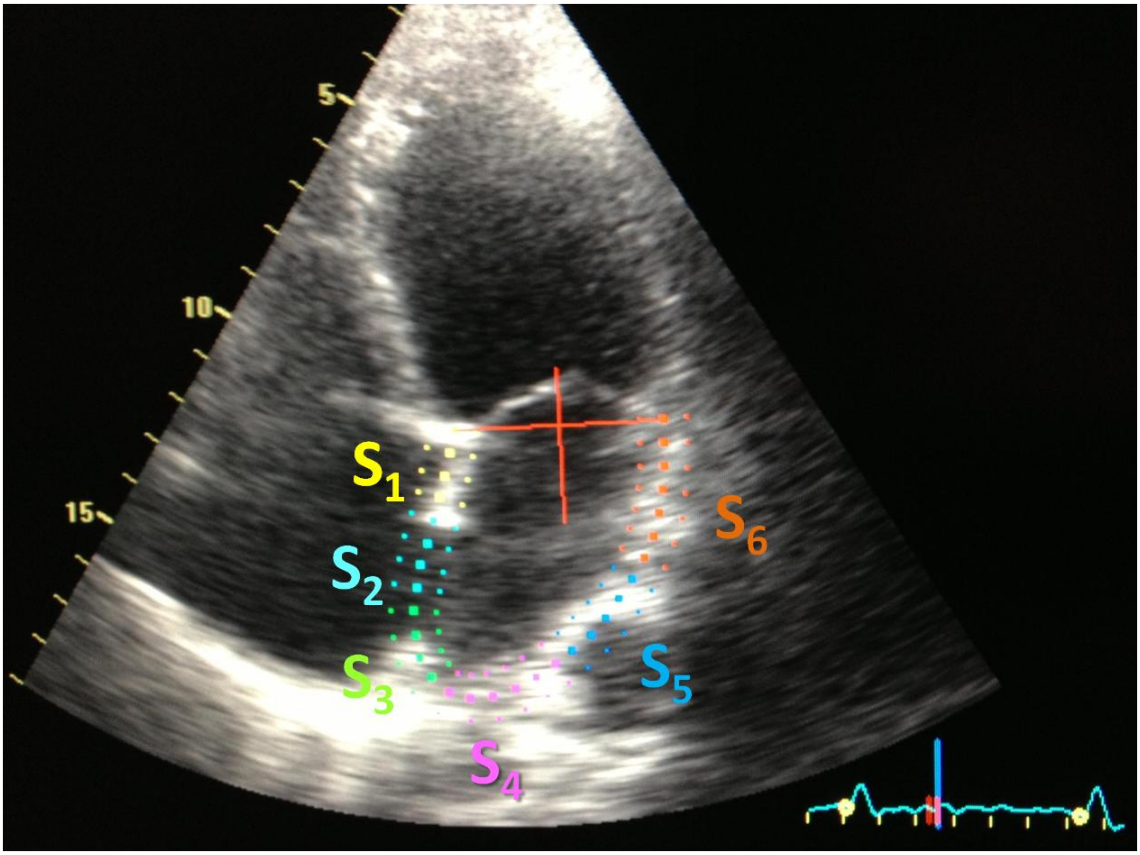

Figure 1 – Assessed segments in the left atrial region of interest.

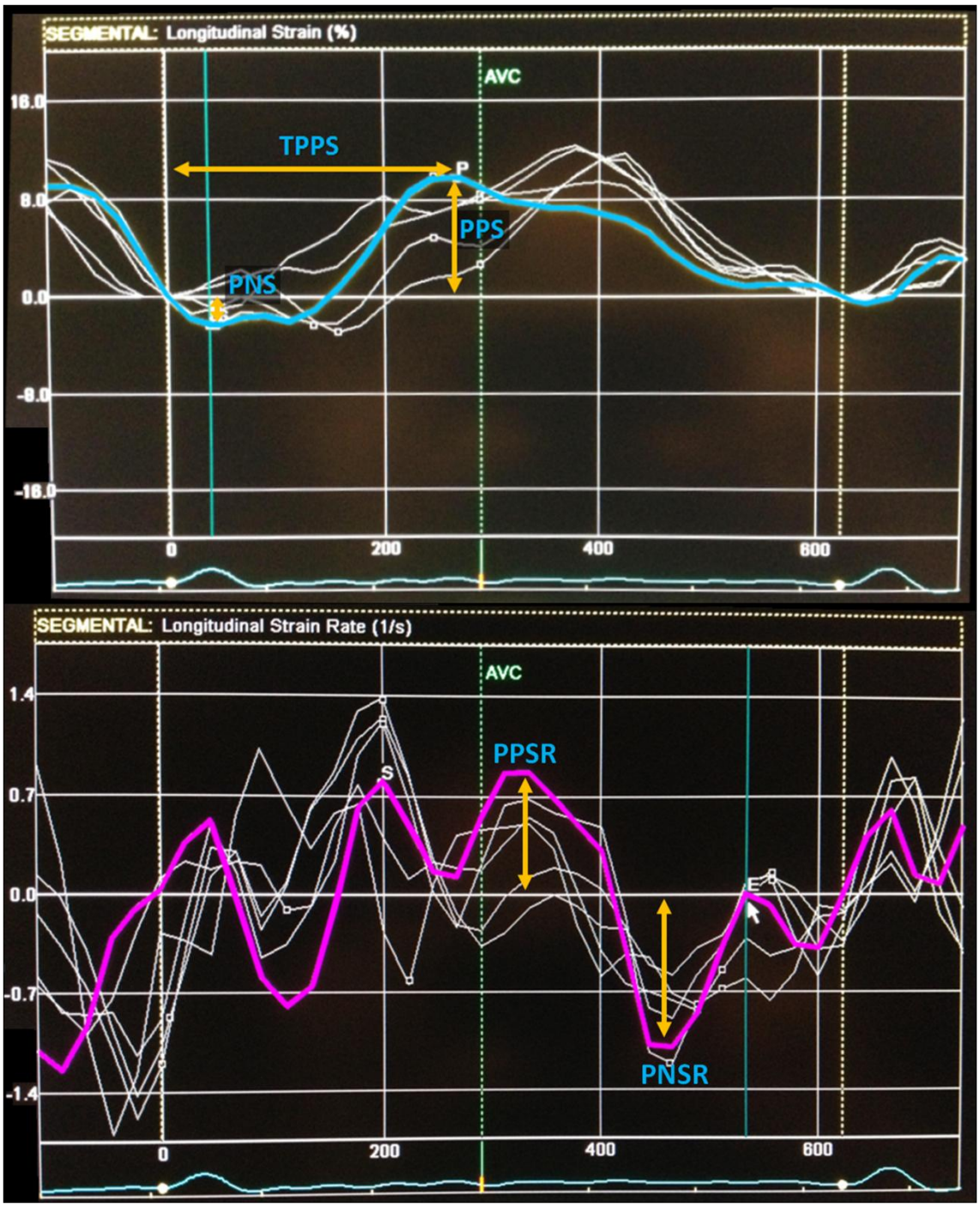

Figure 2 – Left atrial longitudinal deformation and dyssynchrony measurements.

Legend: Peak negative strain (PNS) and peak positive strain (PPS) were measured of each segment from baseline to the peak negative or peak positive value of longitudinal strain, respectively; Peak positive strain rate (PPSR) and peak negative strain rate (PNSR) of each segment were measured from baseline to the peak positive or peak negative value of longitudinal strain rate, respectively. The average of all 6 segments during 3 cardiac cycles was calculated. Time to peak positive strain (TPPS) was the time interval measured from the beginning of the cardiac cycle to the timing of peak positive strain; the standard deviation of all 6 segments during 3 cardiac cycles was calculated.

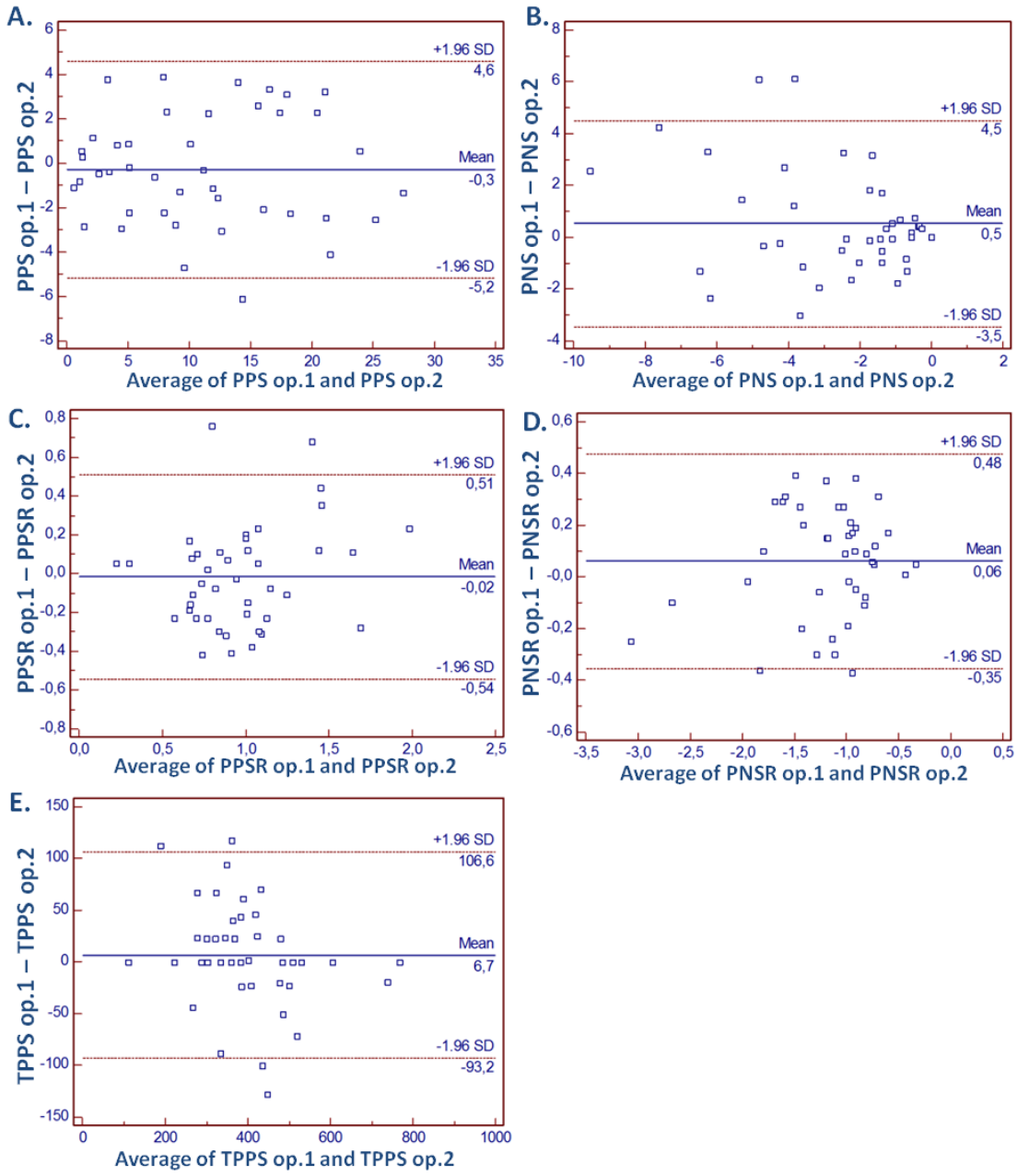

Figure 3 – Results of Bland-Altman analysis for interobserver variability of peak positive strain (PPS – A.), peak negative strain (PNS – B.), peak positive strain rate (PPSR – C.), peak negative strain rate (PNSR – D.) and time-to-peak systolic strain (TPPS – E.).

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II.A.3

The role of echocardiography in thromboembolic risk assessment of patients with non-valvular atrial fibrillation

Rui Providência, Joana Trigo, Luís Paiva, Sérgio Barra. The role of echocardiography in thromboembolic risk assessment of patients with nonvalvular atrial fibrillation. J Am Soc Echocard 2013; 26(8):801-12
doi: 10.1016/j.echo.2013.05.010.

Abstract

Echocardiography is a widely used and versatile technique that can provide comprehensive information concerning thromboembolic risk in patients with atrial fibrillation.

This paper reviews the potential contributions of echocardiography to thromboembolic risk stratification and to decreasing the thromboembolic risk associated with procedures such as cardioversion and ablation.

Unsolved questions and new possibilities that have arisen from the development of strain and strain rate imaging will also be discussed.

Keywords: atrial fibrillation; stroke; thromboembolism; transthoracic echocardiogram; transesophageal echocardiogram; strain; strain rate

Introduction:

Echocardiography is a widely used and versatile technique that can provide comprehensive information concerning thromboembolic risk in patients with atrial fibrillation (AF).

Although transesophageal echocardiography (TEE) is a mainstay tool for preventing cardioversion and catheter ablation-related thromboembolism, the potential role of transthoracic echocardiography (TTE) in the risk stratification of AF and in decision-making about long-term thromboembolism prophylaxis has been overlooked. However, recent investigations have shown that despite the generalized used of clinical risk stratification based solely on $CHADS_2$ and CHA_2DS_2-VASc scores (measures that have very modest discriminative capability, with c-statistics ranging from 0.54 to 0.65 [(1)]), echocardiography may be useful for fine-tuning these classifications.

In the next sections, we will review the echocardiographic parameters that play a role in patients with AF in three different situations:

- Evaluation prior to cardioversion or ablation
- Predicting the presence of left atrial (LA) appendage thrombus on TEE
- Thromboembolic risk stratification to select the appropriate anti-thrombotic strategy.

Emphasis will be placed on different cardiac structures according to the chosen image acquisition technique (transthoracic or transesophageal) and the provided information. For the sake of clarity, TTE and TEE should be interpreted as 2D unless clearly specified as otherwise (e.g., 3D-TTE or 3D-TEE).

The promising development of strain and strain rate imaging, alongside the unsolved matters in the field of thromboembolic risk assessment of patients with non-valvular AF will also be explored.

1. Transesophageal echocardiogram for assessment of the LA appendage

2D-TEE provides excellent characterization of the LA appendage and LA environment due to the anatomical relationship of these structures to the esophagus. Despite being a narrow tubular structure with very complex anatomy (variable shape, size and orientation, with the possibility of several lobes and branches), the LA appendage thrombi can be very accurately identified using 2D-TEE, with values of sensitivity and specificity approaching 99% [(2)]. Figure 1 illustrates the capabilities of 2D-TEE for providing very clear and diagnostic images of LA thrombi (see accompanying online video). However, careful examination is required to avoid false negatives. Furthermore, the muscular ridges and pectinate muscles must be carefully observed because they can be misinterpreted as clots [(3)].

3D-TEE allows a more comprehensive assessment of multiple lobes of the LA appendage, which may be located in different planes, and a more accurate estimation of LA appendage geometry and size [(4)]. This is advantageous as 2D-TEE only shows a "slice" of the LA appendage at a given time (which may result in under or overestimation of orifice size, depth and number of lobes). Another advantage of 3D-TEE is better distinction between the pectinate muscles and thrombi [(5, 6)].

The use of contrast has also been proposed as an option for improving LA thrombus detection in 2D-TEE, thereby reducing the rate of adverse events in patients undergoing cardioversion [(7)].

An epiphenomenon of intracardiac thrombus is the presence of spontaneous echocardiographic contrast (SEC), also known as "swirl" or "smoke", which is associated with low blood flow velocity [(8)]. The dynamic smoke-like echoes are thought to be composed either of aggregated activated platelets and leucocytes [(9)] or aggregates or of red blood cells that are

interacting with plasma proteins [10, 11]. SEC can be classified into 4 groups (1 to 4+ depending on the intensity, location and presence of the swirling movement) according to the method proposed by *Fatkin et al* [12]. Figure 2 illustrates the presence of dense spontaneous echocardiographic contrast with swirling movements in the LA and LA appendage (see accompanying online video). Increasing grades of SEC have been associated with decreased LA appendage flow velocity and increased LA size [12].

Sludge is a dynamic and gelatinous, but not solid or well-formed, echodensity present throughout the cardiac cycle (Figure 3 - see accompanying online video). It is often difficult to differentiate sludge from a thrombus. Along the continuum of thrombus formation, sludge is thought to represent a stage beyond SEC (the stages are: mild, moderate and severe SEC, sludge and thrombus) and may have greater prognostic significance [13].

The presence of thrombi in the LA appendage [14], SEC [14, 15], low LA appendage flow velocities [41, 43] and complex aortic plaques on TEE [14, 16] has long been associated with stroke, thromboembolism and adverse prognosis. The presence of at least one of the following - LA appendage thrombus, low LA appendage flow velocities or SEC - is designated as a LA abnormality and is associated with a high risk of stroke [16].

A high likelihood of cerebral embolism (either clinically assessed or observed on magnetic resonance images) and/or death at medium-term despite anticoagulation in patients with AF and dense SEC (3+ or 4+) has been described [17, 18].

LA appendage thrombus and dense SEC are very powerful predictors of cardiovascular death independent of other known clinical risk factors, including congestive heart failure, diabetes mellitus, hypertension and vascular disease [19].

The following TEE changes are part of a dynamic process: LA appendage thrombus disappear either because of embolization or adequate anticoagulation; SEC appears or increases over

time alongside with dilatation, fibrosis and progressive atrial dysfunction or stunning; LA appendage flow decreases with time as AF episode duration progresses or increases some weeks after an effective cardioversion. Therefore, one TEE examination is like a single photograph of the LA milieu and may not be fully representative of past and future changes at this level [20, 21].

The presence of a thrombus in the LA appendage is a contraindication to the performance of cardioversion due to the associated risk of stroke. Therefore, when a rhythm control strategy is chosen in patients with AF of greater than 24 to 48 hours in duration, the Guidelines [22, 23] recommend TEE to exclude LA appendage thrombus as an alternative to 3 weeks of effective pre-procedural anticoagulation.

This recommendation results from the landmark findings of the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial [24] and was recently tested using the new anticoagulant dabigatran in the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) cardioversion sub-study. In a post-hoc analysis of trial patients undergoing cardioversion (of which 13 to 25% had undergone a previous TEE), no differences in the prevalence of LA appendage thrombus and SEC were found when comparing the 3 treatment arms (adjusted warfarin vs dabigatran 110mg bid or 150mg bid). Moreover, the analysis of data from before, during and 30 days after cardioversion revealed comparable incidences of stroke, systemic embolism and major bleeding [25].

Recent investigations have assessed the ability of $CHADS_2$ and CHA_2DS_2-VASc scores to discriminate TEE risk factors (LA appendage thrombus, SEC, sludge and low LA appendage flow velocities). However, these scores showed low to moderate abilities (AUC ranging from 0.6 to 0.7) to discriminate between the risk factors [26, 27].

According to the 2012 Consensus Statement on Catheter and Surgical Ablation of AF, a pre-procedure TEE is indicated to all patients with AF greater than 48 hours and without

anticoagulation at a therapeutic level in the previous 3 weeks [28]. Still, in many centers, all patients undergoing AF ablation, even those who are in sinus rhythm and are effectively anticoagulated, undergo a pre-procedural TEE. This treatment plan is derived from the fact that patients with $CHADS_2$ [27, 29, 30] or CHA_2DS_2-VASc scores of 0 [30] and a minority of therapeutically anticoagulated patients (1.6% to 2.1%) [31, 32] may develop thrombus or "sludge" in the LA appendage. However, some studies suggest that patients under anticoagulation and with $CHADS_2$ and CHA_2DS_2-VASc scores of less than 2 (negative predictive value approaching 100%) may be spared TEE prior to catheter ablation of AF [33].

Alternatives to TEE in these circumstances (e.g. the ratio of LV ejection fraction to LAV index, among others), will be discussed in the next section.

Other less validated and less frequently used parameters, such as intracardiac intensity variation at the orifice of the LA appendage after contrast infusion and LA appendage ejection fraction evaluated through vector velocity imaging have been associated with cerebrovascular events [34] and the formation of LA appendage thrombus [35].

The most relevant evidence concerning TEE parameters and their association with thromboembolism and prognosis is presented in Table I.

2. Transthoracic echocardiogram

The main focus of TTE derived measures as predictors of stroke or risk stratification in patients with AF has been almost exclusively restricted to depressed left ventricular (LV) ejection fraction (which has strong evidence support). Nevertheless, other parameters, including LA

diameter measured on M-mode, LA area or volume, have already shown some evidence of accuracy, suggesting a possible role in risk stratification.

The incorporation of TTE-derived parameters seems to be plausible for refinement of clinical risk scores. However, despite the recommendations of the National Institute for Health and Clinical Excellence (NICE) [36], TTE-derived parameters play only a minor role in current risk classification schemes.

Another possible use of these non-invasively collected measurements may be the prediction of pro-thrombotic changes in the LA and LA appendage to obviate the need of TEE in individuals thought to be at very low thromboembolic risk.

An overview of the different TTE parameters and their roles is presented in Tables II and III.

2.1. Left ventricular ejection fraction

In the early nineties, the use of TTE for risk stratification of AF patients was proposed following data from the Stroke Prevention in Atrial Fibrillation study [37], where a depressed LV ejection fraction was identified as an independent predictor of ischemic stroke and systemic embolism. However, the results of further testing and prospective validation of this classification were not published.

In a 2008 comparison of 12 risk stratification schemes used to predict stroke in patients with non-valvular AF [38], TTE parameters were present in half of the schemes [39-44] and included depressed LV ejection fraction (2D) and fractional shortening (M-mode).

In the more recent CHA_2DS_2-VASc classification, an LV ejection fraction of less than 40% was included as a surrogate for congestive heart failure ("C") [1].

Another key element is that approximately 90% of thrombi in AF arise from the LA appendage [45]. Thus, a parameter that could refine the predictive models of LA appendage thrombus would be useful for predicting thromboembolic events during follow-up. A normal LV ejection fraction has been associated with the absence of LA appendage thrombus formation in AF patients undergoing TEE [46]. Moreover, assessment of the LV ejection fraction has increased the discriminative capability of clinical classifications ($CHADS_2$ and CHA_2DS_2-VASc) in regards to LA appendage thrombi [46-49] and other markers of LA stasis [27, 48].

2.2. Left ventricular hypertrophy and diastolic dysfunction

The only evidence concerning LV hypertrophy as a possible risk factor for stroke in AF patients is from studies conducted in the '80s and '90s [49, 50]. However, these have also included an important percentage of patients with valvular heart disease, including rheumatic mitral stenosis and aortic stenosis, meaning the results are difficult to interpret.

A recent investigation suggested that indexed LV mass has a very high discriminative capability for the prediction of LA appendage thrombi: the c-statistics for this parameter was 0.98, which was far higher than the value for spontaneous echocardiographic contrast (0.73 to 0.75) [51]. However, these data still need to be reproduced and further validated.

Parameters concerning LV diastolic function have been shown to be related to thromboembolic risk in patients with AF: the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E' ratio) was independently associated with ischemic stroke [52]; systolic (S') and early diastolic (E') mitral annular velocities were independent predictors of a composite endpoint of cardiovascular death, recurrent heart failure and ischemic stroke [53].

2.3. Left atrial size

A relationship between increased LA dimensions (measured on M-mode), AF and stroke was proposed in the 80's in a small, retrospective, case-control study of 40 patients with AF, of which 20 had a previous ischemic stroke [54]. Similar evidence was presented by *Aronow* and colleagues [49, 50]. However, the fact that some of the patients from these two studies had rheumatic heart disease or valvular heart-disease renders the data difficult to validate in the context of non-valvular AF.

In the Stroke Prevention in Atrial Fibrillation study [37], LA size (measured on M-mode) was an independent predictor of thromboembolism and added incremental predictive value to the clinical risk factors.

The majority of investigations performed in the 80's and 90's, including LA dimensions, only focused on LA diameter measured on M-mode, which is now known to be an inappropriate and outdated method. The current recommendations of the European Association of Echocardiography and American Society of Echocardiography support measuring LA biplane volume using either the area-length formula or the modified Simpson's rule as the preferred method for assessing LA size [55]. However, when more recent studies are evaluated, favorable evidence concerning parameters such as indexed LA volume results from small size studies [56]. Some of the studies that failed to confirm an association between LA volume and thromboembolic events were not appropriately powered for AF [57]. Nonetheless, a normal LA volume index has been associated with the absence of LA appendage thrombi formation in AF patients [46].

Based on the fact that TEE is a semi-invasive procedure that carries risks over transthoracic imaging, finding TTE-derived parameters that can accurately separate patients with AF into groups of very low risk (who can be spared TEE) and moderate/high risk (who must undergo TEE) of having a LA appendage thrombus has been the aim of recent investigations.

A combination of LA size and LV ejection fraction has been shown to have a good discriminative capability for detecting patients with LA appendage thrombus or other TEE findings. A ratio of LV ejection fraction to indexed LA volume greater than 1.5 has recently been shown to be highly accurate at excluding the presence of an LA appendage thrombus in patients with AF who are candidates for AF catheter ablation or cardioversion [46]. This ratio has been successfully validated, confirming its clinical applicability [58].

Another possibility is to combine TTE parameters with clinical data to further refine the prediction rules. LA area and LV ejection fraction were found to increase the discriminative capability of $CHADS_2$ and CHA_2DS_2-VASc scores in regards to LA appendage thrombus, dense SEC and low LA appendage flow velocities (≤20 cm/s) [15]. *Ayirala* and colleagues have also shown that higher $CHADS_2$ scores, increased left atrial volume indexes and lower LV ejection fractions were predictors of LA appendage thrombus [46].

A risk score that combines clinical data with biomarkers and echocardiographic parameters has been recently developed to accurately detect AF patients with very low risk of thromboembolism who can be spared TEE [59]. Indexed LA volume was an included variable in this model, which may prove very useful in the pre-cardioversion or pre-ablation assessment. However, validation of these results is still needed.

2.4. Imaging of the left atrial appendage

Some attempts have been made to examine and acquire indexes of LA appendage function using 2D-TTE. This can be accomplished using a parasternal short-axis or apical two-chamber views. In a small study that compared 2D-TTE and 2D-TEE, imaging of the LA appendage was possible in 75% of patients using 2D-TTE, at expense of a lower sensitivity for the detection of thrombus [60].

A very good correlation between the peak velocities in the LA appendage measured by 2D-TTE and 2D-TEE was also described [61, 62]. In another small study, LA appendage emptying velocities were reduced on 2D-TTE in patients with acute ischemic stroke with LA appendage thrombus or SEC [63].

TDI of the LA appendage has been shown using 2D-TTE and presented a strong correlation with the values acquired using 2D-TEE. This parameter seems to be compromised in patients with AF and high thromboembolic risk [64]. In the Comprehensive Left Atrial Appendage Optimization of Thrombus (CLOTS) study, LA appendage thrombi were accurately detected on 2D-TTE with intravenous contrast. Cutoff values and the best segments of the LA appendage for TDI assessment and measurement of peak S' and E' to predict LA appendage thrombi, sludge or severe SEC were also defined [65].

However, despite these promising results, imaging of the LA appendage using 2D-TTE is operator-dependent and has a learning curve.

Two studies have shown that 3D-TTE may be as accurate as 2D-TEE for assessing the LA appendage if the acoustic window is accurate [66, 67]. However, strong evidence concerning this technique as a substitute for 2D-TEE is still lacking, as the sample size of the studies was small and more than 50% of the participants evaluated had conditions other than AF.

3. The promise of strain and strain rate imaging

Measuring strain and strain rate is an accurate way to assess LA function in normal subjects [68] and in disease states, namely AF [69-71].

A good correlation between atrial myocardial deformation (strain and strain rate measured with TDI) and classical indexes of atrial function derived from TTE data (mitral inflow and pulmonary vein velocities, tissue Doppler and LA volumes) has been established [68].

Kuppahally and colleagues have demonstrated that LA wall fibrosis, as assessed by delayed enhancement magnetic resonance imaging, is inversely related to the strain and strain rate derived from vector velocity imaging (VVI) echocardiography [70] in patients with persistent AF. Patients with persistent AF had significantly greater delayed enhancement (as a marker for fibrosis) and decreased strain and strain rates, compared to patients with paroxysmal AF, supporting the concept that progressive remodeling occurs once AF develops [72]. LA relaxation and lengthening during ventricular systole are characterized by positive strain and strain rate, which illustrates LA compliance and seems to be impaired in AF due to fibrosis.

Patients with permanent AF and a history of stroke seem to have lower peak systolic LA strain rates (assessed using speckle tracking (ST)) during the reservoir phase when compared to matched controls with no history of stroke [71].

In a cross-sectional study of patients with AF, global longitudinal LA strain (assessed through ST) was reduced when compared to controls and was a predictor of a high risk for thromboembolism ($CHADS_2$ score ≥ 2) [73]. A recent case-control study composed of patients with AF and a low-risk $CHADS_2$ score (≤ 1 assessed prior to cerebrovascular events) suggested

that reduced peak negative LA strain might identify those at risk for stroke [69]. These results reinforce the possible role of LA strain as a predictor of stroke risk and poorer cardiovascular outcomes in patients with AF.

Data also exists concerning LA strain and its association with TEE findings. A good correlation between mean LA systolic strain (obtained by placing a TDI sample in the midsegment of the LA lateral – 4C, anterior and inferior walls –2C) and LA appendage emptying velocities (r=0.73; p=0.007) was recently described [74]. Preliminary data from our group suggests an association between compromised LA deformation, assessed using ST, and LA stasis (LA appendage thrombus and SEC) [75, 76] (Figures 4 and 5). Variation in the patterns and magnitudes of deformation within different areas (walls) of the LA has been described [77]. We found that there are specific regions within the LA (the septal wall) whose deformation, assessed using ST, shows higher correlation with the presence of TEE changes [76].

Parvathaneni and colleagues described a good correlation between LA appendage peak TDI and flow velocity. Furthermore, they observed that in patients with sinus rhythm and normal LA appendage flow velocities, changes in TDI provided additional information and, therefore, complemented flow velocities as a part of risk assessment for thromboembolic events [78].

Compromised LA appendage deformation measured through ST analysis also seems to be associated with the presence of dense SEC and thrombi and has a moderate correlation with LA appendage flow velocities of ≤ 20 cm/s [79]. In a cross-sectional study of 260 patients with persistent non-valvular AF, peak systolic LA appendage strain and LA appendage ejection fraction (cutoff ≤ 21%), as assessed by VVI were associated with the presence of a thrombus [80]. However, only the LA appendage ejection fraction remained an independent predictor of LA appendage thrombus on multivariate analysis.

4. Unsolved questions

Additional studies of the association between LA volume and clinically evident thromboembolism in AF patients, preferably including larger numbers of patients, are currently needed in order to provide strong support for the use of LA volume in algorithms for stratifying stroke risk. The role of 3D-TTE for the measurement of indexed LA volume in that setting, or as a predictor of LA appendage thrombus or stasis, has not yet been assessed. However, the use of 3D-TTE remains a very promising option, since a recent study has demonstrated that compared to 2D-TTE, 3D-TTE is a practical and more accurate way to determine LA volume [81].

Echocardiographic variables, concerning LA size or function have never been included any former risk assessment schemes. Given that LA thromboembolism is the cause of stroke in ≥ 75% of patients with AF [82], it would be expected that parameters associated with LA stasis (e.g., LV ejection fraction and indexed LA volume) [27, 46] could improve the predictive capability of such risk classifications. Despite the fact that these parameters might provide anatomical and functional insights to the major site of thromboembolism in AF patients, they have not yet been incorporated into risk stratification scores. *Choong YP* has several explanations for that omission [83]. First, the initial studies assessing the possible contribution of LA size to risk stratification in patients with AF relied on anteroposterior diameter as assessed by M-mode, which is now known to be an improper method for assessing atrial size. Therefore, the lack of studies assessing LA dimensions in a more appropriate way may be responsible for the absence of LA size in the current risk stratification schemes. An ongoing echocardiographic sub-study from the ENGAGE-AF TIMI-48 trial will assess the role of several TTE variables to clarify this matter [84]. Second, most LA thrombi form in the LA appendage [45], which is highly variable in terms of shape and size. These features seem to be independent of the main

chamber's morphological characteristics. Third, some investigations have shown that LA appendage dimensions are not associated with increased risk for stroke [14, 85]. Conversely, these studies reinforced the role of functional parameters. Therefore, the two last points suggest that function may be more important than size. We are led to believe that LA function and the dynamic nature of the dimensions have a more profound impact on blood stasis than LA size alone, which renders individuals more prone to thromboembolism.

A new treatment algorithm that uses TEE to adjust anti-thrombotic therapy is currently being tested in the TIARA pilot study. The TIARA study included 310 AF patients, previously assessed with TEE, with moderate risk of thromboembolism and a conventional indication for oral anticoagulation. Patients with LA abnormalities or protuberant aortic plaques were not randomized and followed the conventional oral anticoagulation pathway (n = 69). The remaining 241 patients, without any of the described changes, were randomly assigned either to treatment with aspirin or to a vitamin-K antagonist. This study, with a planned one-year follow-up, aims to demonstrate the non-inferiority and safety of aspirin treatment in patients previously assessed using TEE to rule out markers of thromboembolic risk (echo-guided antithrombotic strategy) [86].

The previously described TTE and TEE data concerning atrial deformation suggest that these parameters may help in treatment decisions regarding the prevention of thromboembolism. Our knowledge concerning these techniques is at an early stage and there are many unsolved questions and issues regarding their reproducibility and large-scale applicability. The best method for assessing LA deformation still needs to be clarified. Further investigations are needed to define the best technique (TDI, ST or VVI; 2D or 3D [87]), to determine which parameter (strain, strain rate or both) and cutoff to use, to determine where to place the sample for data measurement (regional vs. global deformation; if regional, which wall provides

the best information) and the best portion of the cardiac cycle (reservoir or conduit phase) in which to retrieve information.

Additionally, more studies using other techniques (ST and TDI derived strain and strain rate) will be necessary to reproduce the findings that correlate LA deformation and MRI delayed-enhancement, as the current data only assessed VVI.

Table IV illustrates some of the ongoing studies and unsolved questions concerning the role of echocardiography in thromboembolic risk stratification of patients with atrial fibrillation.

Conclusions:

In the next few years, the role of echocardiography in thromboembolic risk assessment of patients with non-valvular atrial fibrillation may undergo dramatic changes. There are many parameters currently being tested (namely those related to myocardial deformation) that hold promise and may change the way we assess and treat patients.

Concerning risk stratification, the role of echocardiography is currently restricted to the use of left ventricle systolic dysfunction in the CHA_2DS_2-VASc score. Nonetheless, the ongoing ENGAGE-AF TIMI 48 echocardiographic sub-study may bring change to the paradigm. The use of echocardiographic measures of atrial structure and function, such as volume, contractility or deformation, instead of clinical risk factors, including hypertension and diabetes, that are surrogate markers of atrial disease, may be validated by this trial.

Transesophageal echocardiography is still the gold standard for the exclusion of left atrial appendage thrombus in patients referred for cardioversion or ablation. Nevertheless, promising parameters derived from transthoracic echocardiography may be used in the future,

sparing some patients from a semi-invasive technique and restricting the use of TEE to a higher risk subset of the patient population.

Table I – Key evidence* concerning transesophageal echocardiogram parameters, thromboembolic risk and prognosis in patients with atrial fibrillation.

Author, year	Study design and setting, n	Main Findings
Leung et al. 1994 [15]	Cohort, 272 patients with non-valvular AF undergoing TEE, mean follow-up 17.5 months	**SEC** was the only positive predictor (odds ratio 3.5, p = 0.03) of stroke or embolic events on multivariate analysis.
Zabalgoitia et al. 1998 [14]	Cross-sectional, 789 participants undergoing TEE at the entry of the SPAF III trial	**LA appendage thrombi** (RR = 2.5, p = 0.04), **dense SEC** (RR = 3.7, p < 0.001), **LA appendage peak flow velocities** ≤ 20 cm/s (RR = 1.7, p = 0.008) and **complex aortic plaque** (RR = 2.1, p < 0.001) were independently associated with increased thromboembolic risk (predefined categories for the SPAF III trial).
The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. 1998 [16]	Cohort, 382 high risk patients with non-valvular AF, Adjusted-dose vs low-intensity warfarin plus aspirin 325mg i.d. (combination therapy), 1.1 year mean follow-up	The presence of **LA abnormality** was associated with a high risk of stroke (7.8% per year) in patients under combination therapy. In the presence of a **complex aortic plaque** the stroke rate was 12.0% per year and reached 20.5% when both LA appendage abnormality and complex aortic plaques were present. In patients without any of these changes the stroke rate was 1.3% per year.
Klein et al. 2001 [24] ACUTE trial	Multicenter, randomized, prospective, 1.222 patients with AF > 48 hours, Anticoagulant treatment vs TEE-guided strategy, 8 weeks follow-up	Similar efficacy for the prevention of thromboembolic events: 0.8% **TEE-guided strategy** vs 0.5% conventional oral anticoagulant therapy (p=0.50). Patients in the TEE-guided strategy presented less bleeding complications (2.9% vs 5.5%; p=0.03). Greater rate of successful restoration of sinus rhythm with the TEE-guided strategy (71.1% vs 65.2%; p=0.03), but no differences were found at eight weeks concerning maintenance of sinus rhythm, functional status and death.
Bernhardt et al. 2005 [17]	Single-center prospective, 128 consecutive patients with dense SEC and AF vs 143 patients with faint SEC and AF, all under continued oral anticoagulation, 12 months follow-up	A very high (22%) likelihood of cerebral embolism (either clinically assessed or by magnetic resonance images) and/or death was observed in patients with **dense SEC**.
Dawn et al. 2005 [19]	Cohort, 175 patients with AF and no or only mild mitral regurgitation, 31 months mean follow-up	**LA appendage thrombus** (RR = 5.52; P = 0.024) and **LA SEC** (RR = 7.96; P = 0.013) were the only predictors of cardiovascular death, independently of other known clinical risk factors like congestive heart failure, diabetes mellitus, hypertension and vascular disease
Bernhardt et al. 2006 [18]	Cohort, 43 patients with LA appendage thrombi and persistent or permanent AF, all under oral anticoagulation, 3 years follow-up	Cerebral embolism and/or death occurred in 22 (51%) patients. **Thrombi** disappeared in 31 (72%) subjects (those with smaller thrombi, lower echogenicity and lower LA volume), either due to embolism or effective anticoagulation.

Legend: SPAF III – Stroke Prevention in Atrial Fibrillation III trial; AF – atrial fibrillation; TIA – transient ischemic attack; TTE – transthoracic echocardiogram; TEE – transesophageal echocardiogram; LA – left atrium; LV – left ventricle; PV – pulmonary vein; LVEF – left ventricle ejection fraction; SEC – spontaneous echocardiographic contrast; RR – relative risk; ACUTE - Assessment of Cardioversion Using Transesophageal Echocardiography trial.

* investigations in the tables have been placed in chronologic order.

Table II – Key evidence concerning transthoracic echocardiogram parameters and prediction of stroke and thromboembolism in patients with non-valvular atrial fibrillation.

Author, year	Study design and setting, n	Main Findings
The Stroke Prevention in Atrial Fibrillation Investigators. 1992 [37]	Cohort, 568 patients with non rheumatic AF Mean follow-up 1.3 years	Fourteen TTE variables were assessed for predicting ischemic stroke or systemic embolism. Only **LA size** (measured on **M-mode**) and depressed **LVEF** were independent predictors of thromboembolism on multivariate analysis and improved risk stratification when combined with three clinical risk factors: history of hypertension, recent congestive heart failure and previous thromboembolism.
Osranek et al. 2005 [56]	Cohort, 45 patients with lone AF, 27 years mean follow-up	Individuals with **indexed LA volume** ≥ 32ml/m^2 had a worse event free survival (HR 4.46, p=0.005). Cerebral infarction occurred in 7 patients, all with an indexed LA volume ≥ 32ml/m^2.
Lee et al. 2008 [52]	Cross-sectional, 330 patients with persistent AF and preserved LVEF	**E/E' ratio** was independently associated with ischemic stroke on multivariate analysis
Shin et al. 2010 [53]	Cohort, 148 patients with AF and heart failure with preserved LVEF, 27 months median follow-up	**S'** and **E'**, particularly when combined, were independent predictors of a composite of cardiovascular death, recurrent heart failure and ischemic stroke
Azemi et al. 2013 [69]	Case-Control (57 patients each group) Non-valvular AF $CHADS_2$ ≤ 1 before the index event	Patients with stroke presented lower **peak negative** and higher **peak positive LA strain** values than controls.

Legend: AF – atrial fibrillation; TIA – transient ischemic attack; TTE – transthoracic echocardiogram; TEE – transesophageal echocardiogram; TDI – tissue Doppler imaging; LA – left atrium; LV – left ventricle; PV – pulmonary vein; LVEF – left ventricle ejection fraction; SEC – spontaneous echocardiographic contrast; S' – systolic mitral annular velocity; E' – early diastolic mitral annular velocity; E/E' ratio - the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity.

Table III – Key evidence concerning Transthoracic echocardiogram parameters and prediction/detection of left atrial stasis in patients with non-valvular atrial fibrillation.

Author, year	Study design and setting, n	Main Findings
Omran et al. 1999 [60]	Cross-sectional, 117 patients with stroke or TIA, TTE and TEE were performed	**Imaging of the LA appendage** was possible using TTE in 75% of patients. Both methods were concordant for the detection of LA appendage thrombus in 10 patients. TTE failed to detect a thrombus in one patient that was later diagnosed on TEE.
Moreira et al. 2005 [63]	Cross-sectional, 51 patients with acute ischemic neurologic event undergoing both TTE and TEE	Doppler and **LA appendage area** evaluation was possible by TTE in 98% of patients. A moderate correlation was found between **LA appendage peak velocities** (r=0.63; p<0.001) and LA appendage area (r=0.73; p<0.001) when comparing both techniques.
Karaus et al. 2008 [67]	Cross-sectional, 92 patients referred for exclusion of LA appendage thrombus underwent 2D and 3D-TTE and 2D-TEE	**3D-TTE** findings had a very high correlation with 2D-TEE. Compared with 3D-TTE, 2D-TEE seemed to more frequently misdiagnose the pectinate musculature as thrombus.
Sallach et al. 2009 [65]	Cross-sectional, multicenter, 118 patients with AF > 2 days, Undergoing both TTE and TEE	**Thrombi in the LA appendage** were detected using TTE using harmonic imaging and intravenous contrast. **LA appendage apical peak E'** ≤ 9.7cm/s and **anterior S'** ≤ 5.2cm/s on TTE-TDI could identify patients with sludge or thrombus.
Puwanant et al. 2009 [47]	Cross-sectional, 1.058 patients undergoing TEE before catheter ablation of AF	**LVEF < 35%** and congestive heart failure were independent predictors of LA thrombus or sludge. 50% of patients with a $CHADS_2$ score of 1 and LA thrombus had a LVEF ≤ 35%.
Kleemann et al. 2009 [48]	Prospective, single-center, 295 non-valvular AF patients with a $CHADS_2$ score of 0 or 1, undergoing TEE before cardioversion	**LVEF <40%** and **LA dimension ≥ 50mm** were independent predictors for the presence of SEC and thrombus. Echocardiography was proposed as a tool to further stratify patients with a low $CHADS_2$ score.
Ayirala et al. 2011 [46]	Cross-sectional, 334 AF patients undergoing TEE	**LVEF**, **indexed LA volume** and $CHADS_2$ score were independent predictors of LA appendage thrombus formation and their combination was a useful measure for identifying patients at low risk of LA appendage thrombus formation. A normal LV ejection fraction and normal LA volume index were associated with the absence of LA appendage thrombus.
Providência et al. 2012 [27]	Cross-sectional, 376 non-valvular AF patients undergoing TEE	The addition of **LA area** and **LVEF** to the $CHADS_2$ and CHA_2DS_2-VASc scores increased their discriminative capability as regards LA appendage thrombus, dense SEC and low LAA flow velocities.
Providência et al. 2012 [59]	Cross-sectional, 180 patient with nonvalvular AF undergoing TEE before cardioversion	The incorporated independent predictors in a model to detect the presence of LA appendage thrombus were: C-reactive protein, **indexed LA volume**, troponin I, episode duration and previous stroke or embolism. This model displayed a high discriminative capability (AUC = 0.816) for LA appendage thrombus. No patients with LA appendage thrombus were observed in patients with scores ranging from "0" to "2", which corresponded to 49.4% (n=89) of the sample.
Doukky et al. 2013 [58]	Cross-sectional, 245 nonvalvular AF patients undergoing TEE before cardioversion or electrophysiology procedures	External validation of the **ratio of LVEF to indexed LA volume**, which confirms its high discriminative power (AUC = 0.83) for the presence of LA appendage thrombus, which were not detected in patients with a ratio ≥ 1.5 (i.e. 50.7% of the population).

Legend: AF – atrial fibrillation; TIA – transient ischemic attack; TTE – transthoracic echocardiogram; TEE – transesophageal echocardiogram; TDI – tissue Doppler imaging; LA – left atrium; LV – left ventricle; PV – pulmonary vein; LVEF – left ventricle ejection fraction; SEC – spontaneous echocardiographic contrast; S' – systolic mitral annular velocity; E' – early diastolic mitral annular velocity; E/E' ratio - the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; AUC – area under the curve.

Table IV – Future perspectives for the role of echocardiography in thromboembolic risk assessment of patients with atrial fibrillation

Risk stratification
Possible use of transthoracic echocardiogram parameters other than left ventricle systolic dysfunction: Results from the ENGAGE-AF TIMI 48 echocardiographic sub-study [83]
Transesophageal echocardiography guided approach: Results from the TIARA pilot study [85]
Prevention of cardioversion related thromboembolism
Creation of risk models based on transthoracic echocardiogram parameters to detect low risk patients who can safely be spared transesophageal echocardiography [58, 59]
Left atrial and left atrial appendage deformation
Validation of the different techniques using clinical endpoints
Understanding which is the most adequate, reproducible and accurate among the different available parameters
Assessment of global versus regional deformation: which (if any) is better for this purpose?
Direct comparison of the different methods: tissue Doppler imaging, speckle tracking and velocity vector imaging
Clarification of the strengths and limitations of the different methods
Assessment of new parameters

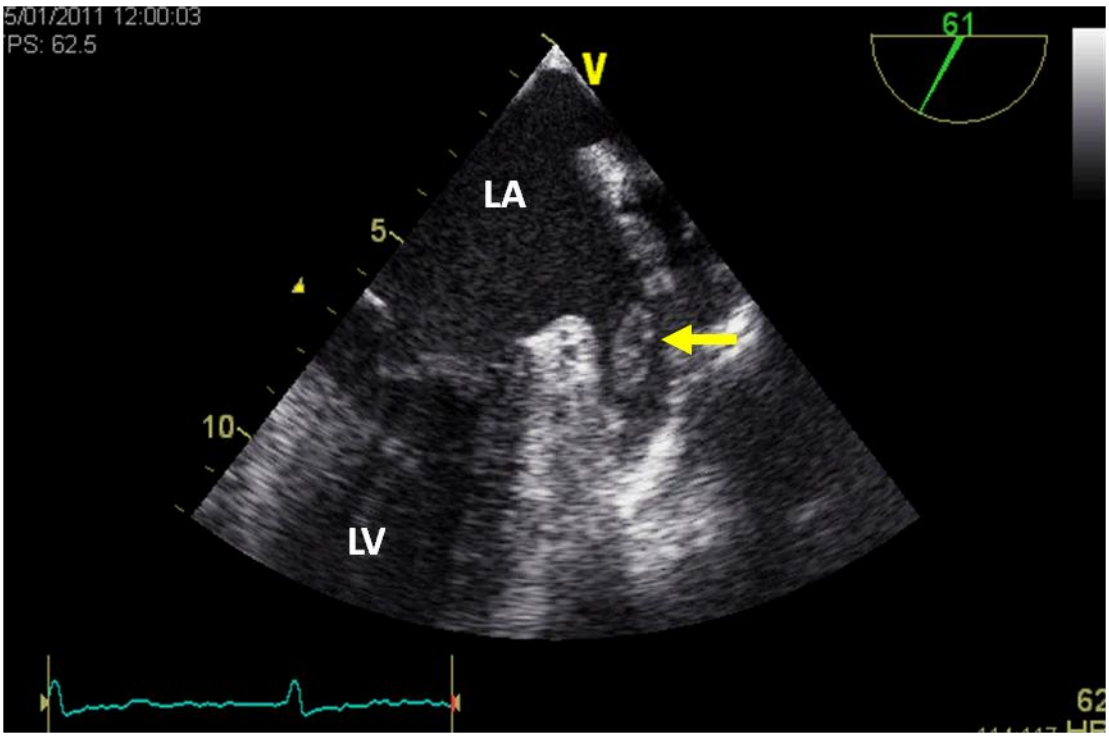

Figure 1 - Two-dimensional transesophageal echocardiogram, midesophageal view, allowing the identification of an left atrial appendage thrombus (yellow arrow). LA, Left atrium; LV, left ventricle.

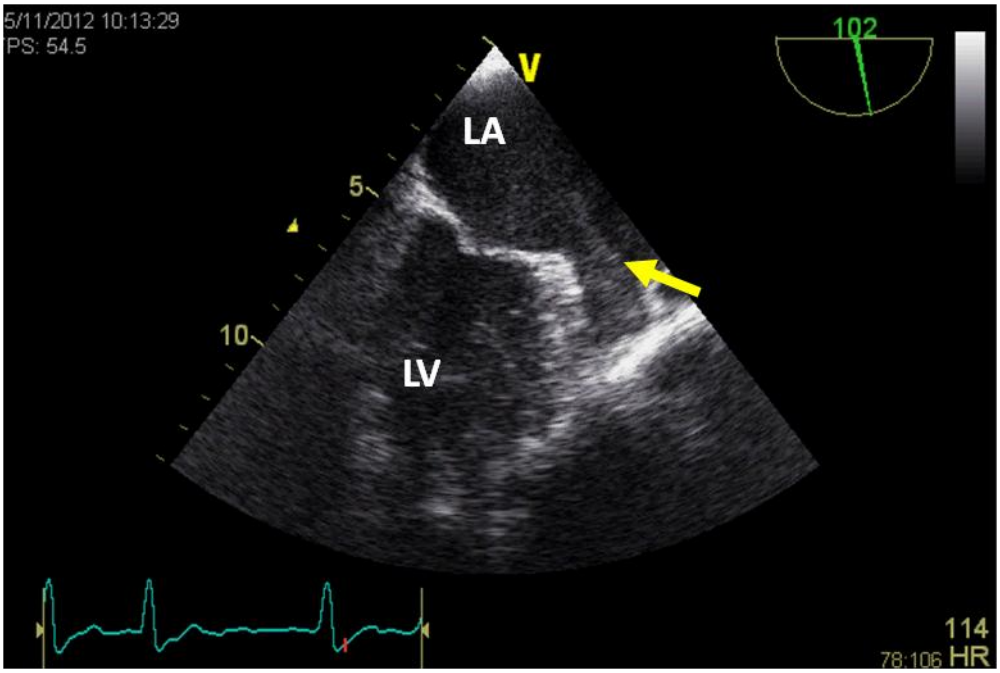

Figure 2 - Dense SEC (yellow arrow) with swirling movements in the left atrium (LA) and left atrial appendage can be seen in this transesophageal echocardiographic image. LV, Left ventricle.

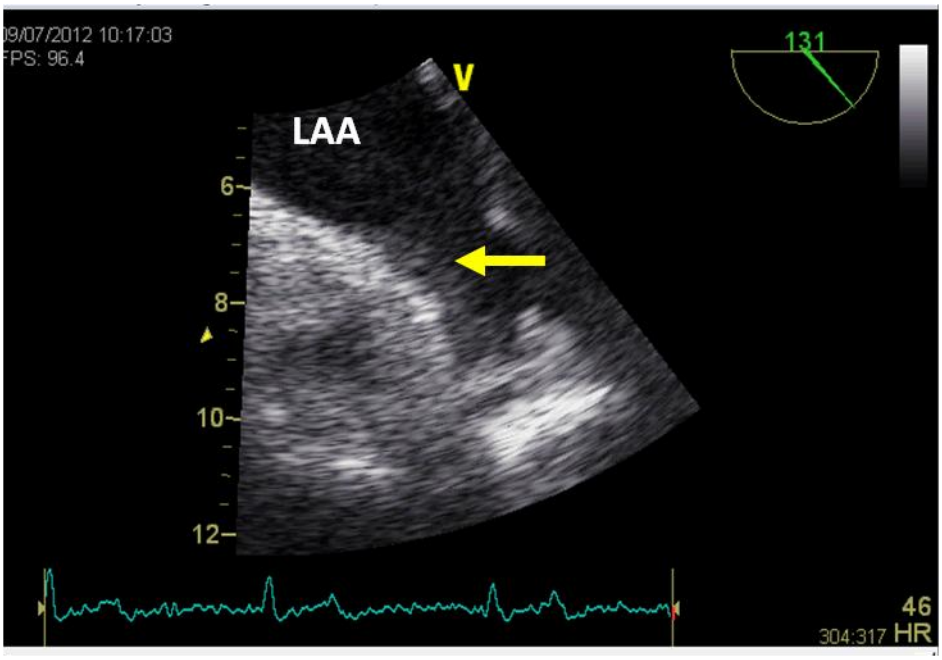

Figure 3 - Two-dimensional transesophageal echocardiogram, midesophageal view, with a zoom of the LA appendage (LAA) illustrating the presence of a sludge (yellow arrow).

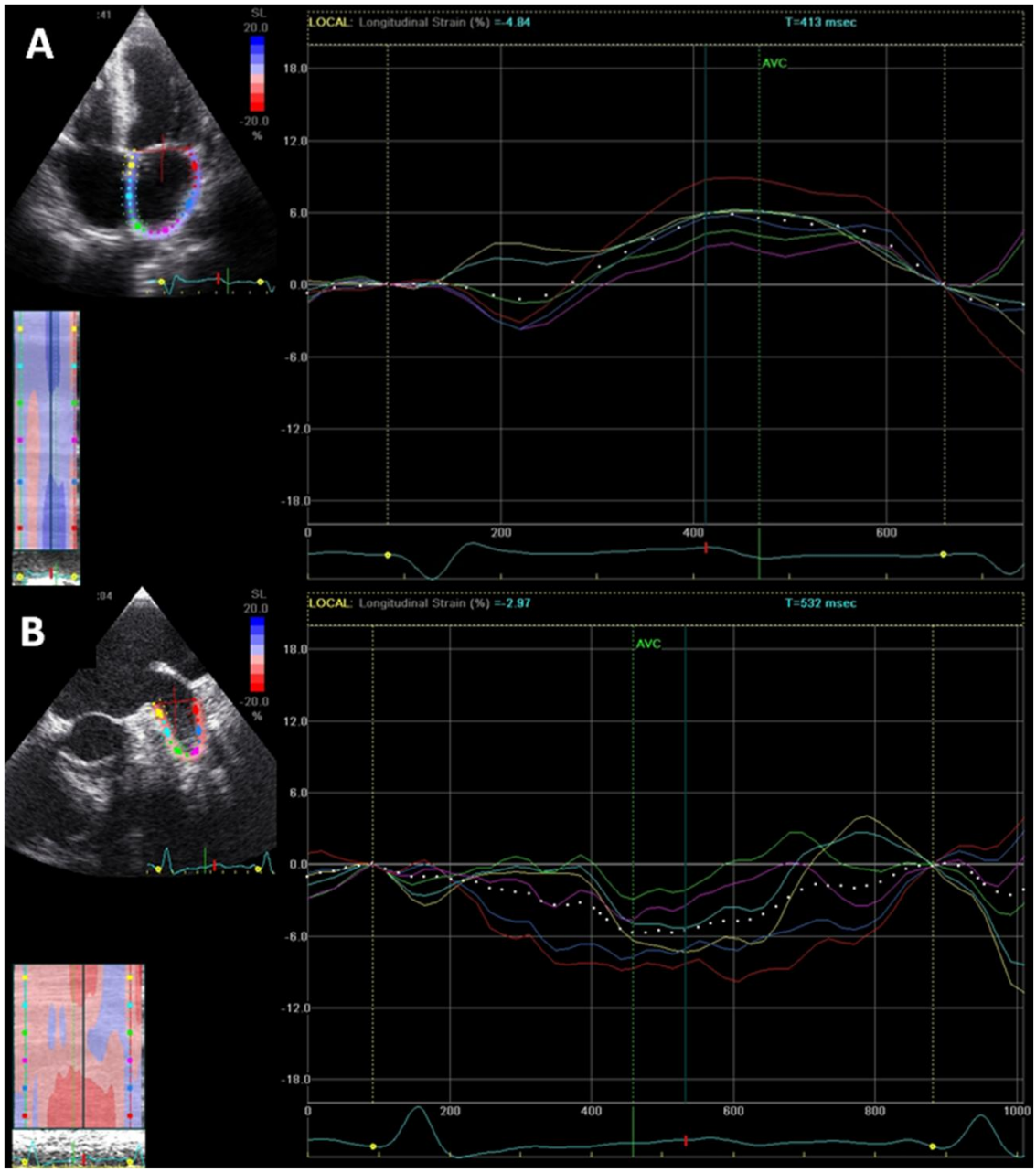

Figure 4 – The two panels illustrate the case of a patient with atrial fibrillation undergoing echocardiographic imaging as part of the pre-cardioversion work-up. **Panel A** (Transthoracic apical 4-chamber view) shows low peak positive left atrial strain values (average value of 6% measured with speckle tracking) in a patient with atrial fibrillation. **Panel B** illustrates a decreased peak negative left atrial appendage strain value (average value of -5%) alongside the presence of dense spontaneous echocardiographic contrast in a transesophageal echocardiogram (at 45º) performed on the same day.

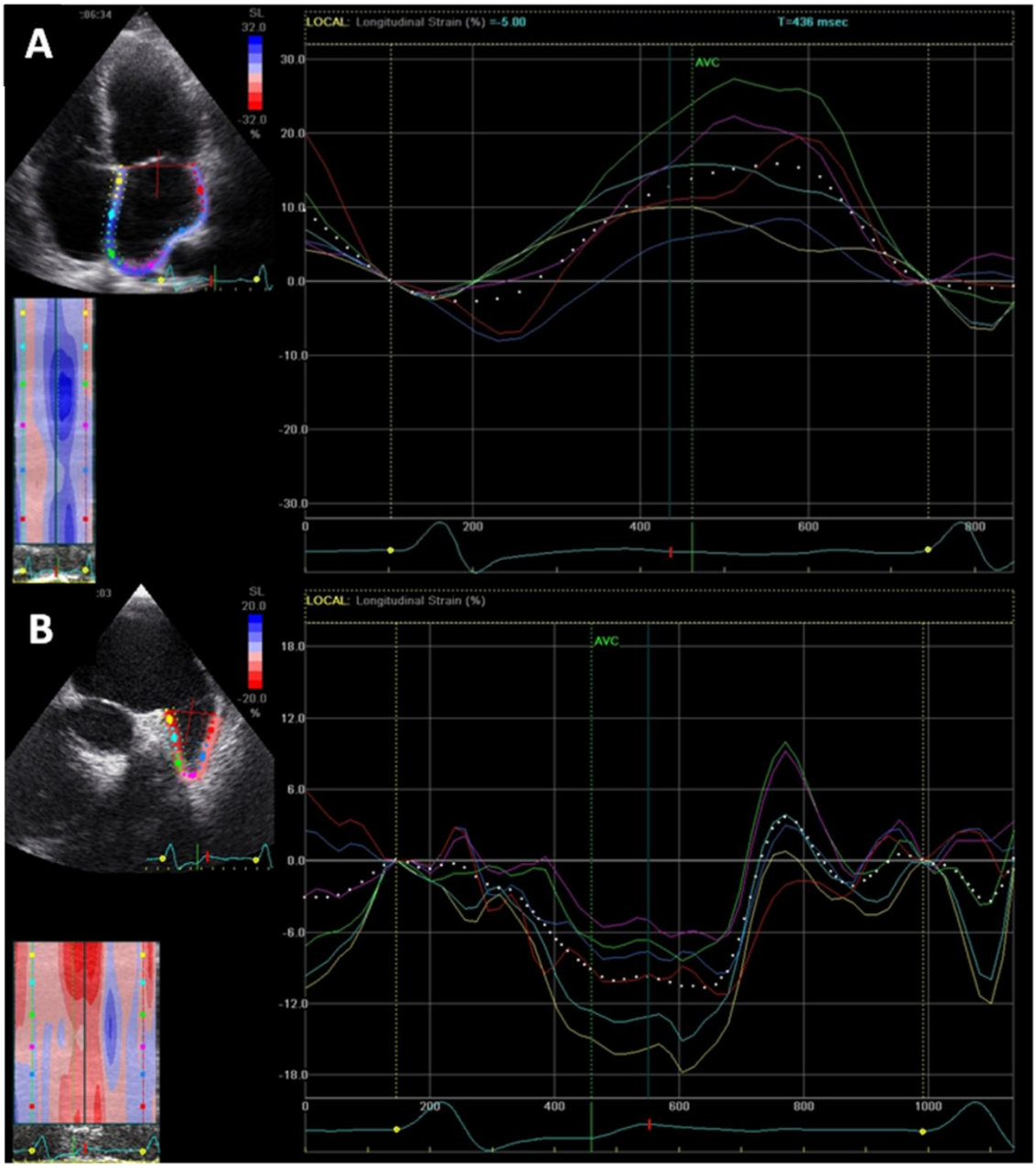

Figure 5 – These two images illustrate a patient undergoing echocardiographic assessment before cardioversion of atrial fibrillation and the information that can be retrieved using speckle tracking. **Panel A** shows a peak positive left atrial strain value that is higher (average of 15%) than that observed in the patient in Figure I. **Panel B** excludes the presence of a left atrial appendage thrombus and demonstrates a lower peak negative left atrial appendage strain value (average value -11%) at 45º transesophageal echocardiogram.

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Goal II.B

The Role of Biomarkers

II.B.1

Cardiac Troponin I: Prothrombotic Risk Marker in Non-valvular Atrial Fibrillation

Rui Providência, Luís Paiva, Ana Faustino, Ana Botelho, Joana Trigo, João Casalta-Lopes, José Nascimento, A.M. Leitão-Marques. Cardiac troponin I: prothrombotic risk marker in non-valvular atrial fibrillation. Int J Cardiol. 2013;167:877-882 doi: 10.1016/j.ijcard.2012.01.093

Abstract:

Background: Evidence of a link between small rises in cardiac troponin I (cTnI) and an increased risk of thromboembolic events (TE) in atrial fibrillation (AF) is currently scarce.

Objectives: We aimed to assess the relation between cTnI and findings of an increased thromboembolic risk in patients with non-valvular AF using transesophageal echocardiography.

Methods: We have included 245 patients performing transthoracic and transesophageal echocardiogram, alongside with laboratory assessment (including cTnI) in a cross-sectional survey. Changes associated to TE were sought on transesophageal echocardiogram: left atrial or left atrial appendage thrombus, dense spontaneous echocardiographic contrast, low flow velocities in the left atrial appendage and protuberant aortic plaques. Comparisons were performed according to the baseline concentration of cTnI, regarding the prevalence of these changes. We have added cTnI to $CHADS_2$ and CHA_2DS_2-VASc scores in order to assess its capability to refine risk stratification using transesophageal markers as surrogate endpoints and assessed it by means of ROC-curve analysis and Net Reclassification Improvement (NRI).

Results: A direct relation between rising concentrations of cTnI and a higher prevalence of transesophageal echocardiogram changes was found. Furthermore, the addition of cTnI to $CHADS_2$ and CHA_2DS_2-VASc scores improved their ability to predict changes associated to TE on transesophageal echocardiography both through ROC-curve analysis and NRI.

Conclusion: cTnI seems to be associated to thromboembolic risk in patients with AF. The possible role of cTnI in the refinement of risk stratification schemes needs to be tested in further prospective studies using clinical endpoints.

Keywords: atrial fibrillation; thromboembolism; stroke; cardiac troponin I; biomarkers; $CHADS_2$; CHA_2DS_2-VASc.

Introduction:

The use of biomarkers for risk stratification of patients with atrial fibrillation is a fastly expanding field of growing interest [(1)]. Cardiac Troponin I (cTnI) is a very sensitive marker of myocardial lesion which has been extensively studied in the diagnosis of acute myocardial infarction (AMI). However, detection of a small rise in cTnI is not a synonym of AMI, since it may increase in a range not consistent with this diagnosis reflecting cardiomyocite injury, with subsequent leakage of material, due to several other cardiac or non-cardiac conditions [(2)].

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia and thromboembolism is amongst its most serious complications [(3)]. Risk stratification for these events is currently managed on the basis of clinical risk scores: the $CHADS_2$ [(4)] or the CHA_2DS_2-VASc score [(3)]. Further improvement of these scores seems to be necessary since patients placed in low risk using $CHADS_2$ score still have a risk of thromboembolic events (patients with a $CHADS_2$ score = 0 have a 1.9% annual stroke risk) [(5)]. Conversely, despite being very sensitive for defining a truly low risk category, CHA_2DS_2-VASc tends to be very inclusive and places most patients under a category with an indication for oral anticoagulation [(6)]. These patients are therefore exposed to a higher risk of bleeding.

The presence of thrombi in the left atrium or left atrial appendage (LAAT) [(7)], dense spontaneous echocardiographic contrast (DSEC) [(7-9)], and low flow velocities (LFV) in the left atrial appendage [(7)] sought using transesophageal echocardiography are well known independent predictors of stroke and thromboembolism. When at least one of these is present, a situation defined by left atrial abnormality (LA ABN), an annual thromboembolism (TE) rate of 7.8% is expected, according to the SPAF III study. When aortic plaques are identified alongside with LA ABN the risk rises further to 12% [(9)].

Evidence of a link between small rises in cTnI and an increased risk of embolic events in AF, illustrated by these transesophageal echocardiogram markers is currently absent. Due to its overspread use and the fact that it reflects myocardial injury, this biomarker might be a suitable candidate for the refinement of the currently available risk stratification schemes.

Purpose:

We aimed to assess the relation between cTnI and findings of an increased thromboembolic risk in patients with non-valvular atrial fibrillation using transesophageal echocardiography.

Methods:

We have performed a cross-sectional study of 285 patients undergoing transesophageal echocardiogram assessment for AF cardioversion during a 24 months period. All patients had cTnI measured in the preceding 24 hours. Of these, 5 subjects had chest pain complaints and had a final diagnosis of non-ST elevation acute myocardial infarction, being therefore excluded from analysis. 35 patients were also removed from analysis due to valvular AF (10 had mitral valve stenosis, 11 had moderate or severe aortic stenosis and 14 had prosthetic valves or previous valve repair).

The remaining 245 patients were included for purpose of our study. All subjects provided their informed consent to undergo the necessary investigations and to allow the usage of their data for investigation purposes, preserving their anonymity.

Baseline overall group characterization with demographic, anthropometric, clinical, laboratory and echocardiographic data, alongside with information on medication were obtained for all patients. This data was retrieved from clinical records (outpatient clinic evaluations, emergency department and hospital ward admissions).

Blood samples were collected at admission in all patients. cTnI was measured using the Ortho-Clinical Diagnostics VITROS® Troponin I ES Assay. The lower limit of sensitivity and detection and the 99th percentile of this test were 0.012ng/mL and 0.034ng/mL, respectively. C-Reactive Protein (CRP) was measured using the CRP VITROS Chemistry Products assay. The lower limit of sensitivity was <0.5mg/dL and the reference interval for normal values was < 1.0mg/dL. A rise in cTnI and CRP was defined as the observed value over the lower limit of sensitivity (eg. 0.001ng/mL is the observed rise in cTnI in a patient with a value of 0.013ng/ml, assuming the 0.012ng/mL lower limit of sensitivity).

Transthoracic and transesophageal echocardiogram (TTE and TEE) were performed using a GE Vivid 7 echocardiograph alongside with a M4S (1.5–4.0 MHz) and a 6T phased array multiplane transoesophageal probe (2.9–7.0 MHz). All examinations were performed by two cardiologists with accreditation in transthoracic and transesophageal echocardiography by the European Society of Cardiology. TEE was performed without anesthesia or sedation in more than 95% of patients. Offline analysis was made possible using the GE Health Care EchoPac Dimension software, PC version 108.1.4. Left atrium volume was measured using the single-plane area length method [10, 11]. Left ventricle ejection fraction (LVEF) was qualitatively assessed and classified as normal, mildly, moderately, or severely depressed using the cutoff values defined in the guidelines [12, 13]. On TEE, the LA and LAA were imaged in different tomographic planes to detect the presence of LAA T and SEC. Spontaneous echo contrast was classified according to the classification (1 to 4+) proposed by Fatkin et al. [14]. Grade 3+ or 4+ was defined as DSEC. Left atrial appendage flow velocities were assessed with a pulsed Doppler sample placed 1 cm

from the entry of the LAA into the body of the LA. Maximum emptying and filling velocities were estimated from an average of five well-defined emptying and filling waves. Patients with maximum emptying and filling velocity ≤20 cm/s were classified as having low flow velocities (LFV). The thoracic aorta was examined according to the methods described by Amarenco et al [15] and plaques ≥ 4mm were designated as protuberant plaques (PP). The cardiologists performing the TTE and TEE were blind for the lab results and clinical information of the patients other than the fact that they were in AF and there was need for excluding TEE changes that could contraindicate cardioversion. TTE and TEE were performed after admission in the first 3 hours in 71.8% (n=176), 3 to 12 hours after in 19.6% (n=48) and 12 to 18 hours after admission in the remaining 8.6% (n=21).

Patients were divided into three groups according to the levels of cTnI: 112 patients had values < 0.012ng/mL, which were immeasurable (group A). Patients with measurable cTnI, ranging from 0.013 to 0.036ng/mL were placed on group B (n=66) and those with values from 0.037 to 0.163 were put on group B (n=67). Since no cutoff values exist in the literature for this purpose, we have arbitrarily decided to group all patients with immeasurable cTnI and distribute the remaining by two equally sized groups. Comparisons were performed for different variables according to the presence of LA ABN and the previously defined cTnI groups.

ROC curve analysis was performed for the prediction of the following TEE endpoints: LAAT, DSEC, LFV and LA ABN. $CHADS_2$ and CHA_2DS_2-VASc scores were assessed individually and alongside with refinement using cTnI values (0 points for cTnI < 0.012ng/mL, 1 point for cTnI 0.013 to 0.036ng/mL and 2 points for cTnI ≥ 0.037ng/mL).

Patient categorization with the aforementioned risk classifications schemes was further stratified into low, moderate and high risk: a low risk was defined as a score of “0” using $CHADS_2$, CHA_2DS_2-VASc and $CHADS_2$ plus cTnI and a score of “0 to 1” with CHA_2DS_2-VASc plus

cTnI. Moderate risk was defined as a score of "1" using $CHADS_2$, CHA_2DS_2-VASc and $CHADS_2$ plus cTnI and a score of "2 to 3" with CHA_2DS_2-VASc plus cTnI. High risk was defined as a score ≥ 2 using $CHADS_2$, CHA_2DS_2-VASc and $CHADS_2$ plus cTnI and a score ≥ 4 with CHA_2DS_2-VASc plus cTnI. Prevalence of TEE changes (LAAT, DSEC, LFV, LA ABN and PP) was compared according to the different risk categories using the different classifications.

Cross tabulation was performed between the different classification schemes (according to the level of risk that was estimated by each of them: low, intermediate or high), in order to elucidate the amount of patients migrating to higher or lower risk classes for each of the TEE endpoints. Net reclassification improvement (NRI) was calculated according to the method described by *Pencina et al.* [16] to quantify these reclassifications. A positive and significant NRI translates a net overall successful reclassification of subjects into more appropriate risk categories (e.g. a patient with a TEE endpoint that is reclassified from low risk with the initial risk classification into high risk with the new classification). The amount of overall reclassification is translated by the extent of the NRI, that represents a percent value. In this way, positive values for NRI represent an adequate reclassification into the right risk category, while a negative NRI represents a worse reclassification with the new risk stratification scheme.

PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis: comparison of nominal variables with chi-square test and Student's t-test and ANOVA were used for comparison of continuous variables, where appropriate; the Levene test was used in order to check the homogeneity of variance; equivalent non-parametric tests were used when Kolmogorov-Smirnov was in favor of absence of normal distribution. The overall tendency of increasing event rates with increasing risk score was tested using chi-square for trend (gamma). Receiver operating characteristic curves were traced for the prediction of LAA T,

dense SEC, low LAA velocities, and LA ABN using the four risk classification schemes. Results with $P < 0.05$ were regarded as significant.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [17].

Results:

The patients' baseline clinical, echocardiographic and analytic characteristics are shown on Table I. Average age was 67.4±11.9 years and 37.1% (n=91) of patients were female. $CHADS_2$ and CHA_2DS_2VASc were 2.1±1.2 and 3.6±1.8, respectively. Estimated glomerular filtration rate assessed by the modified diet in renal disease (MDRD) formula equation was 71.8±27.8ml/min. Out of the 78 subjects (31.8%) under oral anticoagulation, 39 (39.8%) had an INR value ≥ 2.0.In our sample we could identify 69.0% (n=169) subjects without LA ABN. The following TEE endpoints were found: LAAT in 8.2% (n=20), DSEC in 26.9% (n=66), LFV in 14.9% (30 out of 201), LA ABN in 31.0% (n=76) and PP in 19.7% (n=42).

1. **Differences according to changes found on TEE**

Table I illustrates comparisons performed between patients with and without LA ABN. Patients with LA ABN had a higher prevalence of congestive heart failure ($p<0.001$) and diabetes mellitus ($p=0.006$), more frequently had an AF lasting for over than a week ($p=0.005$), displayed higher $CHADS_2$ ($p=0.002$)and CHA_2DS_2-VASc ($p=0.005$) scores, were more frequently

medicated with oral anticoagulants (p=0.005), angiotensin converting enzyme inhibitors (ACE-i), angiotensin II receptor blocker (ARB-II) (p=0.008) and statins, had higher rise in cTNi (p=0.001) and CRP (p=0.031) and displayed a larger indexed left atrial volume (iLAV) (p<0.001), indexed LV diastolic diameter (iLV) (p=0.020) and more frequently an LVEF < 55% (p<0.001).

2. Comparisons according to the observed cTnI values

Using the previously specified cutoffs for the definition of three groups (group A - immeasurable cTnI; group B cTnI ≥ 0.013 to 0.036 ng/mL; group C cTnI ≥ 0.037ng/mL) comparisons were performed and are illustrated on Table II.

Subjects from group A had higher values of haemoglobin (p=0.005) and those from group C had a higher rise in CRP values (p<0.001). Estimated glomerular filtration rate using the MDRD equation progressively decreased with increasing values of cTnI (p=0.001). A larger dilatation of the left atrium and left ventricle (iLAV and iLV) (both p<0.001) was observed for increasing cTnI values.

The prevalence of LAA T, DSEC, LFV and LA ABN gradually increased alongside with cTnI values: Gamma = 0.484 (p=0.005) for LAAT; Gamma = 0.395 (p<0.001) for DSEC; Gamma = 0.439 (p=0.005) for LFV and Gamma = 0.363 (p<0.001) for LA ABN. Non significant changes were found for PP (p=0.438).

3. Role of cTnI in the refinement of risk stratification schemes

On Figure 1, ROC-curves can be seen illustrating the predictive ability of TEE changes using the different clinical risk stratification schemes (isolated and alongside with cTnI). The addition of cTnI to $CHADS_2$ and CHA_2DS_2-VASc score improved the observed AUC for the prediction of LAAT, DSEC, LFV and LA ABN.

Using the pre-specified cutoff values for defining low, moderate and high risk, we observed: 7.76% (n=19) low risk, 25.71% (n=63) moderate risk and 66.53% (n=163) high risk subjects using the $CHADS_2$ score. According to the CHA_2DS_2-VASc score, 3.7% (n=9) were considered low risk, 8.98% (n=22) moderate risk and 87.4% (n=214) high risk subjects. Using the $CHADS_2$ score plus cTnI, 7.8% (n=19) patients were categorized under low risk, 13.9% (n=34) as moderate risk and 81.2% (n=199) as high risk. If cTnI was added to CHA_2DS_2-VASc and the previously described cutoff values were used, 9.4% (n=23) would be classified as low risk, 20.0% (n=49) as moderate risk and 70.6% (n=173) as high risk.

Figure 2 displays the prevalence of TEE changes (LAAT, DSEC, LFV, LA ABN and PP) according to the level of predicted risk using the different risk classifications with and without cTnI.

Refinement of the $CHADS_2$ score using cTnI was not successful into reclassifying subjects into the risk category through NRI analysis: -1.44% of LAAT (p=0.437), -3.68% of DSEC (p= 0.252), 6.96% of LFV (p=0.228), -4.59% of LA ABN (p=0.192) and -9.09% of PP (p=0.048).

The addition of cTnI to CHA_2DS_2-VASc displayed a positive and significant NRI of 13.56% for the reclassification of LAAT (p=0.041), 18.28% for DSEC (p<0.001), 14.15% for LFV (p=0.035), 17.28% for LA ABN (p<0.001) and 19.44% for PP (p<0.001).

Discussion:

This study seems to indicate that small elevations of cTnI levels are markers of risk of thromboembolism in AF and that the magnitude of the cTnI elevation is directly associated to the probability of presenting TEE changes.

Still, our data also shows that in subjects with immeasurable cTnI levels, the risk of thromboembolism, despite being lower, is still present. In face of this low sensitivity, cTnI seems to be more adequate to use alongside with other variables, namely clinical parameters.

We think that this association may be explained by the fact that these small elevations in cTnI reveal underlying structural cardiac disease, that is known to be associated to an increased risk of thromboembolism, and may also be a manifestation of endothelial dysfunction and platelet activation, making the subject more prone to developing left atrial or left atrial appendage thrombi.

On the other side, we have shown that the addition of cTnI to the currently available clinical risk stratification schemes further improves their predictive power: it can improve $CHADS_2$ sensitivity and CHA_2DS_2-VASc specificity, preserving its very high sensitivity.

The high sensitivity of CHA_2DS_2-VASc for detecting low risk individuals is well demonstrated in this cohort of patients where in those categorized as low risk no TEE changes were found, confirming that they are truly at low risk. This has previously been demonstrated in a large nationwide cohort study [18]. Still, we have observed that CHA_2DS_2-VASc tends to classify most patients into the high risk category, at expense of a low specificity. This opens room for new risk stratification schemes that can preserve CHA_2DS_2-VASc superior sensitivity and further improve its specificity.

Recently, the combination of clinical risk markers and a biomarker (CRP) has been suggested as a way of detecting LAAT and DSEC in low risk patients [19]. Our data (see Table I) also seems to

support this association, with patients with LA ABN displaying a higher rise in CRP. The combination of transthoracic echocardiogram parameters (left atrial area and LVEF) and conventional clinical risk stratification schemes has also been proposed as a way of refining risk assessment of these patients [20].

Preliminary results of the biomarkers' sub-study of The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial [21] have shown promising results, not only for cTnI [22] but also for NTproBNP [23], supporting a role for biomarkers in refinement of risk stratification.

Despite the fact that these parameters still need to be validated for clinical endpoints in order to confirm their acuity and widespread applicability, we are led into believing that more sophisticated risk stratification schemes combining clinical parameters, alongside with biomarkers and echocardiographic parameters may be proposed in the near future.

Study Limitations:

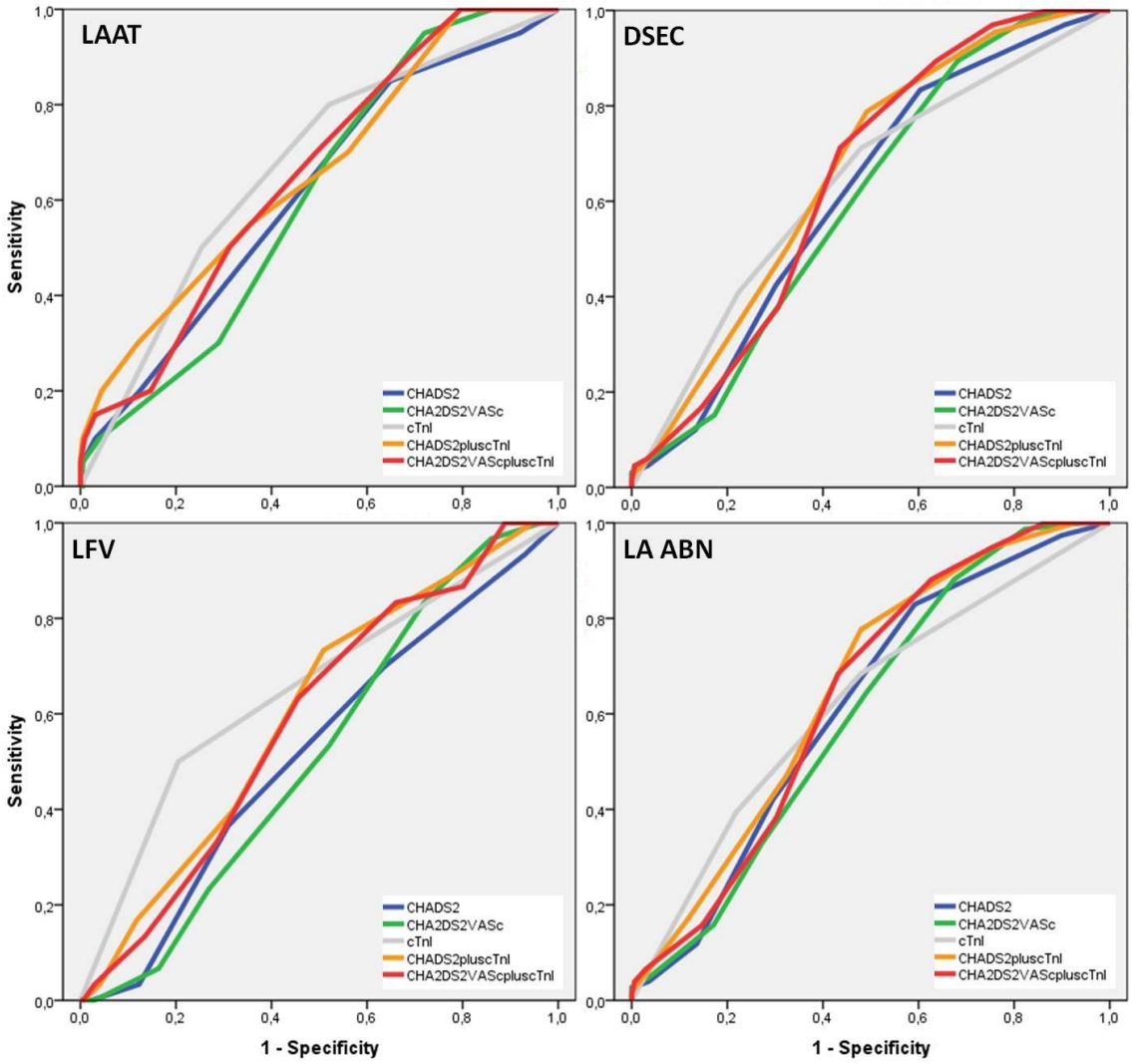
We recognize that the fact of some patients being under oral anticoagulation may have had some impact in the study's results. Still, since nowadays more and more patients are under anticoagulant treatment, it would be difficult or even unethical to include a reasonable number of non-anticoagulated patients. Moreover, we think that a treated population is more representative of the subjects observed in our everyday practice. The impact of anti-thrombotic treatment can be assessed in Tables I and II, where similar INR values and % of patients with therapeutic INR over 2.0 could be found among different comparisons. Still, despite presenting equal INR values, individuals with LA ABN were more frequently under oral anticoagulation.

In a not negligible number of patients (44 out of 245; 17.9%) echocardiographic data was classified as unsuitable for accurate assessment of LAA flow velocities or the patients did not tolerate the probe and therefore TEE was performed without measurement of LAA flow velocities when the presence of LAAT and DSEC could be excluded right away. We do not think that this had any real influence, since the observed results for LFV are similar to what was found with the other TEE endpoints.

Conclusions:

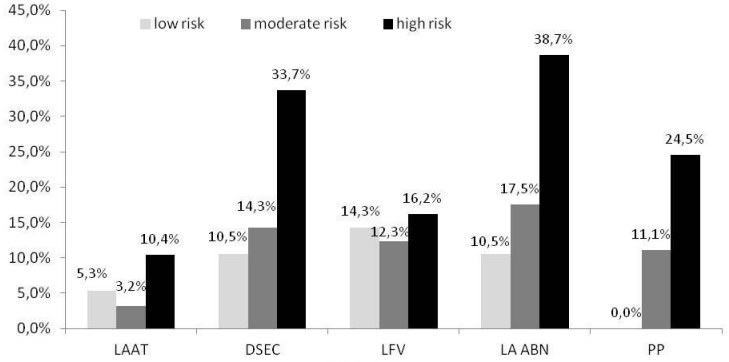
We have demonstrated a relation between rising concentrations of cardiac troponin I and a higher prevalence of transesophageal echocardiogram changes that are associated to an increased risk of thromboembolic events in patients with non-valvular atrial fibrillation. Regarding a possible role of cardiac troponin I in the refinement of the available clinical risk stratification schemes, further prospective studies using clinical endpoints still have to be conducted in order to assess and validate this hypothesis that was raised by using surrogate transesophageal markers.

Figure 1 – ROC-curves illustrating the predictive ability of the $CHADS_2$ and CHA_2DS_2-VASc score (isolated and plus cardiac troponin I) for the detection of transesophageal echocardiogram changes.

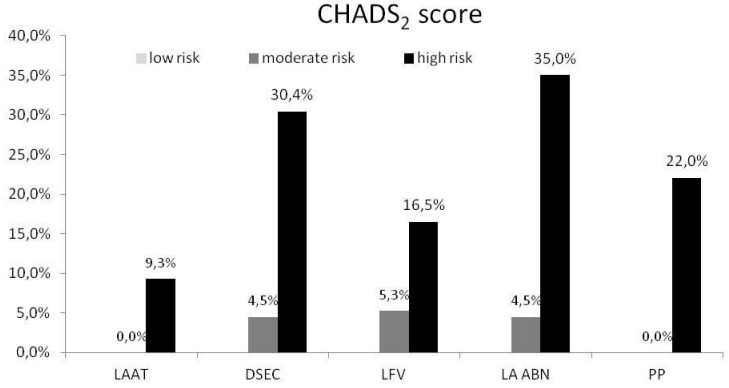


Legend: LAAT – left atrium or left atrial appendage thrombus; DSEC – dense spontaneous echocardiographic contrast; LFV – low flow velocities (maximum value ≤ 20cm/s); LA ABN – left atrial abnormality; PP – protuberant aortic plaque. ROC curves for LAAT: $CHADS_2$ AUC 0.614 ($CI_{95\%}$ 0.490-0.738; p = 0.046), CHA_2DS_2-VASc AUC 0.608 ($CI_{95\%}$ 0.501-0.715; p = 0.055), cTnI AUC 0.669 ($CI_{95\%}$ 0.549-0.788; p = 0.012), $CHADS_2$ plus cTnI AUC 0.658 ($CI_{95\%}$ 0.536-0.779; p =0.001) and CHA_2DS_2-VASc plus cTnI AUC 0.653 ($CI_{95\%}$ 0.542-0.763; p=0.012). ROC curves for DSEC: $CHADS_2$ AUC 0.611 ($CI_{95\%}$ 0.536-0.685; p = 0.004), CHA_2DS_2-VASc AUC 0.601 ($CI_{95\%}$ 0.528-0.674; p = 0.008), cTnI AUC 0.635 ($CI_{95\%}$ 0.556-0.713; p = 0.001), $CHADS_2$ plus cTnI AUC 0.659 ($CI_{95\%}$ 0.589-0.730; p <0.001) and CHA_2DS_2-VASc plus cTnI AUC 0.643 ($CI_{95\%}$ 0.574-0.713; p<0.001). ROC curves for LFV: $CHADS_2$ AUC 0.520 ($CI_{95\%}$ 0.414-0.627; p = 0.361), CHA_2DS_2-VASc AUC 0.517 ($CI_{95\%}$ 0.421-0.614; p = 0.381), cTnI AUC 0.651 ($CI_{95\%}$ 0.538-0.765; p = 0.008), $CHADS_2$ plus cTnI AUC 0.603 ($CI_{95\%}$ 0.502-0.704; p = 0.036) and CHA_2DS_2-VASc plus cTnI AUC 0.589 ($CI_{95\%}$ 0.489-0.689; p=0.060). ROC curves for LA ABN: $CHADS_2$ AUC 0.614 ($CI_{95\%}$ 0.542-0.686; p = 0.002), CHA_2DS_2-VASc AUC 0.601 ($CI_{95\%}$ 0.530-0.672; p = 0.006), cTnI AUC 0.622 ($CI_{95\%}$ 0.546-0.698), $CHADS_2$ plus cTnI AUC 0.653 ($CI_{95\%}$ 0.583-0.722; p < 0.001) and CHA_2DS_2-VASc plus cTnI AUC 0.638 ($CI_{95\%}$ 0.568-0.707; p < 0.001).

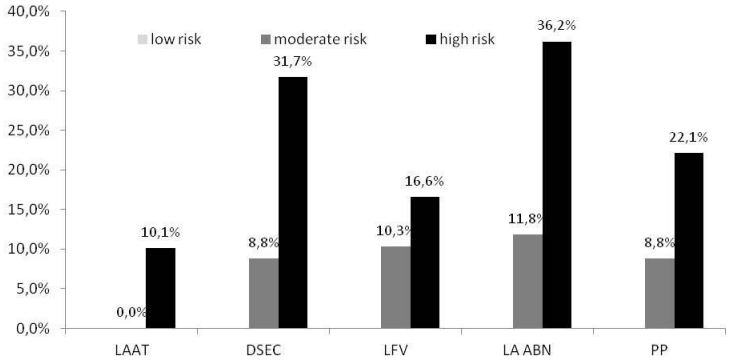
Figure 2 – Prevalence of changes on transesophageal echocardiogram among the different risk categories defined by the risk classification schemes with and without the addition of cardiac troponin I.



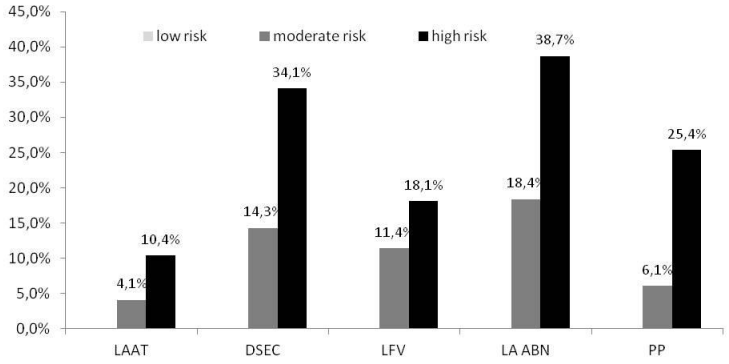
$CHADS_2$ score



CHA_2DS_2-VASc score



$CHADS_2$ score plus cTnI



CHA_2DS_2-VASc score plus cTnI

Legend: LAAT – left atrium or left atrial appendage thrombus; DSEC – dense spontaneous echocardiographic contrast; LFV – low flow velocities (maximum value ≤ 20cm/s); LA ABN – left atrial abnormality; PP – protuberant aortic plaque; cTnI – cardiac troponin I.

Table I – Population baseline characteristics and sub-analysis according to the presence of left atrial abnormality.

	Overall (n=245)	With LA Abn (n= 76)	Without LA Abn (n= 169)	P
Demographics				
Age	67.36±11.93	69.20±8.40	66.53±13.15	0.240
♀	37.14% (91)	42.11% (32)	34.91% (59)	0.141
Body Mass Index (Kg/m^2)	28.99±4.45	28.68±4.03	29.16±4.66	0.528
Clinical Data				
Congestive heart failure	49.00% (120)	64.47% (49)	42.01% (71)	<0.001
Hypertension	82.45% (202)	86.84% (66)	80.47% (136)	0.113
Diabetes mellitus	22.86% (56)	32.89% (25)	18.34% (31)	0.006
Stroke or TIA	13.06% (32)	15.79% (12)	11.83% (20)	0.198
Vascular disease [a]	48.16% (118)	52.63% (40)	46.15% (78)	0.174
AF episode duration > 1 week	74.29% (182)	84.21% (64)	69.82% (118)	0.005
$CHADS_2$ score	2.10±1.24	2.41±1.12	1.96±1.26	0.002
CHA_2DS_2-VASc score	3.63±1.77	4.09±1.47	3.42±1.85	0.005
Medication				
Oral anticoagulants	31.84% (78)	43.42% (33)	26.63% (45)	0.005
Antiplatelet agents	49.80% (122)	43.42% (33)	52.66% (89)	0.091
ACE-i or ARB-ii	71.02% (174)	81.58% (62)	66.27% (112)	0.008
Statin	38.78% (95)	50.00% (38)	33.73% (57)	0.008
Laboratory Assessment				
Haemoglobin (g/dL)	13.81±1.81	13.83±1.48	13.80±1.94	0.885
Platelets (10^3/uL)	218.85±82.65	213.40±67.48	221.26±88.66	0.671
INR	1.36±0.64	1.39±0.60	1.34±0.65	0.106
INR ≥ 2.0	15.92% (39)	18.42% (14)	14.79% (25)	0.478
Rise in cTnI (ng/mL)	0.2311±0.0709	0.0427±0.1201	0.0143±0.0245	0.001
Rise in CRP (mg/dL)	1.13±3.00	1.44±3.64	0.99±2.67	0.031
Estimated GFR using MDRD (ml/min)	71.78±27.83	71.91±28.91	71.72±27.41	0.948
Echocardiographic characterization				
Indexed left atrial volume (ml/m^2)	59.40±22.69	69.41±24.07	54.83±20.55	<0.001
Indexed LV diastolic diameter (mm/m^2)	30.02±5.43	31.26±5.53	29.36±5.29	0.020
LV Ejection Fraction < 55%	25.71% (63)	42.11% (32)	18.34% (31)	<0.001

Legend: TIA – transient ischemic attack; AF – atrial fibrillation; ACE-i - angiotensin converting enzyme inhibitor; ARB-II – angiotensin II receptor blocker; INR – international normalized ratio; cTnI – cardiac troponin I; CRP –C reactive protein; GFR – glomerular filtration rate; MDRD – modified diet in renal disease formula; LV – left ventricle.

[a] vascular disease is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque.

Table II – Comparison of demographic, clinical, analytical and echocardiographic variables according to level of cardiac troponin I changes.

	cTnI 0 ng/mL (n=112)	cTnI 0.013 to 0.036 ng/mL (n=66)	cTnI ≥0,037ng/mL (n=67)	P
Age	65.78±13.23	69.29±11.38	68.09±9.76	0.324
♀	33.93% (38)	46.97% (31)	33.33% (22)	0.153
Congestive heart failure	43.75% (49)	50.0% (33)	56.72% (38)	0.120
Hypertension	80.36% (90)	81.82% (54)	86.57% (58)	0.283
Diabetes mellitus	22.32% (25)	18.18% (12)	28.36% (19)	0.370
Previous stroke or TIA	9.82% (11)	16.67% (11)	14.93% (10)	0.185
Vascular disease [a]	51.79% (58)	34.85% (23)	55.22% (37)	0.037
AF episode duration > 1 week	68.75% (77)	78.79% (52)	79.10% (53)	0.076
$CHADS_2$ score	1.98±1.26	2.14±1.24	2.25±1.20	0.140
CHA_2DS_2-VASc score	3.49±2.00	3.64±1.66	3.76±1.33	0.306
Oral anticoagulants	30.36% (34)	31.82% (21)	34.33% (23)	0.430
Antiplatelet agents	50.89% (57)	45.45% (30)	52.24% (35)	0.701
ACE-i or ARB-II	68.75% (77)	75.76% (50)	70.15% (47)	0.599
Statin	30.04% (37)	43.94% (29)	43.28% (29)	0.119
Rise in troponin I (ng/mL)	0	0.0094±0.0076	0.0752±0.1211	<0.001
Rise in C-reactive protein (mg/dL)	0.88±2.81	0.87±2.16	1.82±3.84	<0.001
Estimated GFR using MDRD (ml/min)	78.44±25.57	71.21±30.08	61.45±26.19	0.001
Platelets (10^3/uL)	217.20±67.18	237.86±112.94	203.06±66.60	0.067
Haemoglobin (g/dL)	14.23±1.80	13.41±1.65	13.52±1.85	0.005
INR	1.36±0.65	1.26±0.51	1.43±0.71	0.201
INR ≥ 2.0	17.86% (20)	10.61% (7)	17.91% (12)	0.416
Indexed left atrial volume (ml/m^2)	51.53±19.88	61.93±23.10	66.31±22.96	<0.001
Indexed LV diastolic diameter (mm/m^2)	28.65±4.72	29.32±5.36	32.30±5.69	<0.001
LV Ejection Fraction < 55%	21.43% (24)	27.27% (18)	31.34% (21)	0.161
LAA max. emptying velocity (cm/s)	34.15±13.97	30.81±16.12	30.84±19.40	0.024
LAA max. filling velocity (cm/s)	39.23±16.80	39.41±17.14	33.50±17.14	0.066
LAAT	3.57% (4)	9.10% (6)	14.93% (10)	0.013
DSEC	16.96% (19)	30.30% (20)	40.30% (27)	0.001
LFV	9.68% (9)	10.34% (6)	30.0% (15)	0.002
LA ABN	21.43% (24)	33.33% (22)	44.78% (30)	0.002
PP	17.86% (20)	19.70% (13)	20.90% (14)	0.438

Legend: TIA – transient ischemic attack; AF – atrial fibrillation; ACE-i - angiotensin converting enzyme inhibitor; ARB-II – angiotensin II receptor blocker; cTnI – cardiac troponin I; CRP –C reactive protein; GFR – glomerular filtration rate; MDRD – modified diet in renal disease equation; INR – international normalized ratio; LV – left ventricle; LAA – left atrial appendage; LAAT – left atrium or left atrial appendage thrombus; DSEC – dense spontaneous echocardiographic contrast; LFV – low flow velocities (maximum value ≤ 20cm/s); LA ABN – left atrial abnormality; PP – protuberant aortic plaque.

[a] vascular disease is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque.

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II.B.2

Atrial fibrillation, elevated troponin, ischemic stroke and adverse outcomes: understanding the connection.

Rui Providência, Sérgio Barra, Luís Paiva. Atrial fibrillation, elevated troponin, ischemic stroke and adverse outcomes: understanding the connection. Clin Res Cardiol 2013;102(10):701-11.
doi: 10.1007/s00392-013-0591-0.

Abstract

Cardiac troponin is widely used for the diagnosis of acute myocardial infarction. In addition to this indication, the elevation of troponin has been found to play a prognostic role in ischemic stroke. It is hypothesised that approximately 15 to 20% of all ischemic strokes are associated with atrial fibrillation and that these events are more often fatal. Recent studies have demonstrated that troponin elevation can also be used as a prognosticator in patients with atrial fibrillation and for risk stratification to predict which patients are more prone to stroke or other thromboembolic events. Therefore, troponin appears to play a pivotal role in the overlap of atrial fibrillation and ischemic stroke and the subsequent development of an adverse outcome. The different aspects of this association will be addressed and novel explanations will be proposed to better clarify the underlying mechanisms.

Keywords: atrial fibrillation; troponin; ischemic stroke; death; prognosis;

Introduction

Medicine in the XXI century is strongly based on the use of biomarkers. In particular, cardiac troponin is currently widely used for the diagnosis of acute myocardial infarction. However, an elevation in the troponin level is also been found in other disease states, such as heart failure, chronic kidney disease, sepsis, ischemic stroke and atrial fibrillation (AFib) [1]. In all of these cases, the troponin elevation is associated with a worse outcome. AFib is the most common type of sustained arrhythmia and is highly prevalent in patients with ischemic stroke [2]. Therefore, a close connection appears to exist not only between AFib and stroke but also between elevated troponin levels and an adverse prognosis.

The following sections will separately explain the different aspects of this interplay and new mechanisms that link all of these elements will be proposed.

1. Cardiac troponin: basics and current applications

Troponin I (cTnI), troponin T (cTnT) and troponin C form part of the troponin-tropomyosin complex, which is situated on the thin filament of striated muscle and thus plays an important role in muscle contraction. Unlike troponin C, cTnI and cTnT have high cardiac specificity and are known as cardiac troponins. It is known that cTnI binds to actin and that cTnT binds to tropomyosin. Although these proteins are bound to myofibrils, approximately 4 to 8% of these proteins can be found in the cytosol [3]. Despite some small differences, the diagnostic and prognostic efficacies of cTnI and cTnT appear to be comparable [4].

It is still debated whether cytosolic troponin can be released in the absence of necrosis, which would represent reversible injury. Nevertheless, the detection of cardiac troponin in the peripheral blood always indicates cardiomyocyte injury [5]. In almost all cases, this injury should be interpreted as a sign of an underlying structural or functional cardiovascular disease, and thus the detection of cardiac troponin in the peripheral blood has prognostic impact [1].

According to the Universal definition of myocardial infarction (2007), an elevation of the cTnI or cTnT levels above the 99th percentile of the upper reference limit of a control population can be used as a cutoff for the diagnosis of acute myocardial infarction [6]. However, these levels can be elevated in several other conditions and not just in acute myocardial infarction[1].

2. Elevated troponin and cardiac changes during acute ischemic stroke

Ischemic changes on the ECG have been shown to occur during acute cerebrovascular events: these were initially described in subarachnoid haemorrhage and were later reported in ischemic stroke [7, 8].

The release of cardiac enzymes (CK-Mb) during acute ischemic stroke has been described since the late 1970's [9]. The earlier reports on the association between the troponin levels and the prognosis of ischemic stroke were published over a decade ago [10, 11] (Table 1). Nevertheless, conflicting results have been found by various studies that have assessed the efficacy of using cardiac troponin as a prognostic marker for acute ischemic stroke [10, 12-13]. A major limitation of these studies was the lack of routine coronary angiograms that should have been performed to exclude the presence of coronary artery disease. This issue will be

addressed and clarified in the upcoming “Troponin elevation in acute ischemic stroke” (TRELAS) trial [14].

In 2009, a systematic review of 15 articles of stroke patients (11 of the studies included only patients with ischemic stroke) found an overall prevalence of positive troponin levels in 18.1% ($CI_{95\%}$ = 13.6-22.6%) of the patients. The studies described a high likelihood of ECG changes compatible with myocardial ischemia (OR = 3.0 and $CI_{95\%}$ = 1.5-6.2) and the occurrence of death (OR = 2.87 $CI_{95\%}$ = 1.72-4.78) and death or disability (OR = 2.31 $CI_{95\%}$ = 0.91-5.86) was described in these patients [15].

The most frequent explanation for the association of elevated cardiac troponin levels and ischemic stroke is the following: ischemic stroke may lead to sympathoadrenal activation with a massive temporary release of catecholamines, which leads to myocardial changes [16], myocytolysis [17] and subsequent release of troponin into the bloodstream.

This activation is thought to occur more frequently in the presence of insular cortex damage. It has been shown that insular involvement is associated with a more frequent occurrence of cardiac complications due to a loss of central inhibitory control, which leads to an increased sympathetic tone [18]. This results in an increased heart rate and blood pressure, impairment of the autonomic control of the heart rate variability and QT prolongation [19]. An additionally increased risk of cardiac arrhythmias has also been proposed in patients with right insular damage [17]. The increased cTnI level in patients with ischemic stroke has been associated with elevated circulating levels of epinephrine [17]. This finding, in addition to the fact that beta-blockade can prevent this damage [20], appears to support the abovementioned hypothesis.

Other possible mechanisms that may mediate this association are the coexistence of coronary artery disease (that may have been previously silent and asymptomatic), pulmonary embolism, heart failure and renal failure, which are known to be associated with troponin elevation.

Myocardial stretch (an acute change in the sarcomere length and subsequent myocardial damage) [21], cardioembolic cerebral ischemia due to myocardial disease and cerebral disease-related heart failure [22] are also thought to play a role in this association.

On autopsy, these ECG changes and troponin elevations can be correlated either with the presence of myocardial myocytolysis or with a lack of changes [23-24].

It is hypothesised that approximately 15 to 20% of all ischemic strokes are associated with AFib [25]. Ischemic stroke in patients with AFib is more often fatal than ischemic stroke in patients without AFib [26].

In a prospective study of 408 patients with ischemic stroke or transient ischemic attack (TIA), new onset AFib was found either through ECG or 24-hour Holter monitoring in 12.5% of the patients (n=51) and was more frequent in those patients with an elevated cTnI level of greater than 0.03 ug/L (34.7% compared with 9.7%; p = 0.004 through multivariate analysis). This finding may either represent a new-onset arrhythmia due to neurogenic-induced cardiac injury (stress-related cardiomyopathy) or a previously undiagnosed AFib. These authors also found an association between an elevated troponin level and the following endpoints, which were assessed 90 days after admission: death, myocardial infarction and disability, according to the modified Rankin Scale [27].

In addition to AFib, cardiac arrhythmogenesis following ischemic stroke (mostly in the presence of insular involvement [28]) can also be translated as multifocal ventricular beats, couplets and unsustained ventricular tachycardia [29]. However, these changes appear to be more frequent in the presence of subarachnoid haemorrhage [30].

As part of stress-related cardiomyopathy (SRC), wall motion abnormalities can also be found in ischemic stroke. There appears to be a broad distribution of wall motion changes, although global left ventricle dysfunction and apical-sparing left ventricle dysfunction predominate [31]. These changes that occur in the absence of obstructive coronary artery disease appear to be mediated by catecholamine, are not dependent on a single coronary territory and have a female preponderance.

Despite some degree of overlap between SRC in ischemic stroke and Takotsubo cardiomyopathy, there are some differences that should be highlighted. Unlike in SRC, most patients with Takotsubo cardiomyopathy exhibit apical and midventricular wall motion abnormalities. In addition, the most frequent ECG changes in SRC are deep negative T waves, whereas ST-segment elevation predominates in Takotsubo cardiomyopathy.

3. Elevated troponin in atrial fibrillation

Studies focusing on elevated troponin levels in AFib have focused on three different settings: patients with AFib documented through the ECG administered upon hospital admission, risk stratification of patients with AFib followed in an outpatient clinic and patients with AFib undergoing transesophageal echocardiogram. Because there are differences between these patients, these studies will be described separately (Table 2). In all of these investigations, patients with recent ST-elevation acute myocardial infarction events were excluded from the analysis.

3.1. Troponin in patients with atrial fibrillation upon hospital admission

Van den Bos and colleagues [32] studied a cohort of 407 consecutive patients admitted to the cardiology ward or coronary care unit with AFib, as determined based on the ECG administered upon admission. These researchers studied the patients during a 2-year follow-up period (median duration = 688 days) and found minor elevations in the cTnI level (below the 99th percentile of the upper reference limit) in 81 patients, which was 20% of the cohort studied. These patients had a median cTnI level of 0.31 ng/mL. These minor elevations in the cTnI level were independently associated with death (HR = 2.35 and $CI_{95\%}$ = 1.17-4.73), a combined endpoint of death/acute myocardial infarction (HR = 1.99 and $CI_{95\%}$ = 1.05-3.80) and major adverse cardiac events (mortality, acute myocardial infarction and revascularisation) (HR = 2.48 and $CI_{95\%}$ = 1.33-4.63). The event rates were even higher in the 77 patients (19% of the sample) with a positive cTnI level greater than ≥ 0.65 ng/mL (median level = 3.41 ng/mL): death (HR = 3.77 and $CI_{95\%}$ = 1.42-10.02), death/acute myocardial infarction (HR = 3.03 and $CI_{95\%}$ = 1.24-7.37) and major adverse cardiac events (HR = 5.60 and $CI_{95\%}$ = 2.40-13.07) [32].

Van den Bos et al proposed five mechanisms that could account for the cTnI released in patients with AFib [32]: (1) increased myocardial oxygen demand independent from the presence of epicardial coronary stenosis (type 2 myocardial infarction), (2) reduced coronary flow despite the greater demand due to alterations in coronary resistance in AFib, (3) co-existence of a fixed coronary artery stenosis (documented in 28% of the patients), (4) increase in left ventricular wall strain due to fast ventricular response and shorter diastolic filling times or due to a reduction in the cardiac output and fluid retention and (5) acute thrombotic coronary event with pre-existing AFib or AFib caused by acute ischemia. Other plausible mechanisms suggested by these authors included cTnI proteolysis due to endothelial damage or the neurohumoral and inflammatory response.

3.2. Troponin for risk stratification of atrial fibrillation

Classifications, such as the $CHADS_2$ [33] and CHA_2DS_2-VASc [34] scores, have been proposed and are used in daily clinical practice to decide which patients with AFib should be subjected to oral anticoagulation [35]. The $CHADS_2$ score is based on clinical data from the patient's history, namely the presence of congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus and previous stroke or transient ischemic attack (TIA). The CHA_2DS_2-VASc score was recently developed to refine risk stratification for predicting stroke and thromboembolism in patients with AFib. The major improvements were the assignment of 2 points to definitive risk factors (e.g., previous stroke, TIA or thromboembolism, and age ≥ 75 years) and 1 point to combination risk factors (e.g., heart failure or moderate to severe cardiac dysfunction, hypertension, diabetes mellitus, vascular disease, female gender and age = 65 to 74 years).

The CHA_2DS_2-VASc score successfully identifies a truly low risk group of patients with an annual stroke risk of 0% [34]. Unfortunately, this score tends to be very inclusive and recommends that a very high percentage of subjects be subjected to oral anticoagulation.

Despite their ease of use and all of the featured advances and developments, these risk scores have shown limited capability to predict thromboembolic events (with c-statistics in the range of 0.54 to 0.65) [34-37].

In the "Randomised Evaluation of Long Term Anticoagulant Therapy" (RE-LY) trial, the superiority of dabigatran over warfarin for the prevention of stroke was clearly demonstrated: 110 mg bid with most benefits on the safety side, e.g., decreases in major bleeding, intracranial bleeding and haemorrhagic stroke, and 150 mg bid with superior efficacy, e.g., decreases in ischemic stroke, stroke/systemic embolism, along with less intracranial bleeding and haemorrhagic stroke [38]. A recently published sub-analysis of this trial, which comprised

6,189 patients studied during a median follow-up period of 2.2 years, assessed the prevalence of cTnI elevation and its role in the risk stratification of patients with AFib [40]. A high prevalence of detectable (≥ 0.010 μg/L in 57.0% of patients; n=3,526) and elevated (≥ 0.020 μg/L in 24.6% of patients; n=1,520) levels of cTnI was found. The rates of stroke and vascular mortality were independently associated with the levels of cTnI: 2.09%/year and 6.56%/year, respectively, in patients with cTnI ≥ 0.040 μg/L compared with 0.84%/year and 1.04%/year, respectively, in patients with cTnI < 0.010 μg/L (HR = 1.99 and $CI_{95\%}$ = 1.17-3.39 and HR = 4.38 and $CI_{95\%}$ = 3.05-6.29, respectively).

The measured levels of cTnI added prognostic information beyond the $CHADS_2$ and CHA_2DS_2-VASc scores, which resulted in a significant increase in the c-statistics, both for the prediction of stroke and systemic embolism and for the prediction of the composite thromboembolic outcome (stroke, systemic embolism, pulmonary embolism, myocardial infarction and vascular death; haemorrhagic death was excluded). Hijazi and colleagues highlighted the role of cTnI in the definition of low risk because patients with a $CHADS_2$ score in the range of 0 to 1 and elevated levels of cTnI exhibited a higher annual rate of a combination of thromboembolic events compared with patients with higher $CHADS_2$ scores and undetectable levels of cTnI. Moreover, the possibility of reclassifying patients with higher $CHADS_2$ scores and undetectable cTnI levels as low risk was also addressed. The authors also proposed that a third group of patients, who exhibited a high clinical risk of thromboembolic events and positive cTnI should receive other treatment options beyond oral anticoagulation, such as intensified pharmacological treatment (e.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers or statins), left atrial appendage closure and left atrial volume reduction. Furthermore, according to these authors, the risk stratification of coronary artery disease may be advisable for this group [39].

Similar results were obtained in a cohort study performed by Roldán and colleagues [40]. These researchers studied 930 patients under oral anticoagulation and followed them for a period of 2 years. The high sensitivity troponin T that was measured in these patients was an independent predictor of stroke (HR = 2.37 and $CI_{95\%}$ = 1.08-5.02 and HR = 2.44 and $CI_{95\%}$ = 1.13-5.26 in models including the $CHADS_2$ and CHA_2DS_2-VASc scores, respectively), adverse cardiovascular events (combined endpoint: stroke/TIA, systemic embolism, acute coronary syndrome, acute heart failure and cardiac death; HR = 1.67 and $CI_{95\%}$ = 1.09-2.56 and HR = 1.68 and $CI_{95\%}$ = 1.10-2.57, in models including the $CHADS_2$ and CHA_2DS_2-VASc scores, respectively) and mortality (HR = 1.79 and $CI_{95\%}$ = 1.13-2.83 and HR = 1.99 and $CI_{95\%}$ = 1.25-3.20, in models including the $CHADS_2$ and CHA_2DS_2-VASc scores, respectively).

In the "Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation" (ARISTOTLE) trial, apixaban was found to exhibit superior ability in the reduction of ischemic /haemorrhagic stroke/systemic embolism (the primary endpoint) and haemorrhagic stroke, major bleeding and death from any cause compared with warfarin [41]. Preliminary data from the 14,979 ARISTOTLE patients who underwent high-sensitivity troponin T measurement at randomization also appears to provide evidence that supports the role of troponin as a useful biomarker for the refinement of the clinical risk stratification of patients with AFib. Due to the nature of the troponin assay (lower limit of detection = 1.5 ng/L), detectable levels of this marker were found in 73% of the patients. The troponin levels were continuously associated with the risk of stroke and death. The highest rate of events was observed in patients with troponin levels over the 99^{th} percentile upper reference limit (>13 ng/L): HR = 1.86 and $CI_{95\%}$ = 1.36-2.56 for stroke or systemic embolism and HR = 3.84 and $CI_{95\%}$ = 3.07-4.80 for mortality. Furthermore, this information was additive to the $CHADS_2$ risk score [42].

In the acute myocardial infarction setting, the development of new-onset AFib (found in approximately 4% of a 1,991 patient cohort that was followed for a mean duration of 41

months) has been associated with a ten-fold increase in non-fatal stroke events and a 30% increase in the combination of death and non-fatal stroke events despite the use of dual antiplatelet therapy. Even though oral anticoagulation was identified as a significant predictor of stroke-free survival, this treatment was used only in 25% of the patients [43]. This evidence supports the high risk of stroke and adverse events that underlies the association between AFib and elevated troponin levels and the apparent benefit of oral anticoagulation, which was frequently underused in this risk group.

3.3. Transesophageal echocardiogram changes during an atrial fibrillation episode in patients with positive troponin

The presence of thrombi in the left atrium or left atrial appendage (LAAT) [44], dense spontaneous echocardiographic contrast (DSEC) [44-46], and low flow velocities (LFV) in the left atrial appendage [44], which are found through transesophageal echocardiography (TEE), are well-known independent predictors of stroke and thromboembolism in patients with AFib.

Bernhardt et al. found that 22% of all patients with AFib and DSEC are likely to develop cerebral embolism (using cerebral magnetic resonance imaging) and/or die within 12 months despite anticoagulation [47]. These researchers described a 51% event rate (cerebral embolism and/or death) during a 3-year period in patients with AFib and a left atrial thrombus and who were undergoing oral anticoagulation [48, 49].

A cross-sectional survey of 245 patients (not including patients with a final diagnosis of acute myocardial infarction), who were assessed through a transesophageal echocardiogram (TEE) during an AFib episode and a cTnI measurement that was conducted 24 hours prior to TEE,

found a direct relationship between increasing concentrations of cTnI and a higher prevalence of TEE changes [48]. The 112 patients (45.7%) with undetectable cTnI (< 0.012 ng/mL) exhibited a low prevalence of LAAT (3.57%; n=4), DSEC (16.96%; n=19) and LFV (9.68%; n=9). The 66 patients (26.94%) with a minimal increase in cTnI (in the range of 0.013 to 0.036 ng/mL) exhibited increased prevalence of LAAT (9.10%; n=6), DSEC (30.30%; n=20) and LFV (10.34%; n=6). The patients with the highest values of cTnI (≥ 0.037 ng/mL) exhibited even higher prevalences of LAAT (14.93%; n=10), DSEC (40.30%; n=27) and LFV (30.0%; n=15).

The addition of cTnI to the $CHADS_2$ and CHA_2DS_2-VASc scores increased the c-statistic for predicting these TEE endpoints. However, when using the net reclassification improvement index, the addition of cTnI to these scores resulted in the improvement of only the CHA_2DS_2-VASc score [50].

4. Potential tissue-related mechanisms of troponin release during AFib

As previously discussed, patients with AFib and elevated troponin have a higher prevalence of LAAT, DSEC and LFV. It has been found that the degree of the cTnI increase is positively correlated with the prevalence of the TEE changes, which are known to predispose the patient to thromboembolic events (namely embolic stroke) and a worse outcome.

Therefore, we hypothesise that the higher rate of events and the worse outcome that has been described in patients with ischemic stroke and AFib who exhibit elevated troponin is related not only to the mechanisms described in the previous sections but also to changes at the left atrial level. However, how are these TEE changes causing the troponin elevation? Four explanations are possible. First, this elevation may be due to the occurrence of embolisation of

the very small particles that compose DSEC into the coronary tree, which results in microvascular ischemia. Second, it is possible that these patients have left atrial dysfunction due to a more fibrosed left atrium, which will predispose these patients to thrombosis. This fibrosis will most likely be related to ischemia of the left atrium wall, but because the atria are very thin structures, only small increases in troponin are detected. Therefore, these small elevations may reflect an underlying structural cardiac disease (atrial fibrosis and ischemia, in addition to silent coronary artery disease) that predisposes the patients to an increased risk of thromboembolism and a worse outcome. Third, the atrial heart rate is very high (higher than 300 bpm) even in patients with AFib and a controlled left ventricular response. This elevated heart rate will lead to the development of atrial tachymyopathy with dilation, ischemia (due to an imbalance of the demand and supply) and progressive fibrosis. These developments will in turn aggravate the endothelial dysfunction and favour the development of a more thrombogenic milieu. Fourth, the troponin elevation may also be a manifestation of endothelial dysfunction or platelet and coagulation activation that lead to microemboli in the coronary tree and to the development of prothrombotic changes in the left atrium. The interaction of all of these mechanisms is shown in Figure 1.

5. Other potential biomarkers for the risk stratification of stroke in patients with AFib

The aforementioned low-to-moderate discriminative capability of the $CHADS_2$ and CHA_2DS_2VASc scores [34-37] suggests that the risk stratification of patients with nonvalvular AFib is clearly an unresolved problem of modern cardiology, and the improvement of this measure may reside in the use of biomarkers. Furthermore, the mechanisms of thrombus formation in patients with AFib and the pathways involved in this process have not been fully

elucidated. Consequently, many research studies are evaluating novel molecules, besides troponin, that also exhibit a promising role in this field.

Post-hoc analysis of the large phase III novel oral anticoagulant trials in AFib have shown favourable evidence for NTproBNP (in RE-LY [39] and ARISTOTLE [51]), D-dimers (in RE-LY [52] and ARISTOTLE [53]), C-reactive protein and interleukin-6 (in RE-LY [54]), the estimated glomerular filtration rate (assessed with the Modification of Diet in Renal Disease equation in the ROCKET-AF trial [55] and with the Cockroft-Gault and Chronic Kidney Disease Epidemiology Collaboration in the ARISTOTLE trial [56]) and cystatin-C (data from ARISTOTLE [56]). These were independent predictors of stroke and thromboembolism and resulted in improved clinical risk stratification models.

The recently completed "Global study to assess the safety and effectiveness of edoxaban (DU-176b) vs standard practice of dosing with warfarin in patients with atrial fibrillation" (ENGAGE AF-TIMI 48) trial may also yield promising information, because a substudy of biomarkers was also performed [57].

Data from 14,858 patients who belonged to the "Atherosclerosis Risk in Communities" (ARIC) cohort and were followed for a median of 16.8 years showed that factor VIIIc, fibrinogen and the von Willebrand factor (vWf) were associated with a higher risk of cardiovascular outcomes and mortality in the 1.209 patients that developed AFib [58].

In a cohort study of 278 AFib patients, elevated levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) and matrix metalloproteinase-2 (MMP-2) were associated with cardiovascular events (a combination of myocardial infarction, stroke, peripheral embolism and/or death) [59].

Evidence for other markers, such as the mean platelet volume is weaker and mostly derived from single-centre case-control studies [60].

In addition to troponin, the role of other markers of myocardial necrosis or inflammation that have already shown predictive capabilities in other acute cardiac conditions, such as copeptin [61], heart-type fatty acid-binding protein (h-FABP) [62], high-mobility group protein box-1 (HMGB1) [63], has not yet been assessed in the setting of AFib.

Wasmer and colleagues showed that 11 (17%) patients in a set of 65 patients with AFib and left atrial thrombus had a $CHADS_2$ score of zero. If the CHA_2DS_2-VASc score instead of the $CHADS_2$ score was analysed, the prevalence decreased to 8% (n=5). Furthermore, higher $CHADS_2$ and CHA_2DS_2-VASc values corresponded to a minority of the patients with thrombus ($CHADS_2 \geq 3$ corresponded to 20% and CHA_2DS_2-VASc ≥ 4 to 40%) [64].

Support for a cardioembolic mechanism underlying the association of C-reactive protein [65], vWf [66], D-dimers [67], brain natriuretic peptide (BNP) [68] and the estimated glomerular filtration rate [69] has been provided by transesophageal studies, which have demonstrated a higher prevalence of LAAT and other markers of left atrial stasis in nonvalvular AFib patients who exhibit increased levels of these biomarkers.

The possible participation of all of these different markers demonstrates that the formation of a thrombotic milieu in the left atrium is a complex process that involves several different pathways and mechanisms: inflammation, myocardial ischemia, microvascular and endothelial dysfunction, volume overload, hemodynamic impairment, compromised renal clearance and structural remodelling, increased platelet adhesion and activity, and prothrombotic activation of the coagulation system. However, the current challenge is the external validation of all of these findings through additional studies to determine the best combination of these parameters, in addition to clinical risk factors and echocardiographic parameters [70], for the assessment of which patients with nonvalvular AFib are at higher risk of stroke or thromboembolic embolism.

6. Conclusions

A close connection between atrial fibrillation, ischemic stroke and troponin elevation was clearly shown in the previous paragraphs. Thus, a systematic measurement of the troponin levels in patients with ischemic stroke and in patients with atrial fibrillation may improve the risk stratification of these patients.

It is important that practicing neurologists and cardiologists be aware of these aspects because a more aggressive approach may be necessary to avoid the ominous prognosis frequently observed in these patients. Therefore, patients with ischemic stroke and elevated troponin may be candidates for extensive ECG monitoring to diagnose atrial fibrillation and subsequently initiate oral anticoagulation. Whether beta-blockade might be beneficial or not, still remains to be assessed. Conversely, patients with atrial fibrillation and elevated troponin may benefit from aggressive management despite their $CHADS_2$ score due to the high risk of thromboembolic events: patients with a score of 0 or 1 may benefit from oral anticoagulation.

It remains to be proven whether patients with a high $CHADS_2$ score and positive troponin would benefit from even more aggressive treatment. Additional pharmacological measures that provide more intensive control of other cardiovascular risk factors may appear justifiable. However, the usefulness of more aggressive anticoagulant regimens and/or non-pharmacological options (e.g., percutaneous closure of the left atrial appendage) as an adjuvant of anticoagulant therapy for this high risk group still needs to be assessed in future trials.

Table 1 – Changes and outcome measures associated with elevated troponin in patients with ischemic stroke.

Cerebral and cardiovascular changes	Outcomes
Insular cortex damage High circulating catecholamine levels Stress-related cardiomyopathy - Ischemic ECG changes - Left ventricle wall motion abnormalities - Ventricular and supraventricular arrhythmia (including new-onset AFib) AFib (previously known)	Disability (modified Rankin scale) Death

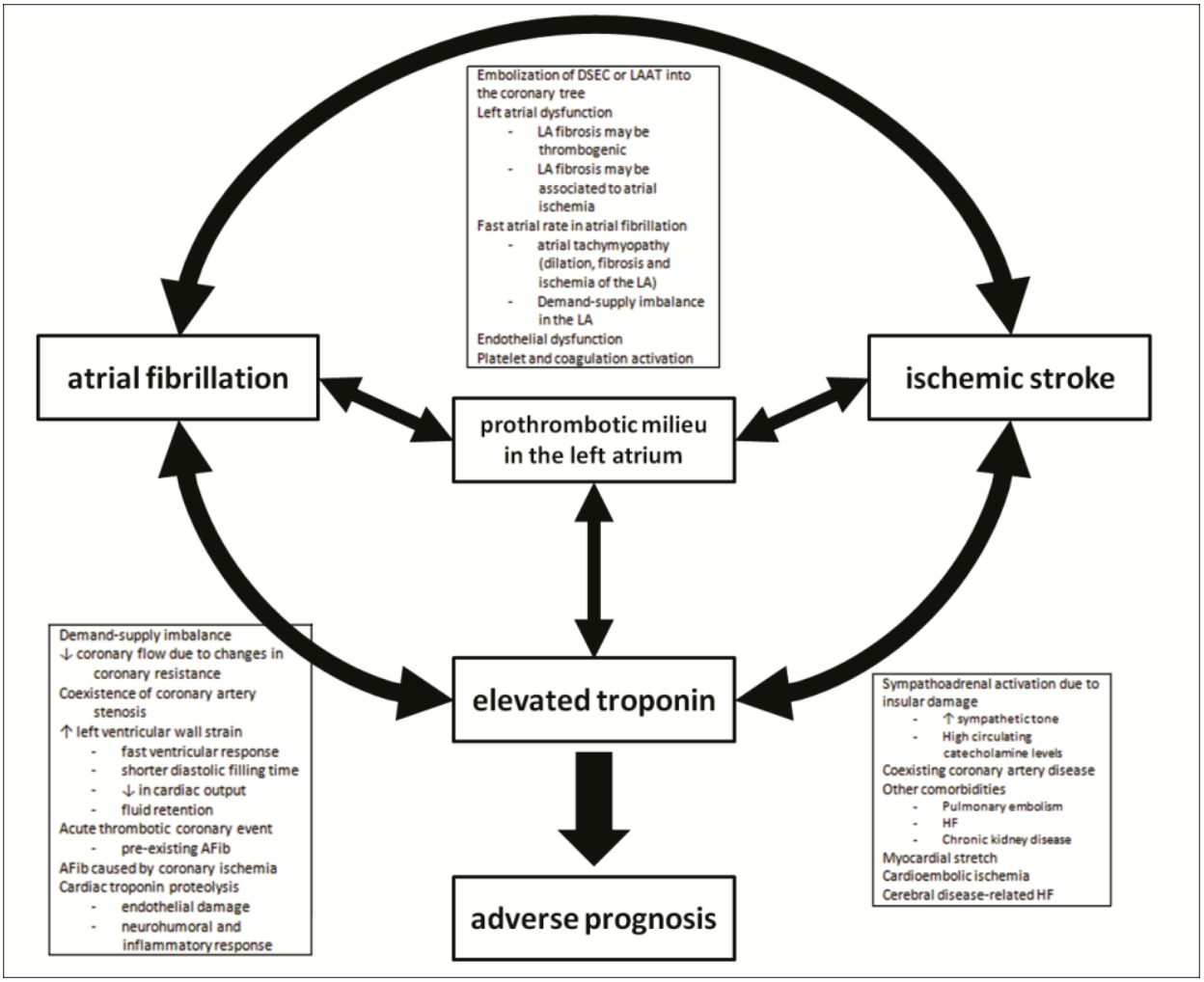
Legend: AFib – atrial fibrillation

Table 2 – Main clinical investigations concerning the outcome measures and changes associated with troponin elevation in patients with atrial fibrillation.

Author and Year	Study Design, n	Troponin levels above the cutoff	Main Findings in Patients with Positive Troponin
Kerr et al. 2009 [15]	- Systematic review of 15 articles * - 2,901 acute stroke patients who underwent troponin measurement within 7 days of symptom onset	- Detectable levels in 18.1% of patients.	- Higher prevalence of: - ECG changes compatible with myocardial ischemia - Death - Death or disability
Beaulieu-Boire et al. 2012 [27]	- Cohort study - 408 patients with ischemic stroke or TIA who underwent cTnI measurement within 24 hours of symptom onset - A baseline ECG was performed in all of the patients and Holter monitoring during the first week was performed in 69.8% of the patients - Previous history of AF and a glomerular filtration rate of less than 60 ml/min were exclusion criteria - Follow-up for 90 days	- 11.3% of the patients had elevated cTnI levels (>0.03µg/L).	- Higher prevalence of ECG changes: - AFib on baseline ECG - AFib on 24-hour Holter - New-onset AFib on 24-hour Holter - Poorer prognosis – higher prevalence of: - Death - Myocardial infarction (MI) - Disability (modified Rankin Scale) - Composite endpoint (Recurrent stroke, MI and/or death)
Van den Bos et al. 2011 [32]	- Cohort study - 407 consecutive patients admitted to the cardiology ward or coronary care unit - AF was shown through the admission ECG - Median follow-up = 688 days - No information concerning antiplatelet agents or anticoagulation	- Detectable (minor elevation) cTnI (>0.15 ng/mL) in 20% of the patients - cTnI above the 99th percentile (>0.65 ng/mL) in 19% of the patients	- Minor elevations in cTnI are associated with: - Death - Death MI - Major cardiovascular events (all-cause mortality, MI and revascularisation) - The risk rises even further in patients with higher troponin values.
Hijazi et al. 2012 [39]	- Randomised controlled trial with 6,189 patients - RE-LY trial patients** undergoing the biomarker substudy - Median follow-up = 2.2 years	Detectable cTnI (≥0.010µg/L) in 57.0% of the patients Elevated cTnI (≥0.020 µg/L) in 24.6% of the patients	- Associated with: - Stroke - Vascular mortality - Refinement of risk stratification using the $CHADS_2$ and CHA_2DS_2-VASc scores
Róldan et al. 2012 [40]	- Cohort study with 930 patients - Paroxysmal or permanent AFib patients under treatment with acenocumarol in therapeutic range > 70% in the previous 6 months and no hospital admission or surgery in the previous 6 months - Median follow-up = 957 days	hsTnT levels above the 99th percentile (>13pg/mL) were found in 31% of the patients	- Associated with: - Adverse cardiovascular events (combination of stroke/TIA, systemic embolism, acute coronary syndrome, acute heart failure and cardiac death). - All cause mortality - Stroke - After adjustment for $CHADS_2$ or CHA_2DS_2-VASc score
Wallentin et al. 2012 [42]	- Randomized controlled trial with 14.979 patients - ARISTOTLE patients *** undergoing the biomarker substudy - Median follow-up = 1.8 years	- Detectable hsTnT (> 1,5 ng/L) in 73% of the patients - hsTnT levels above the 99th percentile (>13 ng/L) present in 25% of the patients	- Associated with: - Stroke and systemic embolism - Death - After adjustment for $CHADS_2$ score
Providência et al. 2012 [50]	- Case-Control study with 245 patients - Nonvalvular AFib patients assessed through transesophageal echocardiogram during an AF episode - Patients with acute myocardial infarction were excluded from the analysis.	- Minimal cTnI elevation was detected (0.012 to 0.036 ng/mL) in 26.9% of the patients - Higher values (≥0.037 ng/mL) were found in 27.3% of the patients	- Higher prevalence of: - Left atrial appendage thrombus - Dense spontaneous echocardiographic contrast - Left atrial appendage with low flow velocities - Findings become more prevalent in the group of patients with higher cTnI levels

Legend: AFib – atrial fibrillation; TIA – transient ischemic attack; MI – myocardial infarction; cTnI – cardiac troponin I; hsTnT – high sensitivity troponin T. * - 11 of these papers included only ischemic stroke patients. ** - AFib documented on ECG at screening or within the previous 6 months and at least one of the following: previous stroke/TIA, left ventricle ejection fraction <40%, HF NYHA II-IV in the previous 6 months, age ≥75 or age = 65 to 74 years plus diabetes mellitus, hypertension or coronary artery disease. *** AFib or flutter at enrolment or ≥ episodes of AFib or flutter documented by ECG at least 2 weeks apart in the 12 months before enrolment plus at least one of the following: age of at least 75 years; previous stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure within the previous 3 months or left ventricular ejection fraction of < 40%; diabetes mellitus; or hypertension requiring pharmacologic treatment.

Figure 1 – Putting the atrial fibrillation, elevated troponin, ischemic stroke and adverse outcome connection into perspective.



Legend: HF – heart failure; AFib – atrial fibrillation; LA – left atrium.

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II.B.3

Mean corpuscular volume and red cell distribution width as predictors of left atrial stasis in patients with non-valvular atrial fibrillation.

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Abstract

Background: The role of erythrocyte indexes for the prediction of left atrial stasis, assessed by transesophageal echocardiography in patients with non-valvular atrial fibrillation, has not been previously clarified.

Methods: Single center cross-sectional study comprising 247 consecutive patients admitted to the emergency department due to symptomatic atrial fibrillation and undergoing transesophageal echocardiogram evaluation for exclusion of left atrial appendage thrombus (LAAT) before cardioversion. All patients had a complete blood count performed up to 12 hours prior to the transesophageal echocardiogram. Markers of left atrial stasis were sought: LAAT, dense spontaneous echocardiographic contrast (DSEC) and low flow velocities (LFV) in the left atrial appendage. Erythrocyte indexes' accuracy for detecting transesophageal echocardiogram changes was evaluated through receiver operating curve analysis. Binary logistic multivariate analysis, using solely erythrocyte indexes and in combination with other variables (i.e. $CHADS_2$, CHA_2DS_2VASc classifications and left ventricle ejection fraction), was used for transesophageal echocardiogram endpoints prediction.

Results: LAAT was found in 8.5%, DSEC in 26.1% and LFV in 12.1%. Mean corpuscular volume and red cell distribution width were independent predictors of LAAT and DSEC. Despite adding incremental predictive value to each other, when clinical risk factors from $CHADS_2$ and CHA_2DS_2VASc classifications and left ventricle ejection fraction were added to the models, only mean corpuscular volume remained an independent predictor of LAAT and DSEC.

Conclusions: These findings suggest that mean corpuscular volume and red cell distribution width may be linked to left atrial stasis markers.

Keywords: atrial fibrillation; stroke; left atrial appendage thrombus; mean corpuscular volume; red cell distribution width; spontaneous echocardiographic contrast.

Background

Thromboembolism is among the most feared complications of non-valvular atrial fibrillation (AF) [1]. However, the mechanisms and pathways underlying thrombus formation and the presence of prothrombotic milieu in the left atrium have not yet been fully clarified.

The presence of left atrial thrombus is associated with thromboembolism in patients submitted to cardioversion [2] or catheter ablation of AF [3], and that is why these procedures are contraindicated in the case of intracavitary thrombus [4]. Although, transesophageal echocardiogram is the gold-standard for the exclusion of thrombus, this procedure is not devoid of risks, is invasive in nature and may be not tolerable for some patients [5]. Furthermore, thrombi are found in only a minority of patients with non-valvular AF if under anticoagulation treatment (1.6%) [3] and 12% in patients without anticoagulation [6].

Patients with AF and left atrial thrombus [7], dense spontaneous echocardiographic contrast (DSEC) [8] and low flow velocities (LFV) in the left atrial appendage [9] are known to have a higher risk of thromboembolism or adverse prognosis.

A better understanding of the thrombogenic mechanisms and pathways in non-valvular AF could have two main benefits: first, providing help in foreseeing which patients have a very low risk of having a left atrial appendage thrombus (LAAT) and, therefore, could be spared transesophageal echocardiogram assessment before cardioversion or catheter ablation of AF; second, a more accurate detection of subjects at a high risk of thromboembolism that would derive benefit from anticoagulation therapies.

The assessment of red blood cell indexes is a low cost and very commonly performed laboratory technique that has been previously shown to provide information concerning prothrombotic status or adverse outcome in other spectra of cardiovascular disease [10, 11]. However, the role of these erythrocyte measures as predictors of left atrial stasis in patients with AF remains to be assessed.

Methods

1. Study population

A single center cross-sectional study was conducted including patients undergoing echocardiographic assessment (comprising transesophageal and transthoracic echocardiogram) due to symptomatic AF, which lead to a hospital admission in a 25-month time period. Among a total of 353 subjects, 302 performed a complete blood count 12 hours prior to transesophageal echocardiogram and were selected for the purpose of our investigation. Among these, 31 subjects with valvular AF (defined as presence of a previous valve repair, a prosthetic valve, rheumatic heart disease, and moderate or severe valve stenosis and/or regurgitation) and 24 with concomitant infection were excluded from analysis. Our study population included the remaining 247 patients. All subjects provided their informed consent to undergo the necessary investigations and to allow the usage of their data for research purposes, preserving their anonymity.

Baseline overall group characterization with demographic, anthropometric, clinical, laboratory and echocardiographic data, alongside with information on medication was obtained for all patients. Data was retrospectively retrieved from clinical records (outpatient clinic evaluations, emergency department and hospital ward admissions). This study was conducted with the approval of our institution's Cardiology Department Supervisor and Ethics Committee.

2. Echocardiographic data

Transesophageal and transthoracic echocardiogram were performed using a GE Vivid 7 echocardiograph alongside with M4S (1.5–4.0 MHz) and 6T phased array multiplane transesophageal (2.9–7.0 MHz) probes. All examinations were performed by two cardiologists with accreditation in transesophageal and transthoracic echocardiography by the European Society of Cardiology. Transesophageal echocardiography was performed without anesthesia or sedation in more than 98% of patients. Images were later reanalysed using the GE Health Care EchoPac Dimension software, PC version 108.1.4. Left atrium volume was measured using the single-plane area length method. On transesophageal echocardiogram, the left atrium and left atrial appendage were imaged in different tomographic planes to detect the presence of LAAT and DSEC. Spontaneous echo contrast was classified according to the classification (1 to 4+) proposed by *Fatkin et al.* [12]. Grade 3+ or 4+ was defined as DSEC. Left atrial appendage flow velocities were assessed with a pulsed Doppler sample placed 1 cm from the entry of the left atrial appendage into the body of the left atrium. Emptying and filling velocities were estimated from an average of five well-defined emptying and filling waves. Patients with emptying and filling velocity ≤20 cm/s were classified as having LFV.

The cardiologists performing the transesophageal and transthoracic echocardiogram were blinded for the laboratory results and clinical information of the patients, other than the fact that they were in AF and there was need for excluding transesophageal echocardiogram changes that could contraindicate cardioversion.

3. Laboratory data

After venous blood was drawn, it was immediately transferred into our hospital's laboratory using an automatic internal tube transference system directly connected from different parts of the hospital into the laboratory. On average laboratory measures were performed within 15 minutes of venous blood sampling.

Erythrocyte index assessment was performed using the Cell-Dyn Sapphire Hematology Analyzer from Abbot Diagnostics. Reference range values according to local calibration from our hospital's laboratory were: red blood cell counting – 4.5 to 5.5 $x10^6$/uL; hemoglobin – 13.0 to 17.5 g/dL; hematocrit – 40 to 50%; mean corpuscular volume 80 to 100 fL; mean corpuscular hemoglobin 27 to 32 pg; mean corpuscular hemoglobin concentration 32 to 35 g/dL; red cell distribution width 11.6 to 14%.

C-reactive protein was measured using the CRP VITROS Chemistry Products assay. The lower limit of sensitivity was <0.5mg/L and the reference interval for normal values was < 1.0mg/L. A rise in C-reactive protein was defined as the observed value over the lower limit of sensitivity (eg. 0.4mg/L was the observed rise in C-reactive protein in a patient with a value of 0.9mg/L, assuming the 0.5mg/L lower limit of sensitivity).

Reference range for activated partial thromboplastin time (aPTT) was 25 to 30 seconds.

4. Erythrocyte indexes and prediction of transesophageal endpoints

PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis. Comparisons were performed according to the presence/absence of markers of left atrial

stasis. Chi-square was used for nominal variables and Student's t-test was used for comparison of continuous variables, where appropriate; the Levene test was used in order to check the homogeneity of variance; equivalent non-parametric tests were used when Kolmogorov-Smirnov was in favor of absence of normal distribution. Results with $P < 0.05$ were regarded as significant.

The discriminative capability of the red blood cell indexes was tested using receiver operating characteristic (ROC) curves and the resulting area under the curve (AUC) summary statistic (c statistic) for the prediction of LAAT. In parameters with an AUC of at least 0.650 we were able to define the optimal cutoff point (Youden index) using the coordinates from the ROC curves. Univariate analysis was then performed using the chi-square test.

Binary logistic multivariate analysis using erythrocyte indexes alone and combined with variables from the $CHADS_2$ and CHA_2DS_2VASc classifications was used for obtaining models for the prediction of transesophageal echocardiogram endpoints. Erythrocyte indexes that were predictors of changes on transesophageal echocardiogram on univariate analysis were used either alone or with the isolated clinical parameters from $CHADS_2$ and CHA_2DS_2VASc and left ventricle ejection fraction for obtaining logistic regression models (using the backward stepwise method trough likelihood ratio; probability for stepwise = 0.1) that could predict transesophageal echocardiogram endpoints: LAAT, DSEC and LFV. Continuous variables such as left ventricle ejection fraction were converted into ordinal variables and then used in the logistic regression analysis. Established cutoff points were: ≥ 55% vs. < 55% for left ventricle ejection fraction. The Hosmer-Lemeshow summary statistic was used to assess the goodness-of-fit of the models.

Results

The patients' baseline clinical, echocardiographic and laboratory characterization is shown on Table I. In 41.7% (n=103) of subjects, there was no previously known history of AF. The following markers of left atrial stasis were found on transesophageal echocardiogram: LAAT in 8.5%, DSEC in 27.1% and LFV in 12.3%.

Table II illustrates the capability of red blood cell indexes to discriminate LAAT, DSEC and LFV, with the respective area under the curve (AUC) values. Only mean corpuscular volume and red cell distribution width had a moderate accuracy for detecting LAAT (AUC=0.668 and AUC=0.657, respectively). Concerning DSEC and LFV, the discriminative capability was low and non-significant. Youden index values for the variables that performed better on table II were the following: mean corpuscular volume < 91.5fL (62% sensitivity and 64% specificity for LAAT) and red cell distribution width (57% sensitivity and 70% specificity for LAAT).

Comparisons of patients with mean corpuscular volume < vs. ≥ 91.5fL and red cell distribution width < vs. ≥ 15.0% are shown on Table I. A higher prevalence of females (p=0.024) and diabetes mellitus (p=0.037) was observed in patients with mean corpuscular volume < 91.5fL. Furthermore, a lower prevalence of subjects medicated with statins (p=0.028), alongside with lower hemoglobin (p=0.029) values was found. Red cell distribution width was higher (p<0.001) in patients with mean corpuscular volume < 91.5fL. Despite the lack of differences concerning depressed left ventricle ejection fraction, left ventricles of patients with mean corpuscular volume < 91.5fL were slightly more dilated.

Concerning patients with red cell distribution width ≥ 15.0%, they had more frequently previous episodes of congestive heart failure and stroke or transient ischemic attack (TIA) (p=0.024 and p=0.001, respectively), which translated into higher $CHADS_2$ and CHA_2DS_2-VASc

scores (p=0.003 and p=0.019, respectively). Lower mean corpuscular volume and estimated glomerular filtration rate (p<0.001 and p=0.004, respectively), alongside with a compromised left ventricle ejection fraction (p=0.005) was also observed among patients with red cell distribution width ≥ 15.0%.

On univariate analysis (Table III) both mean corpuscular volume and red cell distribution width were predictors of LAAT and DSEC (all p<0.05). However, these variables were not predictors of the presence LFV in the left atrial appendage.

When combined (Table IV), mean corpuscular volume and red cell distribution width were both included in backward likelihood ratio logistic regression models for the prediction of LAAT and DSEC. However, when clinical risk factors from $CHADS_2$ and CHA_2DS_2-VASc and left ventricle ejection fraction were added to the models, only mean corpuscular volume remained an independent predictor of LAAT and DSEC.

Discussion

We have identified two parameters (mean corpuscular volume and red cell distribution width) that were linked to an increased prevalence of LAAT and DSEC, which are transesophageal echocardiogram markers that have been previously associated with an increased risk of stroke and adverse outcome in patients with AF [7, 8]. However, despite adding incremental predictive value to each other, when combined with clinical risk factors present within $CHADS_2$ and CHA_2DS_2-VASc classifications and left ventricle ejection fraction, only mean corpuscular volume remained an independent predictor, which may be due to the small size sample.

Thromboembolic risk stratification of patients with AF is currently based on clinical schemes [14, 15]. The $CHADS_2$ [15, 16] and CHA_2DS_2-VASc [17, 18] scores have been shown to possess a moderate ability for the prediction of thromboembolic transesophageal echocardiogram risk factors. Their predictive capability has shown potential for improvement in this setting with the addition of biomarkers like C-reactive protein [19], troponin I [20], von Willebrand factor [21] or D-dimers [22].

To the best of our knowledge, red blood cell indexes had not yet been shown to improve the prediction of LAAT or DSEC provided by clinical risk factors.

Decreased mean corpuscular volume may be a marker of different situations: iron deficiency (caused by inadequate dietary intake or blood loss), chronic disease (e.g. inflammation, chronic kidney disease, hematologic or linfoproliferative disorders) or thalassemia. Patients with ongoing infection were excluded from our study and univariate analysis showed that no difference was observed concerning C-reactive protein and estimated glomerular filtration rate, according to the mean corpuscular volume cutoff level used. Furthermore, no patients with low mean corpuscular volume were identified as having thalassemia.

A high red cell distribution width (signaling the presence of red blood cells of variable sizes) was more frequent in the subset of patients of low mean corpuscular volume and is known to be compatible with iron deficiency in this situation. A high red cell distribution width has previously been associated with cardiovascular events and adverse outcomes [23] and in some investigations these findings were seen independently of the presence of anaemia [24].

Despite our patients were not anemic, those with a mean corpuscular volume < 91.5fL were below the average of our population (see Table I). Therefore, and despite not having assessed their body's iron stores, we wonder if this microcytic trend may lead to a more prothrombotic behavior.

Takahashi et al. have previously described an increase in mean corpuscular volume in patients with AF [25]. If this holds true for our population, this increase in mean corpuscular volume

caused by AF may contribute to partly masking some of the microcytic trend in subjects in the mean corpuscular volume <91.5fL group.

Patients with heart failure frequently have iron deficiency (most of them have no relevant decrease on serum hemoglobin) and improve their outcomes after intravenous iron replacement [26]. Iron deficiency can have deleterious effects, independently of anemia. A possible explanation is the possibility of altered cardiac function illustrated by mitochondrial swelling, abnormal sarcomere function [27] and impaired mitochondrial electron transport [28]. As far as endothelial dysfunction and procoagulant states are concerned, an association with iron deficiency remains to be proved.

Maguire and colleagues suggested that a relation between iron-deficiency anemia and stroke in young children might be caused the hyperviscosity that may occur in this setting [29]. Other reports have focused the same association in adult and elderly cohorts [30]. As far as markers of left atrial stasis are concerned, and according to the Virchow triad, this hyperviscosity hypothesis fits perfectly as an explanation for the observed association.

Another example of an association between iron deficiency, hyperviscosity and thrombosis may occur in patients with *Eisenmenger* syndrome, where repeated phlebotomies may lead to the formation of microcytic erythrocytes, which are thought to have higher viscosity than their normocytic counterparts and thus predispose to embolic events [31].

In our population, patients with a lower mean corpuscular volume had a more dilated left ventricle. This has been previously described to be an effect of iron deficiency [27]. Moreover, women displayed more frequently lower levels of mean corpuscular volume. We hypothesize that besides hormonal factors, the association of female gender with increased thromboembolic risk in AF may be also explained by iron deficiency.

Based on different hypothesis concerning the composition of spontaneous echocardiographic contrast (aggregates of red blood cells interacting with plasma proteins [32, 33]) we are lead

into thinking that the observed association of mean corpuscular volume and red cell distribution width with LAAT and DSEC is not caused by pure chance.

A high bleeding and thrombotic risk frequently coexists in patients with AF, as classifications for bleeding risk (e.g. HAS-BLED [34]) share several common risk factors present within $CHADS_2$ and CHA_2DS_2-VASc scores [13, 14]. Furthermore, some of the recently assessed biomarkers in AF (e.g. troponin I [35], D-dimer [36]) signal both the thromboembolism and bleeding predisposition. The association of anemia or bleeding with adverse outcomes has also been observed in other cardiovascular conditions: in patients with acute myocardial infarction, anemia and bleeding enclose worse outcomes [37] and the same applies to patients with heart failure and concurrent anemia [38].

Study Limitations:

Due to the small size of our single-centre study sample only a limited number of predictors was included in the logistic regression models. However, we think that our data is already indicative that red blood cell indexes (data mostly supportive of mean corpuscular volume) may play a role in predicting transesophageal echocardiogram changes like LAAT and DSEC.

A low prevalence of patients undergoing oral anticoagulation was found in our sample. Still, we reinforce that 103 patients (41.7%) had no previous diagnosis of AF. If we consider only patients with previously known AF the prevalence of patients undergoing oral anticoagulation rises steeply to 39.6% (57 out of 144).

Fifty-two patients (21.1%) had no evaluation of left atrial appendage flow velocities. This was due to technical reasons (echocardiographic data being classified as unsuitable for the

accurate assessment of flow velocities) or lack of probe tolerance by the patient. In these subjects, transesophageal echocardiogram was performed without measurement of left atrial appendage flow velocities if the presence of LAAT and DSEC could be excluded right promptly.

Conclusions

Our findings, using left atrial stasis markers, suggest that mean corpuscular volume and red cell distribution width may be associated with the presence of left atrial appendage thrombus and dense spontaneous echocardiographic contrast in non-valvular atrial fibrillation. However, only mean corpuscular volume seemed to add incremental predictive power to the clinical risk factors present within $CHADS_2$ and CHA_2DS_2-VASc classifications.

Further validation of these findings using transesophageal endpoints in patients undergoing cardioversion or catheter ablation of atrial fibrillation may be useful in identifying low risk groups that can be spared of this imaging procedure. Furthermore, assessment of mean corpuscular volume and red cell distribution width as predictors of thromboembolism in patients with atrial fibrillation may also be a reasonable approach.

Table I - Population baseline characteristics and sub-analysis according to mean corpuscular volume and red blood cell distribution width.

	Overall (n=247)	MCV<91.5fL (n=90)	MCV≥91.5fL (n=157)	P	RDW<15% (n=166)	RDW≥15% (n=81)	P
Demographics							
Age (years)	68.0±10.5	67.0±10.0	68.6±10.7	0.213	67.4±11.3	69.3±8.4	0.383
Female gender	36.4% (90)	45.6%(41)	31.2% (49)	0.024	64.5% (107)	61.7%(50)	0.676
Body Mass Index (Kg/m^2)	29.0±5.0	29.8±5.8	28.6±4.5	0.275	28.8±4.6	29.5±5.9	0.704
Clinical Data							
Congestive heart failure	49.8% (124)	48.9% (44)	51.0% (80)	0.755	45.2% (75)	60.5% (49)	0.024
Hypertension	83.8% (207)	82.2% (74)	84.7% (133)	0.609	82.5% (137)	86.4% (70)	0.436
Diabetes mellitus	22.7% (56)	30.0% (27)	18.5% (29)	0.037	20.5% (34)	27.2% (22)	0.239
Stroke or TIA	15.4% (38)	14.4% (13)	15.9% (25)	0.757	10.2% (17)	25.9% (21)	0.001
Vascular disease[a]	52.2% (129)	54.4% (49)	51.0% (80)	0.597	52.4% (87)	51.9% (42)	0.934
AF episode duration >1 week	67.6% (167)	65.6% (59)	68.8% (108)	0.601	66.9% (111)	69.1% (56)	0.721
$CHADS_2$ score	2.2±1.3	2.1±1.3	2.2±1.3	0.761	2.0±1.2	2.5±1.4	0.003
CHA_2DS_2-VASc score	3.7±1.8	3.8±1.8	3.7±1.8	0.804	3.5±1.7	4.2±1.9	0.019
Medication							
Oral anticoagulants	23.1% (57)	25.6% (23)	21.7% (34)	0.484	21.7% (36)	25.9% (21)	0.458
Enoxaparin	44.1% (109)	40.0% (36)	46.5% (73)	0.322	42.8% (71)	46.9% (38)	0.538
Antiplatelet agents	53.8% (133)	48.9% (44)	56.7% (89)	0.237	55.4% (92)	50.6% (41)	0.477
ACE-i or ARB-II	71.3% (176)	67.8% (61)	73.2% (115)	0.361	72.3% (120)	69.1% (56)	0.607
Statin	41.3% (102)	32.2% (29)	46.5% (73)	0.028	41.6% (69)	40.7% (33)	0.902
Laboratory Assessment							
RBC (10^6/uL)	4.51±0.65	4.48±0.66	4.40±0.62	0.001	4.52±0.61	4.48±0.72	0.658
Haemoglobin (g/dL)	13.8±1.8	13.4±1.8	14.0±1.8	0.029	14.0±1.7	13.2±1.9	0.001
Hematocrit (%)	41.6±5.7	40.7±5.6	42.2±5.6	0.040	42.3±5.2	40.2±6.2	0.005
MCV (fL)	92.7±5.7				93.8±4.4	90.3±7.0	0.001
MCV<91.5fL	36.4% (90)				28.9% (48)	51.9% (42)	<0.001
MCH (pg)	30.7±2.2	28.8±2.1	31.7±1.4	<0.001	31.1±1.7	29.7±2.7	<0.001
MCHC (g/dL)	33.0±1.3	33.0±1.2	33.1±1.3	0.697	33.1±1.3	32.9±1.2	0.068
RDW (fL)	14.1±1.4	14.6±1.4	13.7±1.3	<0.001			
RDW ≥ 15	32.8% (81)	46.7% (42)	24.8% (39)	0.001			
INR	1.2±0.5	1.2±0.6	1.2±0.5	0.199	1.2±0.4	1.3±0.7	0.054
INR ≥ 2.0	7.7% (19)	5.6% (5)	8.9% (14)	0.340	5.4% (9)	12.3% (10)	0.055
aPTT time (s)	33.1±5.5	33.2±5.4	33.0±5.6	0.899	33.2±5.8	32.8±5.2	0.876
Rise in CRP (mg/L)	0.9±2.5	1.0±2.5	0.9±2.5	0.698	0.8±2.0	1.1±3.3	0.158
GFR assessed with MDRD (ml/min)	71.4±28.2	73.6±29.7	70.2±27.2	0.362	75.0±27.2	63.9±28.9	0.004
Transthoracic echocardiogram data							
Indexed left atrial volume (ml/m^2)	62.0±25.5	65.0±27.7	60.4±24.4	0.302	57.5±19.9	73.1±33.8	0.007
Indexed LV diastolic diameter (mm/m^2)	29.7±5.6	30.8±4.5	29.2±5.9	0.011	29.2±5.6	30.9±5.3	0.026
LV ejection fraction < 55%	27.9% (69)	21.1% (19)	31.8% (50)	0.070	22.3% (37)	39.5% (32)	0.005

Legend: MCV – mean corpuscular volume; MPV – mean platelet volume; TIA – transient ischemic attack; AF – atrial fibrillation; ACE-i - angiotensin converting enzyme inhibitor; ARB-II - angiotensin II receptor blocker; RBC – red blood cells; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; RDW – red cell distribution width; INR - international normalized ratio; CRP – C reactive protein; GFR – glomerular filtration rate; MDRD - modified diet in renal disease formula; LV – left ventricle; aPTT - activated partial thromboplastin time.

[a] vascular disease is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque. [b] only 148 subjects had assessment of left atrial appendage flow velocities due to technical or procedural reasons (see discussion).

Table II – Discrimination of left atrial stasis by erythrocyte indexes.

Variable	LAAT		DSEC		LFV	
	AUC $CI_{95\%}$	P	AUC $CI_{95\%}$	P	AUC $CI_{95\%}$	P
RBC (10^6/uL)	0.507 0.381-0.634	0.910	0.505 0.429-0.582	0.902	0.533 0.418-0.649	0.597
Hgb (g/dL)	0.430 0.304-0.555	0.285	0.503 0.424-0.581	0.946	0.536 0.425-0.646	0.570
MCV (fL) [a]	0.668 0.558-0.777	0.011	0.528 0.442-0.613	0.505	0.432 0.308-0.556	0.278
Hematocrit (%)	0.434 0.309-0.560	0.320	0.515 0.436-0.594	0.715	0.563 0.450-0.675	0.322
MCH (pg) [a]	0.609 0.484-0.735	0.098	0.507 0.425-0.590	0.865	0.490 0.365-0.615	0.874
MCHC (g/dL)	0.489 0.365-0.614	0.873	0.468 0.386-0.550	0.439	0.435 0.315-0.555	0.302
RDW (%)	0.657 0.544-0.771	0.017	0.570 0.489-0.652	0.089	0.514 0.395-0.634	0.820

Legend: LAAT - left atrial appendage thrombi; DSEC - dense spontaneous echo contrast; LFV - low flow velocities in the left atrial appendage; AUC – area under the curve; CI – confidence interval; RBC – red blood cells; Hgb – hemoglobin; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; RDW – red cell distribution width; [a] A lower value was defined as a more positive test for MCV and MCH.

Table III – Presence of left atrial stasis on transesophageal echocardiogram and sub-analysis according to mean corpuscular volume and red cell distribution width.

Atrial stasis transesophageal echocardiogram markers									
	Overall (n=247)	MCV < 91.5fL	MCV ≥ 91.5fL	OR $CI_{95\%}$ P	P	RDW < 15%	RDW ≥ 15%	OR $CI_{95\%}$ P	P
LAAT	8.5% (21)	14.4% (13)	5.1% (8)	3.14 1.25-7.91	0.011	5.4% (9)	14.8% (12)	3.03 1.22-7.53	0.013
DSEC	27.1% (67)	35.6% (32)	22.3% (35)	1.92 1.09-3.41	0.024	22.3% (37)	37.0% (26)	2.05 1.15-3.67	0.014
LFV	12.3% (24)[b]	9.9% (7/71)	13.7% (17/124)	0.69 0.27-1.75	0.431	11.9% (16/135)	13.3% (8/60)	1.14 0.46-2.84	0.771

Legend: MPV – mean platelet volume; RDW – red cell distribution width; LAAT - left atrial appendage thrombi; DSEC - dense spontaneous echo contrast; LFV - low flow velocities in the left atrial appendage.
[a] only 195 subjects had assessment of left atrial appendage flow velocities due to technical or procedural reasons (see discussion).

Table IV – Binary logistic regression multivariate analysis models for predicting the presence of markers of left atrial stasis.

Erythrocyte indexes alone						
Endpoint	Variable	Wald	B	Exp β CI95%	P	Hosmer and Lemeshow test
LAAT	MCV <91.5fL	3.864	0.952	2.591 1.003-6.695	0.049	χ^2 = 2.071 df = 2 p = 0.355
	RDW ≥ 15%	3.568	0.903	2.467 0.967-6.296	0.059	
	Constant	15.098	1.369	3.933	<0.001	
DSEC	MCV <91.5fL	3.078	0.528	1.695 0.940-3.057	0.079	χ^2 = 3.306 df = 2 p = 0.191
	RDW ≥ 15%	3.930	0.604	1.829 1.007-3.323	0.047	
	Constant	1.136	0.286	1.331	0.287	
Erythrocyte indexes plus clinical risk factors from $CHADS_2$ and CHA_2DS_2-VASc and left ventricle ejection fraction						
Endpoint	**Variable**	**Wald**	**B**	**Exp β $CI_{95\%}$**	**P**	**Hosmer and Lemeshow test**
LAAT	Stroke / TIA	8.275	1.480	4.394 1.603-12.046	0.004	χ^2 = 1.065 df = 3 p = 0.786
	MCV <91.5fL	7.321	1.339	3.816 1.446-10.068	0.007	
	LVEF < 55%	3.443	0.921	2.521 0.949-6.648	0.064	
	Constant	0.007	-0.051	0.950	0.932	
DSEC	MCV <91.5fL	9.872	1.050	2.858 1.484-5.501	0.002	χ^2 = 6.128 df = 6 p = 0.409
	Age ≥ 65	3.307	0.642	1.901 0.951-3.799	0.069	
	LVEF < 55%	28.341	1.811	6.118 3.140-11.917	<0.001	
	Stroke	3.188	0.740	2.097 0.930-4.726	0.074	
	Constant	9.732	-1.640	0.194	0.002	
LFV	Stroke / TIA	4.051	1.092	2.980 1.029-8.631	0.044	χ^2 = 0.629 df = 1 p = 0.428
	LVEF < 55%	3.193	0.841	2.320 0.922-5.838	0.074	
	Constant	0.608	0.469	1.598	0.436	

Legend: Legend: LAAT - left atrial appendage thrombi; DSEC - dense spontaneous echo contrast; LFV - low flow velocities in the left atrial appendage; LA ABN – left atrial abnormality; CI – confidence interval; TIA – transient ischemic attack; MCV – mean corpuscular volume; LVEF – left ventricle ejection fraction; MPV – mean platelet volume.

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II.B.4

Mean Platelet Volume and markers of left atrial stasis in patients with non-valvular atrial fibrillation.

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doi: 10.1186/1471-2261-13-40.

Abstract

Background: Mean platelet volume has been associated with stroke in patients with atrial fibrillation. However, its role as a predictor of left atrial stasis, assessed by transesophageal echocardiography, in patients with non-valvular atrial fibrillation has not yet been clarified.

Methods: Single center cross-sectional study comprising 427 patients admitted to the emergency department due to symptomatic atrial fibrillation and undergoing transesophageal echocardiogram evaluation for exclusion of left atrial appendage thrombus before cardioversion. All patients had a complete blood count performed in the 12 hours prior to transesophageal echocardiogram. Markers of left atrial stasis were sought: left atrial appendage thrombus, dense spontaneous echocardiographic contrast and low flow velocities in the left atrial appendage. The presence of at least one of the former markers of left atrial stasis was designated left atrial abnormality. Binary logistic multivariate analysis was used for obtaining models for the prediction of transesophageal echocardiogram endpoints.

Results: Left atrial appendage thrombus was found in 12.2%, dense spontaneous echocardiographic contrast in 29.7%, low flow velocities in 15.3% and left atrial abnormality in 34.2%. Mean platelet volume (exp β=3.41 p=0.048) alongside with previous stroke or transient ischemic attack (exp β=5.35 p=0.005) and troponin I (exp β=5.07 p=0.041) were independent predictors of left atrial appendage thrombus. Mean platelet volume was also incorporated in the predictive models of dense spontaneous echocardiographic contrast, low flow velocities and left atrial abnormality, adding predictive value to clinical, echocardiographic and laboratory variables.

Conclusions: These findings suggest that mean platelet volume may be associated with the presence of markers of left atrial stasis, reinforcing a likely cardioembolic mechanism for its association with stroke in patients with non-valvular atrial fibrillation.

Keywords: atrial fibrillation; stroke; left atrial appendage thrombus; mean platelet volume.

Background

Thromboembolism is one of the most feared complications of atrial fibrillation (AF) [1]. It may arise due to AF in the course of time or it may be facilitated by procedures like cardioversion or percutaneous AF ablation, when a thrombus is present in the left atrium. Therefore, before undergoing risk procedures like catheter ablation or cardioversion of AF a pre-procedural transesophageal echocardiogram may be advisable in order to minimize post-procedure thromboembolic complications [2, 3].

The possibility of using biomarkers for thromboembolic risk stratification of patients with atrial fibrillation is a field of growing interest. The role of mean platelet volume (MPV) as a predictive marker of stroke in patients with AF has been recently suggested by Ha and colleagues [4]. In this investigation, MPV was shown to add incremental predictive value to the clinical variables present in the $CHADS_2$ score.

Very recently, it was also shown in a case-control study that stroke patients with AF displayed higher MPV levels than patients with AF without stroke history of stroke [5]. These authors established a cut-off level of MPV > 9.4fL for this association (OR 4.021 $p<0.001$).

However, the precise mechanism underlying this relationship (cardiac embolism or peripheral thrombosis due to increased platelet reactivity) is not completely understood. It is thought that at least 90% of thrombi in patients with AF originate in the left atrial appendage [6]. Other markers of left atrial stasis, like dense spontaneous echo contrast (DSEC) and low flow velocities (LFV) in the left atrial appendage [7], are also known to be associated with thromboembolic complications in patients with AF.

The association of MPV with the different markers of left atrial stasis (i.e. its role as a marker of increased risk of cardioembolic stroke) in patients with non-valvular AF has not yet been addressed.

Aim

To test the accuracy of MPV for predicting markers of left atrial stasis, detected while using transesophageal echocardiogram, in patients with non-valvular AF.

Methods

1. **Study population**

A single center cross-sectional study was conducted using the following inclusion and exclusion criteria for the definition of the assessed population:

Inclusion criteria:

- All patients undergoing echocardiographic assessment, comprising both transesophageal and transthoracic echocardiogram, due to symptomatic AF leading to admission to the Emergency Department during a 36 months period.

Step-wise exclusion criteria:

- Lack of assessment of MPV in the 12 hours immediately before the echocardiographic assessment.
- Valvular AF, defined as rheumatic heart disease, prosthetic heart valve or previous valve repair and moderate to severe mitral or aortic valve stenosis or regurgitation.

- Presence of ongoing infection.
- Diagnosis of acute myocardial infarction during the index event or in the previous month.

Among a total of 611 subjects, 507 had performed a complete blood count 12 hours prior to transesophageal echocardiogram and were selected for possible inclusion the purpose of our investigation. Among these, 28 subjects with valvular AF, 49 with concomitant infection and 3 with final diagnosis of acute myocardial infarction were excluded from analysis. Our study population included the remaining 427 patients. All subjects provided their informed consent to undergo the necessary investigations and to allow the usage of their data for research purposes, preserving their anonymity.

Baseline overall group characterization with demographic, anthropometric, clinical, laboratory and echocardiographic data, alongside with information on medication was obtained for all patients. Data was retrospectively retrieved from clinical records (outpatient clinic evaluations, emergency department and hospital ward admissions). This study was conducted with the approval of our Institution's Cardiology Department Supervisor and Ethics Committee.

2. Echocardiographic data

Transthoracic and transesophageal echocardiogram were performed using a GE Vivid 7 echocardiograph alongside with M4S (1.5–4.0 MHz) and 6T phased array multiplane transesophageal (2.9–7.0 MHz) probes. All examinations were performed by two cardiologists with accreditation in transthoracic and transesophageal echocardiography by the European Society of Cardiology. Transesophageal echocardiogram was performed without anesthesia or

sedation in more than 97% of patients. Images were later reanalyzed using the GE Health Care EchoPac Dimension software, PC version 108.1.4. Left atrium volume was measured using the single-plane area length method. On transesophageal echocardiogram, the left atrium and left atrial appendage were imaged in different tomographic planes to detect the presence of LAAT and DSEC. Spontaneous echo contrast was classified according to the classification (1 to 4+) proposed by *Fatkin et al.* [8]. Grade 3+ or 4+ was defined as DSEC. Left atrial appendage flow velocities were assessed with a pulsed Doppler sample placed 1 cm from the entry of the left atrial appendage into the body of the left atrium. Emptying and filling velocities were estimated from an average of five well-defined emptying and filling waves. Patients with emptying and filling velocity ≤20 cm/s were classified as having LFV. The presence of at least one of the previous markers of left atrial stasis (LAAT, DSEC or LFV) was designated as left atrial abnormality (LA ABN).

The cardiologists performing the transthoracic and transesophageal echocardiogram were blinded for the lab results and clinical information of the patients other than the fact that they were in AF and there was need for excluding transesophageal echocardiogram changes that could contraindicate cardioversion.

3. Laboratory data

After venous blood was drawn, it was immediately transferred into our hospital's laboratory using an automatic internal tube transference system directly connected from different parts of the hospital into the laboratory. On average laboratory measures were performed within 15 minutes of venous blood sampling.

Automated blood cell counting was performed using the Cell-Dyn Sapphire Hematology Analyzer from Abbot Diagnostics. Reference range values for complete blood count data according to local calibration from our hospital's laboratory were: hemoglobin – 13.0 to 17.5 g/dL; leukocytes – 4.0 to 10.0 $x10^3/\mu L$; platelets – 150 to 400 $x10^3/\mu L$; plaquetocrit – 16.7 to 29.3%; MPV 8.17 to 9.65 fL; platelet distribution width (PDW) 14.7 to 17.4 %.

4. Prediction of transesophageal endpoints

PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis. Comparisons were performed according to the presence/absence of all markers of left atrial stasis. Chi-square was used for nominal variables and Student's t-test was used for comparison of continuous variables, where appropriate; the Levene's test was used in order to check the homogeneity of variance; equivalent non-parametric tests were used when Kolmogorov-Smirnov was in favor of absence of normal distribution. Results with $p < 0.05$ were regarded as significant.

Univariate analysis was performed using the chi-square test. Predictors from univariate analysis were used for obtaining logistic regression models (using the backward stepwise method likelihood ratio; probability for stepwise = 0.10) that could predict all the transesophageal echocardiogram endpoints: LAAT, DSEC, LFV and LA ABN.

Continuous variables such as left ventricle ejection fraction (LVEF), and MPV were converted into ordinal variables and then used in the logistic regression analysis. Established cutoff points according to data available in the literature were: ≥ 55% vs. < 55% [9] and < 40% vs. ≥ 40% [10] for LVEF; indexed left atrial volume ≥ $60ml/m^2$ vs. < $60ml/m^2$ [10]; MPV > 9.4fL vs. ≤ 9.4fL [5]; troponin I > 0.012ng/mL vs. non-detectable [11]; body mass index ≥ $27.0Kg/m^2$ vs. < $27.0Kg/m^2$ [12]. When cut-off values were not available in the literature, receiver operating characteristic

(ROC) curves were traced and using their coordinates we were able to define the optimal cutoff point (Youden index). The Hosmer-Lemeshow summary statistic was used to assess the goodness-of-fit of the models.

Results

The patients' baseline clinical, echocardiographic and laboratory characterization is shown on Table I. Average $CHADS_2$ and CHA_2DS_2-VASc values were 2.1±1.2 and 3.7±1.7, respectively. Only 147 patients (34.4%) were under oral anticoagulation and 73 of these (49.7%) had an INR ≥ 2.0. In 38.6% (n=165) of subjects there was no previously known history of AF.

1. **Mean platelet volume and changes found on transesophageal echocardiogram**

Comparisons of patients with MPV ≤ vs > 9.4fL are shown on Table I. Patients with MPV > 9.4fL had a higher prevalence of previous stroke of transient ischemic attack (TIA) (OR=1.706 $_{95\%}$CI 1.004-2.901), a higher $CHADS_2$ score and were more frequently medicated with angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers. These patients also displayed lower platelet count levels, higher rise in troponin I levels and a more dilated left atrium and left ventricle.

The following prevalence of markers of left atrial stasis was found on transesophageal echocardiogram: LAAT in 12.2%, DSEC in 29.7%, LFV in 15.3% and LA ABN in 34.2% (Table II). These were more frequent in patients with MPV > 9.4fL (Tables II and III).

After the analysis of ROC curves concerning the discrimination of LAAT, the following cutoff values for platelet count and indexed left ventricle diastolic diameter were found: ≥ $240x10^3$/uL (sensitivity = 46.8% and specificity = 67.6%)and ≥ 3.23 mm/m^2 (sensitivity = 58.3% and specificity = 75.1%), respectively.

On univariate analysis MPV was a predictor of all markers of left atrial stasis. Congestive heart failure, stroke or TIA, AF episode duration, platelet count, troponin I, iLVdd, iLAV and LVEF were among the other predictors of LAAT on univariate analysis.

Predictors of DSEC, LFV and LA ABN on univariate analysis are shown on Table III.

2. Incremental value of mean platelet volume to other predictors of left atrial stasis

On logistic regression, MPV remained an independent predictor of all markers of left atrial stasis, adding predictive value to clinical variables (stroke or TIA, congestive heart failure and diabetes mellitus), troponin I and echocardiographic parameters (indexed left atrial volume, indexed left ventricle diastolic diameter and LVEF) that were also included in the predictive models (Table IV).

MPV was the only variable that could independently predict the presence of all markers of left atrial stasis.

Discussion

Our data shows that MPV was associated to an increased prevalence of LAAT, DSEC, LVF and LA ABN, echocardiographic markers that are known to associate with cardioembolic stroke and an adverse prognosis in patients with AF. Thus, on logistic regression multivariate analysis MPV was able to add additive predictive value to clinical parameters from the $CHADS_2$ score (congestive heart failure, stroke or TIA and diabetes mellitus), echocardiographic parameters (indexed left atrial volume, indexed left ventricle diastolic diameter and LVEF) and other biomarkers (troponin I), as far as prediction of all transesophageal echocardiogram markers of left atrial stasis are concerned.

These results suggest that the recently described increased prevalence of stroke in patients with AF and elevated MPV [5] is possibly due to cardioembolism, which reinforces the importance of our findings in the management of patients with AF:

First, in patients undergoing procedures like cardioversion or AF ablation, a transesophageal echocardiogram (a semi-invasive and highly uncomfortable exam for most patients) is frequently needed in order to rule out the presence of LAAT. By proving the association of MPV with this type of marker, we may contribute to the future development of probabilistic risk scores, combining several variables, that may allow the selection of patients who can be spared this examination (since they are very low risk), or identify those that are very high risk, and therefore must necessarily perform it to prevent thromboembolic complications related to the procedure.

Second, a possible explanation for the association of MPV with stroke could be the increased platelet reactivity leading to peripheral thrombi formation. By showing that this may, in fact, be due to cardioembolism, adequate therapeutic interventions may be pursued or developed for targeting these alterations in patients with AF who test positive for this marker.

Third, novel biomarkers are now being tested in patients with AF in order to improve thromboembolic risk stratification [13]. By demonstrating that MPV possibly associates with stroke due to a cardioembolic mechanism, we provide rationale for its future prospective assessment both separately and as part of risk scores designed for the AF population.

Larger platelets are thought to be younger, more reactive and more thrombogenic [14, 15]. MPV seems to reflect both proinflammatory and prothrombotic states [16]. An association of increased MPV with risk factors like diabetes mellitus, hypertension and smoking has been known for some time [17]. An elevated MPV has been found in paroxysmal AF patients when compared to subjects in sinus rhythm [18]. In our study, patients with MPV > 9.4fL displayed a trend for a higher prevalence of AF episodes lasting for more than one week, which is concordant with these results.

The only investigation assessing the relation between left atrial stasis markers (focusing only on LAAT) and MPV provided negative results towards an association [19]. Still, some points need to be clarified regarding that study: first, it included 18.0% (n=37) patients with severe mitral stenosis (the number of patients with lower levels of mitral stenosis is not clarified in the manuscript), which may account for the highly unusual elevated prevalence of LAAT (46.8%; n=96) that was described. Second, the average MPV value was approximately 10.6fL. That was well over the one we found in our sample (9.3±1.1fL). Therefore, in our perspective these two studies cannot be appropriately compared.

Based on investigations concerning the composition of spontaneous echocardiographic contrast (thought to be composed of aggregated activated platelets and leucocytes [20]) we are lead into thinking that the association of mean platelet volume with left atrial stasis is not merely due to chance.

Thromboembolic risk stratification of patients with AF is currently based on clinical schemes: the $CHADS_2$ [20] and CHA_2DS_2-VASc score [21]. Still, these classifications have not proved to be as effective in the setting of evaluating patients before AF ablation or cardioversion [23]. In our

population, some of the parameters that are part of these classifications, like age, female gender, hypertension and vascular disease, were not independent predictors of left atrial stasis. The same applies to body mass index [12] that displayed no predictive value in our sample.

Troponin I has already been associated both with thromboembolism [13] and with markers of left atrial stasis [11] in AF patients. Concerning indexed left atrial volume, it has been shown to be a predictor of LAAT formation in AF patients [24], but it is still currently lacking a definite proof of its role in thromboembolic risk stratification of patients with AF.

As far as echocardiographic assessment of the left ventricle is concerned, evidence has been more robustly in favor of an association between both LVEF and LAAT [23, 25] and between LVEF and systemic embolism [10]. Conversely, evidence is very scarce concerning the role of indexed left ventricle diastolic diameter for the prediction of any thromboembolic endpoint.

To best of our knowledge this is the first report of an association between MPV with markers of left atrial stasis. In face of these results, we may hypothesize that mean platelet volume may be used in the future for assessing patients that are candidates to procedures like catheter ablation or cardioversion of atrial fibrillation. Moreover, these data support the need of its prospective assessment for risk stratification of AF. Due to its wide availability and low cost, mean platelet volume is a potential candidate for this setting.

Study Limitations:

A low prevalence of patients undergoing oral anticoagulation was found in our sample. Still, we reinforce that 165 patients (38.6%) had no previous diagnosis of AF. If we consider only

patients with previously known AF the prevalence of patients undergoing oral anticoagulation rises steeply to 56.1% (147 out of 262). Therefore, our results can be applied to patients presenting to the emergency department due to symptomatic AF, but probably not to different subsets of patients, like those undergoing percutaneous AF ablation, who have an expected very high prevalence of oral anticoagulation.

Patients over age of 75 displayed a lower prevalence of DSEC on univariate analysis, that was not confirmed after correction for other variables. This may be due to a selection bias, as we only select elderly patients who are very symptomatic and have a preserved biological age for the transesophageal echocardiogram and subsequent cardioversion strategy. As they usually have less risk factors and less severe disease than frail elderly who are directly referred to rate control strategy, this leads to the observed trend for lower prevalence of some markers of left atrial stasis in the transesophageal echocardiogram plus rhythm control strategy.

73 patients (17.1%) had no evaluation of left atrial appendage flow velocities. This was due to technical reasons (echocardiographic data being classified as unsuitable for the accurate assessment of flow velocities) or lack of probe tolerance by the patients (sedation was used in less than 3% of patients). In these subjects, transesophageal echocardiogram was performed without measurement of left atrial appendage flow velocities if the presence of LAAT and DSEC could be excluded right away.

Conclusions

Our results, using left atrial stasis markers, suggest that mean platelet volume are associated with the presence of left atrial stasis in non-valvular atrial fibrillation. These findings support the likely role of a cardioembolic mechanism in the association between mean platelet volume

and stroke in patients with non-valvular atrial fibrillation, reinforcing the possible usefulness of anticoagulation in this patient subset.

Further prospective investigations (derivation and validation studies) will be necessary to confirm the plausibility and role of mean platelet volume as a part of risk models aiming to discriminate the presence of left atrial appendage thrombus in atrial fibrillation patients undergoing procedures like percutaneous ablation or cardioversion.

Table I - Population baseline characteristics and sub-analysis according to mean platelet volume.

	Overall (n=427)	MPV ≤ 9.4fL (n=245)	MPV > 9.4fL (n=182)	P
Demographics				
Age	68.2±10.7	67.5±11.5	69.0±9.3	0.133
♀	32.1% (137)	31.4% (77)	33.0%(60)	0.736
Body Mass Index (Kg/m^2)	28.7±5.2	29.2±4.4	28.1±6.0	0.014
Clinical Data				
Congestive heart failure	49.4% (211)	45.7% (112)	54.4% (99)	0.076
Hypertension	83.4% (356)	83.3% (204)	83.5% (152)	0.945
Diabetes mellitus	24.6% (105)	24.1% (59)	25.3% (46)	0.777
Stroke or TIA	15.2% (65)	12.2% (30)	19.2% (35)	0.047
Vascular disease[a]	49.6% (212)	46.5% (114)	53.8% (98)	0.135
AF episode duration >1 week	77.8% (332)	74.7% (183)	81.9% (149)	0.078
$CHADS_2$ score	2.1±1.2	2.0±1.2	2.3±1.3	0.034
CHA_2DS_2-VASc score	3.7±1.7	3.5±1.8	3.9±1.7	0.081
Medication				
Oral anticoagulants	34.4% (147)	33.9% (83)	35.2% (64)	0.782
Enoxaparin	31.1% (133)	32.2% (79)	29.7% (54)	0.570
Antiplatelet agents	48.9% (209)	48.6% (119)	49.5% (90)	0.857
ACE-i or ARB-II	69.6% (297)	65.7% (161)	74.7% (136)	0.045
Statin	41.2% (176)	39.6% (97)	43.4% (79)	0.428
Laboratory Assessment				
Haemoglobin (g/dL)	13.8±1.9	13.9±1.9	13.6±1.8	0.089
Leukocytes (10^3/uL)	7.5±3.1	7.4±2.8	7.8±3.6	0.247
Platelets (10^3/uL)	222.6±86.2	240.6±95.2	198.4±65.1	<0.001
Plaquetocrit (%)	20.5±7.2	20.8±7.9	20.2±6.2	0.774
MPV (fL)	9.3±1.1			
PDW (%)	16.2±1.3	16.1±1.4	16.3±1.2	0.151
INR	1.4±0.7	1.4±0.7	1.4±0.7	0.583
INR ≥ 2.0	17.1% (73)	16.3% (40)	18.1% (33)	0.624
aPTT time (s)	34.1±7.7	33.0±6.0	35.6±9.5	0.078
Creatinine (umol/L)	111.7±93.9	111.4±107.8	112.1±71.4	0.329
Estimated GFR – MDRD	71.1±27.5	72.4±26.8	69.3±28.5	0.262
CRP (mg/L)	1.7±3.5	1.5±2.7	2.1±4.3	0.213
Troponin I (ng/mL)	0.03±0.07	0.03±0.04	0.04±0.10	0.032
Transthoracic echocardiogram data				
iLAV (ml/m^2)	60.4±24.5	56.7±21.9	64.7±26.6	0.006
iLVdd (mm/m^2)	29.6±5.6	28.8±5.5	30.5±5.6	0.010
LVEF < 55%	24.8% (106)	24.5% (60)	25.3% (46)	0.853

Legend: MPV – mean platelet volume; TIA – transient ischemic attack; AF – atrial fibrillation; ACE-i - angiotensin converting enzyme inhibitor; ARB-II - angiotensin II receptor blocker; PDW – platelet distribution width; INR - international normalized ratio; CRP – C reactive protein; GFR – glomerular filtration rate; MDRD - modified diet in renal disease formula; LV – left ventricle; LAAT - left atrial appendage thrombi; DSEC - dense spontaneous echo contrast; LFV - low flow velocities in the left atrial appendage; LA ABN – left atrial abnormality; aPTT - activated partial thromboplastin time; iLAV – indexed left atrial volume; iLVdd – indexed left ventricle diastolic diameter; LVEF – left ventricle ejection fraction.

[a] vascular disease is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque.

Table II – Presence of left atrial stasis on transesophageal echocardiogram and sub-analysis according to mean platelet volume.

	Overall (n=427)	MPV ≤ 9.4fL (n=245)	MPV > 9.4fL (n=182)	P
LAAT	12.2% (52)	9.0% (22)	16.5% (30)	0.019
DSEC	29.7% (127)	23.7% (58)	37.9% (69)	0.001
LFV	15.3% (54/354)[a]	9.1% (19/208)	24.0% (35/146)	<0.001
LA ABN	34.2% (146)	27.3% (67)	43.4% (79)	0.001

Legend: MPV – mean platelet volume; LAAT - left atrial appendage thrombi; DSEC - dense spontaneous echo contrast; LFV - low flow velocities in the left atrial appendage; LA ABN – left atrial abnormality.
[a] only 354 subjects had assessment of left atrial appendage flow velocities due to technical or procedural reasons (see discussion).

Table III – Univariate analysis of parameters eventually associated transesophageal echocardiogram endpoints.

Variable	LAAT		DSEC		LFV		LA ABN	
	OR $CI_{95\%}$	P	OR $CI_{95\%}$	P	OR $CI_{95\%}$	P	OR $CI_{95\%}$	P
Congestive heart failure	1.92 1.06-3.50	0.031	2.54 1.65-3.90	<0.001	1.53 0.85-2.74	0.152	2.77 1.83-4.20	<0.001
Hypertension	1.32 0.57-3.07	0.513	1.89 1.01-3.54	0.043	0.78 0.38-1.62	0.507	1.81 1.00-3.24	0.046
Diabetes mellitus	1.58 0.85-2.97	0.148	1.76 1.11-2.80	0.016	0.95 0.48-1.87	0.885	1.83 1.16-2.87	0.009
Age ≥ 65	1.53 0.78-3.02	0.218	1.22 0.77-1.93	0.399	0.97 0.51-1.83	0.925	1.38 0.89-2.16	0.153
Age ≥ 75	0.91 0.47-1.75	0.779	0.58 0.36-0.95	0.030	0.64 0.32-1.27	0.194	0.70 0.45-1.10	0.129
Stroke or TIA	4.12 2.16-7.84	<0.001	1.72 1.00-2.98	0.049	1.48 0.70-3.17	0.314	1.45 0.85-2.49	0.175
Vascular disease	1.58 0.88-2.85	0.125	1.80 1.18-2.74	0.006	1.73 0.96-3.12	0.066	1.62 1.08-2.42	0.019
Female gender	1.14 0.62-2.10	0.677	1.30 0.84-2.02	0.234	1.68 0.93-3.03	0.085	1.34 0.88-2.04	0.178
BMI ≥ 27.0Kg/m^2	0.85 0.45-1.60	0.618	1.17 0.74-1.86	0.497	0.74 0.40-1.37	0.329	1.05 0.68-1.64	0.820
AF episode duration >1 week	5.31 1.62-17.44	0.002	2.09 1.19-3.67	0.009	2.24 0.97-5.16	0.054	2.29 1.34-3.94	0.002
MPV > 9,4fL	2.00 1.11-3.60	0.019	1.97 1.29-3.00	0.001	3.14 1.71-5.75	<0.001	2.04 1.36-3.06	0.001
Platelets ≥ 240x10^3/uL	1.83 0.99-3.39	0.050	1.39 0.90-2.15	0.142	1.07 0.57-2.00	0.846	1.39 0.91-2.13	0.127
Troponin > 0.012ng/mL	4.92 1.39-17.41	0.007	3.35 1.75-6.42	<0.001	3.50 1.40-9.15	0.008	3.46 1.85-6.48	<0.001
iLVdd ≥ 3.23mm/m^2	4.13 2.01-8.49	<0.001	1.81 1.07-3.06	0.027	4.66 2.36-9.22	<0.001	2.40 1.43-4.01	0.001
iLAV ≥ 60ml/m^2	4.54 2.10-9.85	<0.001	4.36 2.57-7.40	<0.001	6.57 3.13-13.82	<0.001	4.62 2.76-7.73	<0.001
LVEF < 55%	2.79 1.53-5.08	0.001	4.17 2.62-6.64	<0.001	1.61 0.83-3.12	0.158	3.76 2.38-5.95	<0.001
LVEF ≤ 40%	3.00 1.57-5.74	0.001	5.79 3.34-10.02	<0.001	1.71 0.79-3.71	0.167	5.54 3.18-9.68	<0.001

Legend: LAAT - left atrial appendage thrombi; DSEC - dense spontaneous echo contrast; LFV - low flow velocities in the left atrial appendage; LA ABN – left atrial abnormality; OR – odds ratio; CI – confidence interval; TIA – transient ischemic attack; BMI – body mass index; AF – atrial fibrillation; MPV – mean platelet volume; iLAV – indexed left atrial volume; iLVdd – indexed left ventricle diastolic diameter; LVEF – left ventricle ejection fraction.

Table IV – Binary logistic regression multivariate analysis models for predicting the presence of markers of left atrial stasis.

Endpoint	Variable	Wald	B	Exp β $CI_{95\%}$	P	Hosmer and Lemeshow test
LAAT	Stroke / TIA	7.812	1.676	5.346 1.650-17.317	0.005	χ^2 = 9.093 df = 6 p = 0.105
	MPV > 9.4fL	3.899	1.226	3.408 1.009-11.512	0.048	
	Troponin > 0.012ng/mL	4.157	1.623	5.070 1.065-24.140	0.041	
	Constant	0	-0.010	0.990	0.984	
DSEC	CHF	7.523	0.845	2.327 1.273-4.256	0.006	χ^2 = 1.391 df = 6 p = 0.966
	MPV > 9.4fL	4.723	0.642	1.900 1.065-3.390	0.030	
	iLAV ≥ 60ml/m^2	16.661	1.221	3.392 1.887-6.097	<0.001	
	Constant	6.084	-0.654	0.520	0.014	
LFV	MPV > 9.4fL	4.629	1.257	3.515 1.118-11.049	0.031	χ^2 = 2.521 df = 5 p = 0.773
	iLAV ≥ 60ml/m^2	6.275	1.397	4.042 1.355-12.058	0.012	
	iLVdd ≥ 3.23mm/m2	3.603	1.066	2.905 0.966-8.737	0.058	
	Constant	0.444	-0.349	0.705	0.505	
LA ABN	MPV > 9.4fL	4.374	0.977	2.656 1.063-6.633	0.036	χ^2 = 5.108 df = 7 p = 0.647
	iLAV ≥ 60ml/m^2	11.504	1.493	4.451 1.878-10.549	0.001	
	Troponin > 0.012ng/mL	8.200	1.387	4.003 1.549-10.345	<0.001	
	DM	4.952	1.065	2.902 1.136-7.418	0.026	
	LVEF < 55%	10.316	1.714	5.551 1.950-15.798	0.001	
	Constant	17.359	-3.249	0.039	<0.001	

Legend: LAAT - left atrial appendage thrombi; DSEC - dense spontaneous echo contrast; LFV - low flow velocities in the left atrial appendage; LA ABN – left atrial abnormality; CI – confidence interval; TIA – transient ischemic attack; LVEF – left ventricle ejection fraction; MPV – mean platelet volume; iLAV – indexed left atrial volume; iLVdd – indexed left ventricle diastolic diameter.

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Goal II.C

Chronic kidney disease as a marker of thrombosis and thromboembolism in atrial fibrillation

The role of anticoagulation in patients with atrial fibrillation and chronic kidney disease

II.C.1

Decreased glomerular filtration rate and markers of left atrial stasis in patients with non-valvular AF

Rui Providência, Andreia Fernandes, Luís Paiva, Ana Faustino, Sérgio Barra, Ana Botelho, Joana Trigo, José Nascimento, António Leitão-Marques. Decreased glomerular filtration rate and markers of left atrial stasis in patients with non-valvular AF. Cardiology 2013;124(1):3-10 doi: 10.1159/000345434

Abstract:

Background: It is currently unknown if the increased risk of stroke in subjects with chronic kidney disease and atrial fibrillation (AF) is due to the presence of left atrial stasis or to any other vascular or systemic conditions.

Methods: Retrospective study of 372 subjects undergoing evaluation during an AF episode. Markers of left atrial stasis were sought on transesophageal echocardiogram: left atrial or left atrial appendage thrombus (LAAT), dense spontaneous echocardiographic contrast (DSEC) and low flow velocities (LFV) in the left atrial appendage. Subgroup comparisons were performed according to the level of estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows: ≥ 90, 45 to 89.9 and <45 ml/min/1.73m^2.

Results: LAAT was found in 11.6%, DSEC in 29.0% and LFV in 14.9%. A significant increase in the prevalence of DSEC was observed in the lower categories of eGFR: 37.8% in eGFR<45 ml/min, 30.7% in eGFR 45 to 89.9 ml/min and 17.0% in eGFR≥90 ml/min (p = 0.009; gamma for trend = 0.297, p = 0.002). The same was observed when assessing left atrial abnormality, the presence of at least one of the former transesophageal echocardiogram changes. On multivariate analysis clinical parameters from $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥ 75, Diabetes mellitus and Stroke) and CHA_2DS_2-VASc (age 65-74, history of vascular disease and female gender alongside with the clinical variables from $CHADS_2$) were predictors of transesophageal echocardiogram changes and an additive predictive value was found for eGFR.

Conclusions: Our results suggest an association between compromised renal function as assessed through eGFR and markers of left atrial stasis in patients with AF. The increased risk of stroke in this population may be due to thromboembolism.

Keywords: atrial fibrillation; stroke; chronic kidney disease; estimated glomerular filtration rate; CKD-EPI equation.

Introduction:

Chronic kidney disease is highly prevalent in patients with atrial fibrillation (AF), ranging from 7 to 27% of cases, as previously described in the literature[1-4].

According to the 2011 European Society of Cardiology AF guidelines, controlled data assessing a link between renal disease and increased risk of AF-related cardiovascular complications, namely stroke, is sparse [5].In the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) trial, higher stroke risk was observed in patients with AF and an estimated glomerular filtration rate (eGFR) under 45 mL/min when adjusted for other confounding variables. An important limitation that is pointed to this proposed association is the lack of supportive prospective studies [5]. Furthermore, vascular disease is also more severe in this population [6].

In patients with AF, left atrial dysfunction and increased thromboembolic risk can be illustrated by the presence of markers of left atrial stasis. The most well studied markers of left atrial stasis are left atrial appendage thrombus (LAAT), dense spontaneous echocardiographic contrast (DSEC) and left atrial appendage low flow velocities (LFV) (defined as ≤ 20cm/s). The presence of at least one of the former markers of left atrial stasis is also known as left atrial abnormality (LA ABN). The presence of left atrial stasis and protuberant aortic plaques has been associated with an increased risk of stroke [7]. An annual thromboembolism rate of 12% has been found in the SPAF III study in subjects with LA ABN alongside with protuberant aortic plaques [8]. *Bernhardt et al.* have described a 22% likelihood of cerebral embolism and/or death at 12 months follow-up despite anticoagulation in patients with AF and DSEC[9].

It is currently unknown if the increased risk of stroke in subjects with chronic kidney disease and AF is mainly due to the presence of left atrial stasis or to other vascular or systemic conditions (a thromboembolic vs. a atherothrombotic mechanism).

Purpose:

To assess the relation between estimated glomerular filtration rate, assessed through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the prevalence of markers of left atrial stasis on transesophageal echocardiogram during an atrial fibrillation episode.

Methods:

1. Study Population

Cross-sectional study of 504 consecutive patients undergoing transesophageal echocardiogram over a period of 32 months during an AF episode. Laboratory criteria for admission to the study were the following: patients who had been admitted to the emergency department were selected if they had a creatinine measurement in the last 24 hours and those performing elective transesophageal echocardiogram were selected only if they had a creatinine measurement in the past 6 months and had been clinically stable during that time window. Among the 479 patients fulfilling laboratory criteria, 107 with valvular AF (defined as presence of previous valve repair, prosthetic valve, rheumatic heart disease and moderate or severe valve stenosis and/or regurgitation) were excluded from analysis. The remaining 372 patients comprised the study population.

Baseline overall group characterization with demographic, anthropometric, clinical, laboratory and echocardiographic data, alongside with information on medication were obtained for all patients. These data were retrieved from clinical records.

Patients' indications for undergoing transesophageal echocardiogram were: 89.8% (n=334) for exclusion of LAAT before direct current cardioversion of AF, 7.5% (n=28) for cardioembolic source evaluation due to recent stroke and 2.7% (n=10) before percutaneous left atrial appendage closure.

2. Echocardiographic data

A GE Vivid 7 echocardiograph was used for transthoracic and transesophageal echocardiogram, alongside with the following probes: M4S (1.5–4.0 MHz) and a 6T phased array multiplane transoesophageal probe (2.9–7.0 MHz). Transesophageal echocardiogram was performed without anaesthesia or sedation in more than 97% of patients.

Left atrium volume was measured using the single-plane area length method [10, 11]. Left ventricle ejection fraction (LVEF) was qualitatively assessed and classified as normal, mildly, moderately, or severely depressed using the cutoff values defined in the guidelines [12, 13]. On transesophageal echocardiogram, the left atrium and left atrial appendage were imaged in different tomographic planes to detect the presence of LAAT and spontaneous echocardiographic contrast. Spontaneous echocardiographic contrast was classified according to the classification (1 to 4+) proposed by *Fatkin et al* [14]. Grade 3+ or 4+ was defined as DSEC. Left atrial appendage flow velocities were assessed with a pulsed Doppler sample placed 1 cm from the entry of the left atrial appendage into the body of the left atrium. Maximum emptying and filling velocities were estimated from an average of five well-defined emptying and filling waves. Patients with maximum emptying and filling velocity ≤20 cm/s were classified as having LFV. Aortic plaques ≥ 4mm were sought on transesophageal echocardiogram

according to the method described by *Amarenco et al* [15] and designated as protuberant aortic plaque.

All examinations were performed by two cardiologists with accreditation in transthoracic and transesophageal echocardiography by the European Society of Cardiology and who were blind for the lab results and clinical information (namely the level of eGFR, risk factors composing the $CHADS_2$ and CHA_2DS_2-VASc score and medication) of the patients other than the fact that they were in AF and their indication for the transesophageal echocardiogram.

Offline analysis was performed using the GE Health Care EchoPac Dimension software, PC version 108.1.4. Reporting of data concerning left atrial stasis resulted of mutual agreement between these two cardiologists after reviewing the images.

3. Laboratory data

Blood samples were collected at admission in all patients. Creatinine was measured using the CREA VITROS Chemistry Products assay. Values from 4 to 1238 umol/L could be detected with this assay and normal expected values were: 58 to 110 umol/L in male and 46 to 92 umol/L in female patients.

4. Assessment of Kidney Function

Kidney function was assessed as the level of estimated glomerular filtration rate (eGFR). This was calculated using the CKD-EPI equation [16], which has shown a higher performance than the Modification of Diet in Renal Disease (MDRD) equation [16, 17]. The last creatinine measurement

before performing transesophageal echocardiogram was used in the formula. Using the eGFR we defined three categories based on the defined cutoff value from the ATRIA study for increased risk of stroke in AF patients with renal disease (<45ml/min) and the cutoff value for normal eGFR (≥ 90 ml/min), according to the National Kidney Foundation classification for Chronic Kidney Disease [18, 19]. The other cutoff values for the different stages of chronic kidney disease in this classification were assessed on univariate analysis as predictors of transesophageal echocardiogram changes.

5. Statistical Analysis

PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis. Comparisons were performed according to the different classes of eGFR. Chi-square was used for nominal variables and ANOVA was used for comparison of continuous variables, where appropriate; equivalent non-parametric tests were used when *Kolmogorov-Smirnov* was in favor of absence of normal distribution. Post-hoc testing of ANOVA was performed using the *Bonferroni* test.

The overall tendency of increasing event rates with increasing risk score was tested using chi-square for trend (gamma).

Univariate analysis was performed using the chi-square test and providing a 95% confidence interval ($_{95\%}$CI). Results with $P < 0.05$ were regarded as significant.

Using the detected predictors from univariate analysis, we tried to obtain models to predict the studied transesophageal echocardiogram endpoints using binary logistic regression with the backward likelihood ratio method (probability for stepwise, removal = 0.10). The *Hosmer-*

Lemeshow summary statistic was used to assess the goodness-of-fit of the models. Information regarding the models' wald and goodness of fit is provided in the results section.

G*Power Version 3.1.2. was used for assessing the power of our sample for establishing a relation between eGFR < 45ml/min/1.73m^2 and a 50% increase in the risk of left atrial stasis. A cutoff power value of 0.80 was considered the standard for adequacy sample size.

Results:

Average age in our sample was 67.15±11.0, 28.5% (n=106) were female and most patients were white Caucasians (98.7%; n=367). The remaining subjects were black. Overall characterization of the study sample can be found on Table 1.

The following distribution of patients was found according to the previously defined eGFR cutoff values: 22.0% (n=82) had <45mL/min/1.73m^2; 54.3% (n=202) had 45 to 89.9 mL/min/1.73m^2 and 23.7% (n=88) had ≥ 90 mL/min/1.73m^2.

Markers of left atrial stasis were found in 32.5% (n=121) of subjects: 11.6% (n=43) had LAAT; 29.0% (n=108) had DSEC; 14.9% (46 out of 309) had LFV. Protuberant aortic plaques were found in 17.5% (n=65).

Population stratification according to eGFR levels

Comparisons according to the eGFR levels can be illustrated on Table 1. Congestive heart failure, arterial hypertension were increasingly more prevalent as eGFR values decreased.

There was an overall increase in $CHADS_2$ and CHA_2DS_2-VASc scores as eGFR values decreased. In the lower eGFR groups, there was a trend for a progressive increase in the prevalence of female gender individuals. Patients with higher eGFR were younger and had a lower prevalence of previous stroke or transient ischemic attack (TIA) and vascular disease (as defined in the CHA_2DS_2-VASc score)

Concerning anti-thrombotic medication and antiplatelet agents, no differences were found among the three eGFR classes. Patients with values ≥ 90 ml/min were less frequently on statins and ACEi/ARB-II.

Patients with eGFR < 45 presented with lower hemoglobin levels. No differences were found in what relates to international normalized ratio (INR) values.

A gradual and significant increase in left atrial volume was observed in the three eGFR categories, with patients in the lower eGFR group presenting higher values. Left ventricle ejection fraction > 55% was more frequent in patients with eGFR ≥ 90ml/min.

The prevalence of LAAT was similar in the 3 eGFR categories. An inverse relationship was found between eGFR levels and the prevalence of DSEC and LA ABN: as the levels of eGFR declined, the prevalence of DSEC and LA ABN significantly rose. The prevalence of protuberant aortic plaque was lower in the ≥ 90ml/min category than in the 45 to 89.9ml/min (10.2% vs 19.8%; $p<0.05$).

Predictors of left atrial stasis and protuberant plaques

Among the clinical risk factors that compose $CHADS_2$ and CHA_2DS_2-VASc alongside with eGFR and chronic hemodialysis, only congestive heart failure and previous stroke or TIA were

predictors of LAAT on univariate analysis: odds ratio (OR)=2.14; p=0.02 and OR=5.01; p<0.001, respectively (Table 2). These remained the only independent predictors of LAAT on multivariate logistic regression (Table IV).

As far as DSEC is concerned, congestive heart failure (OR=3.10; p<0.001), arterial hypertension (OR=2.01; p=0.04), diabetes mellitus (OR=1.63; p=0.05), stroke/TIA (OR=2.35; p<0.001), vascular disease (OR=1.89; p<0.001) and eGFR <30ml/min (OR=2.71; p=0.005), eGFR <45ml/min (OR=1.68; p=0.047) and eGFR <90ml/min (OR=2.37; p=0.005) were predictors on univariate analysis. Still, on multivariate logistic regression only congestive heart failure, stroke or TIA, vascular disease and eGFR < 30ml/min were included in a model to predict DSEC.

Female gender, vascular disease and eGFR <30ml/min were predictors of LFV both on univariate and multivariate analysis.

Congestive heart failure (OR=3.37; p<0.001), diabetes mellitus (OR=1.85; p=0.01), stroke/TIA (OR=2.09; p=0.01), vascular disease (OR=1.76; p=0.01), eGFR <30ml/min (OR=2.57; p=0.008), eGFR <45ml/min (OR=1.65; p=0.05) and eGFR <90ml/min (OR=1.88; p=0.03) were predictors of LA ABN on univariate analysis. Age ≥ 65 and arterial hypertension also displayed a trend for predicting this transesophageal echocardiogram endpoint. On multivariate logistic regression only congestive heart failure, diabetes mellitus, stroke/TIA and eGFR < 30/min were independent predictors of LA ABN.

On univariate analysis, arterial hypertension (OR=3.78; p=0.008), age ≥65 years (OR=2.23; p=0.01), age ≥ 75 (OR=3.32; p=0.04), chronic dialysis (OR=4.90; p=0.03) and eGFR<90ml/min (OR=2.16; p=0.04) were predictors of protuberant aortic plaque. The only independent predictors of protuberant aortic plaque on multivariate logistic regression were arterial hypertension, age ≥ 75 years and chronic dialysis.

The power of our sample for predicting a 50% increase in the risk of LAAT in patients with clearance <45ml/min/1.73m^2 was 0.81 with an estimated effect size of w=0.13 (>0.80, the standard for adequacy). Similar results were found for the remaining and more prevalent left atrial stasis endpoints.

Discussion:

We have found evidence supporting a possible relation between compromised renal function and an increased prevalence of markers of left atrial stasis in our sample composed of patients undergoing transesophageal echocardiogram during an AF episode. This may be possibly explained by the increased levels of endothelium-related factors, abnormalities in coagulations factor levels and activity and inflammation [(3)] that lead to a prothrombotic and inflammatory state in patients with chronic hemodialysis. Extrapolating this data, we wonder if these can also be observed, at least to some degree, in patients with mild to moderate kidney disease.

Moreover, these parameters of renal function added predictive power to the traditional clinical risk factors that compose the $CHADS_2$ and CHA_2DS_2-VASc.

As eGFR decreased, a higher estimated clinical risk as assessed by the $CHADS_2$ and CHA_2DS_2-VASc alongside with a significant increase in the prevalence of transesophageal echocardiogram markers of left atrial stasis (namely DSEC and LA ABN) was observed on univariate analysis. Therefore, we are led into thinking that the increased risk of stroke in patients with chronic kidney disease observed in the ATRIA study [(3)] is possibly due to thromboembolism rather than atherothrombosis. Since thrombi in AF are mainly composed of fibrin, resembling those found in venous thromboembolic disease [(3)], the theoretical benefit of anticoagulation in these subjects is reinforced by our results.

We have also observed a progressive dilatation of the left atrium (volume) alongside with deterioration of renal function. Since we have excluded all patients with valvular disease, we think that this may be due to the higher prevalence of congestive heart failure and arterial hypertension in those eGFR classes.

Other biomarkers like NTproBNP [20], cardiac troponin I [21] and C reactive protein [22] have shown a strong association to the presence of markers of left atrial stasis like LAAT [20-22], DSEC [20-22], LFV [21] and LA ABN[21] and have inclusively shown additive prognostic power when added to the $CHADS_2$[21, 22] and CHA_2DS_2VASc classifications[20, 21]. Transthoracic echocardiographic parameters like left atrial size and left ventricle ejection fraction have also been shown to be associated to markers of left atrial stasis and able to refine the currently available clinical risk schemes [23].

Despite this, extrapolation of these data into clinical endpoints is sometimes difficult, since these markers of left atrial stasis are only surrogate of an increased risk of thromboembolic events. Furthermore, transesophageal echocardiogram takes only one "picture" of the left atrium and left atrial appendage. Patients without left atrial stasis in one isolate evaluation may present a LA ABN at a different time.

The impact of compromised renal function in the presence of markers of left atrial stasis in subjects with AF had not been previously assessed in other investigations. Most of the knowledge concerning the association of compromised renal function to stroke in patients with AF results from the ATRIA study. Besides this data, evidence is controversial. Some studies are in favor of an association [24, 25], while others fail to confirm it [26, 27].

Concerning patients with chronic kidney disease as a whole, instead of analyzing only those with AF, there seems to be some contradiction concerning this association as well. There is evidence that points towards a positive association of chronic kidney disease with stroke [28, 29] but some studies have also failed to confirm the association [30, 31].

Marinigh et al. have recently proposed that the "c" from CHA_2DS_2-VASc could be eventually used as a surrogate for "creatinine clearence" if future evidence proved to confirm the association between chronic kidney disease and increased thromboembolism in AF patients [32]. Our findings seem to support this hypothesis.

Nevertheless, chronic kidney disease is a marker of bleeding risk in patients with AF and has been included in the HAS-BLED score [33]. Thus, the use of oral anticoagulation in these patients must be carefully addressed.

Limitations:

Proteinuria was not assessed in this cohort. Since the majority of patients were admitted to the emergency department and this data was retrospectively assessed, almost none had this measurement, since it is not common practice to assess proteinuria in this type of patients.

Some biases were present in our population. First, it was mainly composed of white Caucasians. Therefore, these results may not be extrapolated to other populations composed by different ethnic groups. Second, our patients were mostly subjects referred for cardioversion and may therefore not be representative of the general AF population. Last of all, patients on chronic dialysis were also underrepresented.

In our cohort, age over 75 displayed a trend for a protective role on univariate analysis, as far as LFV was concerned. Conversely, it was associated with a higher prevalence of protuberant aortic plaques. This may be explained by the fact that we only select elderly patients who are very symptomatic and have a preserved biological age for the transesophageal echocardiogram and subsequent cardioversion strategy. Most of the times, frail elderly are either not so symptomatic or are directly referred to rate control strategy. This may cause a

selection bias of healthier elderly individuals, without so many comorbidities as expected, and the observed trend for lower prevalence of some markers of left atrial stasis in the transesophageal echocardiogram plus rhythm control strategy.

In a subset of patients (63 out of 372; 16.9%) echocardiographic data was not available regarding left atrial appendage flow velocities. Some patients were classified as unsuitable for accurate assessment of this parameter while others did not tolerate the probe. Still, in all these subjects, the presence or absence of LAAT and DSEC could be excluded right away.

This study was not sufficiently powered for demonstrating increases of less than 50% in any of the endpoints. This may, in part, account for the observed lack of association between eGFR and the less prevalent transesophageal echocardiogram changes, like LAAT, LFV and protuberant aortic plaques.

Besides the presented clinical data that leads to hypothesis generation concerning a link between compromised kidney function and a prothrombotic status in patients with AF, further studies will be needed to assess its biological plausibility and eventually confirm and clarify the underlying mechanisms behind this association.

Conclusions

Our results suggest an association between compromised renal function as assessed through estimated glomerular filtration rate and markers of left atrial stasis in patients with atrial fibrillation. Moreover, the estimated glomerular filtration rate was able to increment the predictive ability of clinical parameters from $CHADS_2$ and CHA_2DS_2-VASc scores.

The observed increase in the prevalence of stroke in patients with atrial fibrillation and chronic kidney disease is possibly due to thromboembolism, rather than atherothrombosis.

Table 1 – Overall population characterization and according to the different levels of estimated glomerular filtration rate.

	Overall (n=372)	Estimated glomerular filtration rate by the CKD-EPI equation (mL/min/1.73m²)			
		< 45 (n=82)	45 to 89.9 (n=202)	90 or above (n=88)	p (all groups)
Age	67.08±11.04	71.91±9.23	69.21±8.67	57.69±11.52	<0.001 [B,C]
Female	28.5% (106)	37.8% (31)	27.7% (56)	21.6% (19)	0.061 [B]
Body Mass Index	28.72±5.42	28.42±6.87	28.43±4.66	29.73±5.54	0.186
Est.AF episode duration < 1 week	21.8% (81)	12.2% (10)	22.3% (45)	29.5% (26)	0.023 [B]
Est.AF episode duration >1 month	38.7% (144)	28.0% (23)	37.6% (76)	51.1% (45)	0.008 [B,C]
Chronic Dialysis	1.6% (6)	7.3% (6)	0% (0)	0% (0)	<0.001 [A,B]
Congestive heart failure	46.2% (172)	65.9% (54)	42.1% (85)	37.5% (33)	<0.001 [A,B]
Hypertension	82.5% (307)	91.5% (75)	82.2% (166)	75.0% (66)	0.018 [A,B]
Diabetes mellitus	26.3% (98)	31.7% (26)	22.8% (46)	29.5% (26)	0.222
Previous stroke or TIA	14.8% (55)	18.3% (15)	16.8% (34)	6.8% (6)	0.052 [B,C]
Vascular disease[1]	46.2% (172)	53.7% (44)	50.5% (102)	31.8% (28)	0.005 [B,C]
$CHADS_2$	2.08±1.24	2.75±1.25	2.06±1.18	1.58±1.10	<0.001 [A,B,C]
CHA_2DS_2VASc	3.51±1.74	4.44±1.70	3.59±1.66	2.52±1.45	<0.001 [A,B,C]
Antiplatelet agents	48.5% (180)	56.1% (46)	45.8% (92)	47.7% (42)	0.284
Oral anticoagulants	34.7% (129)	31.7% (26)	38.1% (77)	29.5% (26)	0.301
Enoxaparin	29.3% (109)	25.6% (21)	33.2% (67)	23.9% (21)	0.197
ACEi/ARB-II	70.7% (263)	81.7% (67)	72.3% (146)	56.8% (50)	0.001 [B,C]
Statin	41.1% (153)	50.0% (41)	43.1% (87)	28.4% (25)	0.012 [B,C]
eGFR using the CKD-EPI	67.96±25.85	30.62±10.73	69.57±13.02	99.01±7.49	<0.001 [A,B,C]
Creatinine (umol/L)	108.80±83.88	211.91±148.41	91.03±16.50	66.73±10.49	<0.001 [A,B,C]
Blood urea nytrogen (mmol/L)	8.77±5.18	14.67±7.54	7.79±2.62	5.64±1.68	<0.001 [A,B,C]
INR	1.43±0.70	1.46±0.66	1.45±0.71	1.33±0.73	0.381
Haemoglobin (g/dL)	13.87±1.94	12.69±1.88	14.19±1.78	14.16±1.98	<0.001 [A,B]
INR ≥ 2.0	19.1% (71) [2]	19.5% (16)	21.3% (43)	13.6% (12)	0.311
Left atrium volume (ml/m²)	59.92±24.53	71.03±32.97	59.84±21.20	50.57±18.38	<0.001 [A,B,C]
LVEF < 55%	22.3% (83)	30.5% (25)	22.8% (46)	13.6% (12)	0.030 [B]
LVEF ≤ 35%	9.1% (34)	14.6% (12)	7.9% (16)	6.8% (6)	0.141

Legend: eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration equation; AF – atrial fibrillation; TIA – transient ischemic attack; ACEi - angiotensin converting enzyme inhibitor; ARB-II - angiotensin II receptor blocker; LVEF – left ventricle ejection fraction.
Subgroup comparisons according to eGFR: [A] <45 vs 45 to 89.9 p<0.05; [B] <45 vs ≥ 90 p<0.05; [C] 45 to 89.9 vs ≥ 90 p<0.05.
[1] - vascular disease is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque.
[2] – 55.0% (71/129) of those undergoing oral anticoagulation

Table 2 – Detected transesophageal endpoints according to the different levels of estimated glomerular filtration rate.

		Estimated glomerular filtration rate by the CKD-EPI equation (mL/min/1.73m²)				
	Overall (n=372)	< 45 (n=82)	45 to 89.9 (n=202)	90 or above (n=88)	P (all groups)	P (gamma for trend)
LAAT % (n)	11.6% (43)	11.0% (9)	13.4% (27)	8.0% (7)	0.408	0.475 (gamma = 0.096)
DSEC % (n)	29.0% (108)	37.8% (31)	30.7% (62)	17.0% (15)	0.009 [A,B]	0.002 (gamma = 0.297)
LFV % (n)	14.9% (46) [1]	19.4% (14/72) [1]	15.0% (24/160) [1]	10.4% (8/77) [1]	0.300	0.118 (gamma = 0.212)
LA ABN % (n)	32.5% (121)	41.5% (34)	33.2% (67)	22.7% (20)	0.032 [B]	0.008 (gamma = 0.250)
PP % (n)	17.5% (65)	19.5% (16)	19.8% (40)	10.2% (9)	0.122 [C]	0.080 (gamma =0.198)

Legend: CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration equation; LAAT – left atrial appendage thrombus; DSEC – dense spontaneous echocardiographic contrast; LFV – low flow velocities in the left atrial appendage; LA ABN – left atrial abnormality; PP – protuberant aortic plaque.

Subgroup comparisons according to estimated glomerular filtration rate: [A] <45 vs 45 to 89.9 p<0.05; [B] <45 vs ≥ 90 p<0.05; [C] 45 to 89.9 vs ≥ 90 p<0.05.

[1] – only 309 of patients had LAA flow velocities measured (see discussion).

Table 3 – Univariate analysis for predictors of changes on transesophageal echocardiography among the CHA_2DS_2-VASc score and renal derived parameters.

Variable	LAAT		DSEC		LFV		LA ABN		PP	
	OR 95% CI	P	OR 95% CI	P	OR 95% CI	p	OR 95% CI	p	OR 95% CI	p
CHF	2.14 1.11–4.13	0.02	3.10 1.94–4.95	<0.001	1.54 0.82–2.89	0.18	3.37 2.14–5.32	<0.001	0.74 0.43–1.27	0.27
Arterial hypertension	1.70 0.64–4.49	0.28	2.01 1.03–3.93	0.04	0.72 0.33–1.57	0.41	1.76 0.94–3.28	0.07	3.78 1.32–10.80	0.008
Age≥65	2.00 0.93–4.32	0.07	1.51 0.92–2.47	0.10	0.94 0.48–1.83	0.85	1.58 0.98–2.55	0.06	2.23 1.17–4.28	0.01
Age≥75	1.19 0.58–2.42	0.64	0.70 0.41–1.20	0.19	0.46 0.20–1.07	0.07	0.81 0.48–1.34	0.41	3.32 1.90–5.82	<0.001
DM	1.41 0.71–2.79	0.33	1.63 1.00–2.66	0.05	0.94 0.46–1.91	0.86	1.85 1.15–3.00	0.01	1.69 0.96–3.00	0.07
Stroke /TIA	5.01 2.49–10.07	<0.001	2.35 1.31–4.23	<0.001	1.94 0.88–4.27	0.10	2.09 1.17–3.75	0.01	1.78 0.90–3.50	0.09
♀	1.42 0.72–2.78	0.31	1.43 0.88–2.33	0.15	1.98 1.03–3.79	0.04	1.35 0.84–2.17	0.22	0.96 0.53–1.75	0.90
Vascular disease	1.68 0.88–3.19	0.11	2.03 1.29–3.21	0.002	2.13 1.12–4.04	0.02	1.76 1.13–2.72	0.01	N.A. [1]	N.A. [1]
Chronic dialysis	0.98 0.97–1.00	0.37	0.98 0.96–1.00	0.11	1.15 0.13–10.05	0.90	0.41 0.05–3.54	0.40	4.90 0.97–24.86	0.03
eGFR <30ml/min	1.02 0.34–3.06	0.97	2.71 1.33–5.54	0.005	2.80 1.19–6.59	0.014	2.57 1.26–5.23	0.008	1.01 0.40–2.56	0.98
eGFR <45ml/min	0.93 0.43–2.02	0.85	1.68 1.00–2.82	0.047	1.55 0.77–3.09	0.22	1.65 1.00–2.74	0.050	1.19 0.64–2.23	0.58
eGFR <60ml/min	0.73 0.37–1.44	0.36	1.22 0.77–1.93	0.40	0.87 0.45–1.68	0.68	1.16 0.74–1.81	0.53	1.39 0.81–2.40	0.23
eGFR <90ml/min	1.68 0.72–3.92	0.23	2.37 1.29–4.35	0.005	1.69 0.75–3.80	0.20	1.88 1.08–3.27	0.03	2.16 1.02–4.56	0.04

Legend: OR – odds ratio; CI – confidence interval; LAAT – left atrial appendage thrombus; DSEC – dense spontaneous echocardiographic contrast; LFV – low flow velocities in the left atrial appendage; LA ABN – left atrial abnormality; PP – protuberant aortic plaque. CHF – congestive heart failure; DM – diabetes mellitus; TIA – transient ischemic attack; eGFR – estimated glomerular filtration rate.

Note: Vascular disease was not assessed as a predictor of protuberant plaque since it is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque.

Table 4 – Multivariate analysis models for the prediction of the assessed transesophageal echocardiogram study endpoints.

Model	Variable	Wald	B	Exp β	$CI_{95\%}$	P	Hosmer and Lemeshow test
LAAT	CHF	7.643	0.986	2.678	1.332-5.388	0.006	$\chi^2 = 0.470$ df = 2 p = 0.791
	Stroke or TIA	22.866	1.785	5.958	2.867-12.383	<0.001	
	Constant	0.366	0.217	1.243		0.545	
DSEC	CHF	20.127	1.137	3.116	1.897-5.119	<0.001	$\chi^2 = 6.600$ df = 6 p = 0.359
	Stroke or TIA	8.680	0.958	2.606	1.378-4.930	0.003	
	Vascular disease	5.163	0.562	1.755	1.080-2.851	0.023	
	eGFR < 30ml/min	4.518	0.815	2.260	1.066-4.793	0.034	
	Constant	9.467	-1.452	0.234		0.001	
LFV	Female gender	3.521	0.638	1.892	0.972-3.683	0.061	$\chi^2 = 1.812$ df = 4 p = 0.770
	Vascular disease	5.408	0.781	2.184	1.131-4.219	0.020	
	eGFR < 30ml/min	3.769	0.903	2.468	0.991-6.143	0.052	
	Constant	0.123	0.174	1.190		0.928	
LA ABN	CHF	24.628	1.214	3.366	2.084-5.435	<0.001	$\chi^2 = 7.713$ df = 5 p = 0.173
	Diabetes mellitus	3.131	0.458	1.582	0.952-2.628	0.077	
	Stroke or TIA	8.706	0.945	2.572	1.373-4.817	0.003	
	eGFR < 30ml/min	2.786	0.645	1.907	0.894-4.069	0.095	
	Constant	9.714	-1.553	0.212		0.002	
PP	Arterial hypertension	4.363	1.134	3.109	1.072-9.013	0.037	$\chi^2 = 0.701$ df = 3 p = 0.873
	Age ≥ 75 years	15.821	1.161	3.192	1.802-5.656	<0.001	
	Chronic Dyalisis	3.774	1.654	5.225	0.985-27.709	0.052	
	Constant	1.263	-0.979	0.376		0.261	

Legend: CI – confidence interval; LAAT– left atrial appendage thrombus; DSEC – dense spontaneous echocardiographic contrast; LFV– low flow velocities in the left atrial appendage; LA ABN – left atrial abnormality; PP– protuberant aortic plaque; eGFR– estimated glomerular filtration rate; CHF – congestive heart failure; TIA – transient ischemic attack.

[1] - vascular disease is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque.

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II.C.2

Chronic Kidney Disease and Risk of Thromboembolism in Patients with Atrial Fibrillation: A Systematic Review and Meta-analysis

Rui Providência, Eloi Marijon, Serge Boveda, Sérgio Barra, Kumar Narayanan, Jean-Yves Le Heuzey, Bernard P Gersh, Lino Gonçalves. Chronic kidney disease and risk of thromboembolism in patients with atrial fibrillation: A systematic review and meta-analysis. Am J Cardiol 2014;114(4):646-653. doi: 10.1016/j.amjcard.2014.05.048.

Abstract

Chronic kidney disease (CKD) and atrial fibrillation (AF) frequently coexist. However, the extent to which CKD increases the risk of thromboembolism among patients with non-valvular AF, as well as the benefits of anticoagulation in this group remain unclear. We addressed the role of CKD in the prediction of thromboembolic events and the impact of anticoagulation using a meta-analysis methodology. Data sources included MEDLINE, EMBASE and COCHRANE (from inception to January 2014). Three independent reviewers selected studies. Descriptive and quantitative information was extracted from each selected study and a random-effects meta-analysis was performed. After screening 962 search results, 19 studies were considered eligible. Among patients with AF, the presence of CKD resulted in an increased risk of thromboembolism (HR = 1.46; 95%CI 1.20-1.76, *P*=0.0001), particularly in case of endstage CKD (HR = 1.83; 95%CI 1.56-2.14, *P*<0.00001). Warfarin decreased the incidence of thromboembolic events in patients with non-endstage CKD (HR = 0.39; 95%CI 0.18-0.86, *P*<0.00001). Recent data on novel oral anticoagulants suggested a higher efficacy of these agents, compared to warfarin (HR = 0.80; 95%CI 0.66-0.96, *P*=0.02) and aspirin (HR = 0.32; 95%CI 0.19-0.55, *P*<0.0001) among non-endstage CKD. In conclusion, the presence of CKD in patients with AF is associated with an almost 50% increased thromboembolic risk which can be effectively decreased with appropriate antithrombotic therapy. Further prospective studies are needed to better evaluate the interest of anticoagulation among patients with severe CKD.

Keywords: atrial fibrillation; chronic kidney disease; glomerular filtration rate; dialysis; stroke; thromboembolism; anticoagulants.

Background

Thromboembolic events are one of the most feared complications of atrial fibrillation (AF) [1]. Chronic kidney disease (CKD) is relatively prevalent among patients with AF [2]. The extent to which the presence of CKD may increase the risk of thromboembolism in patients with AF has not yet been fully elucidated. Oral anticoagulation is the mainstay of thromboembolic prevention in patients with AF [3], but data on efficacy and safety in the CKD and dialysis population have been scarce and contradictory [4, 5].

Our aim was to systematically evaluate, through a meta-analysis methodology, the impact of the presence of CKD among AF patients as regards risk of thromboembolism, as well as the potential benefit of anticoagulation in that setting.

Methods

We performed a search on MEDLINE (via OVID and PubMED), EMBASE and COCHRANE (from inception to 3rd January 2014) databases using the following search string: "atrial fibrillation" AND ("renal failure" OR "chronic renal disease" OR “dialysis”) AND ("stroke" OR "thromboembolism"). The reference lists of the accessed full-text articles were further researched for sources of potential information relevant to this analysis. Full-text and abstract authors were contacted by email in order to retrieve additional information.

Only longitudinal studies assessing the occurrence of a composite endpoint of stroke or systemic embolism (and including transient ischemic attack - TIA) during follow-up among patients with AF were considered for inclusion. Both registries and randomized trials were considered eligible for analysis. The methods sections of evaluated studies were reviewed to confirm the suitability and composition of the reported endpoint. Studies assessing only stroke (either ischemic, hemorrhagic or a composite of both) and providing no data on systemic

embolism were not considered representative of the full spectrum of thromboembolism in AF and were excluded from analysis. Similarly, studies only reporting stroke or systemic embolism in association with myocardial infarction, hospitalization or death not due to stroke or systemic embolism were not included.

To be included in the systematic review, the studies needed to have a design allowing extraction of information concerning at least one of the two main aims of this paper: (1) Assessment of the incidence of stroke and systemic embolism among patients with AF according to the presence of CKD (including dialysis treatment); (2) Estimating the impact of anticoagulation in patients with CKD and AF. The population, intervention, comparison and outcome (PICO) approach was used for this aim [6]. The population of interest included non-valvular AF patients with CKD or treated with dialysis. The term endstage CKD was used for patients with disease requiring renal replacement therapy, either dialysis or transplant. Non-endstage CKD was used for the remaining patients with renal disease. The intervention was anticoagulation. Comparisons were performed between the following groups: adjusted-warfarin (target INR of 2 to 3) versus no treatment, aspirin or low dosage non-adjusted warfarin (target INR < 1.5); warfarin versus novel oral anticoagulants; novel oral anticoagulants vs. aspirin. The outcome has been defined above.

Two independent reviewers (RP and SCB) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine the eligibility of the study for the review and meta-analysis. Disagreements regarding eligibility were resolved by consensus with the help of a third reviewer (SB).

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group [7]. The following data were extracted for characterizing each patient sample in the selected studies, whenever available: criteria for defining CKD, number of patients with CKD (and when available, number in each estimated

glomerular filtration rate (eGFR) category of the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative classification [8]) or on dialysis in each study, type and frequency of anti-thrombotic treatment (warfarin or other vitamin K antagonists, novel oral anticoagulants, aspirin or other anti-platelet agents).

Data were pooled using random-effects, according to the Mantel-Haenszel model, through Review Manager (RevMan), Version 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The measurement of treatment effect and AF, CKD or dialysis exposure was performed using dichotomous adjusted hazard-ratios (HR) and 95% confidence intervals (95%CI). Pairwise comparisons were performed for the primary endpoint in the settings defined on section II. Comparison of the treatment effect of adjusted-dose warfarin vs. the novel oral anticoagulants was performed through the use of risk ratios (number of events or the incidence in each treatment group) from randomized controlled trials. Additional sensitivity analyses were performed, whenever data was available, regarding endstage CKD on dialysis treatment. Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I^2 statistic, respectively. The I^2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. Values of less than 25%, 25% to 50% and greater than 50% are by convention classified low, moderate, and high degrees of heterogeneity, respectively. The presence of publication bias was evaluated through the use of funnel plots if the appropriate requisites concerning the minimum number of included studies in a forest-plot were met (at least 10 studies) [9].

Results

Overall, 962 entries were retrieved for title and abstract analysis. Of these, 783 were excluded as they did not meet inclusion criteria for the meta-analysis and 106 were duplicate

entries. The remaining 73 studies were carefully evaluated, and after full-text review, only 19 studies (all full text papers) were finally considered eligible [2, 5, 10-26]. The stepwise selection process is illustrated in Figure 1. There was complete agreement between investigators on the inclusion of all the selected trials. Information on risk stratification, study design, number of participants and main findings in each study are provided on Table 1. Following the pre-defined inclusion and exclusion criteria, five or less studies were included in each of the traced forest-plots. Accordingly, no funnel-plots were drawn.

Among the selected studies, 10 provided information concerning the impact of CKD on the incidence of stroke or systemic embolism among patients with AF [2, 5, 10, 12, 13, 15, 17, 18, 20, 21]. Different equations were used for estimating the eGFR and classifying patients as having CKD: Cockroft-Gault formula was used in 5 studies [15, 18, 20, 21, 25], the Modification of Diet in Renal Disease was used in 5 [2, 10, 12, 23, 25]. Also, in two investigations [21, 25] the CKD-EPI and cystatin C clearance were also used for assessing the safety of efficacy of apixaban and dabigatran in different levels of eGFR. The remaining selected studies for the systematic review did not use any of these, since the diagnosis of CKD was retrieved from codification [5, 13, 14]. A cut-off of 50 to 60mL/min was used in most studies for defining the presence of CKD.

According to data on Figure 2, in patients with AF the presence of CKD was associated with a higher rate of thromboembolic events (HR = 1.46; 95%CI 1.20-1.76; P = 0.0001). All included studies were in favor of the association of CKD with an increase in thromboembolism in AF patients. However, their high heterogeneity is shown by the I^2 statistic ≥ 80%. Information concerning the risk of stroke or systemic embolism in patients with AF who were also on dialysis was provided by only one study: in the National Danish registry thromboembolism was found to be increased in this specific population (HR = 1.83; 95%CI 1.56-2.14; P < 0.00001) [5].

Baseline data, design and the main findings of trials providing information regarding warfarin in this setting [5, 15, 17, 18, 20, 21, 23, 25] are shown on Table 1. Information concerning time in therapeutic range is only known for the 3 included randomized controlled trials of the novel oral anticoagulants controlled with warfarin (64% in RE-LY [25], 55% in ROCKET-AF [18] and 62% in ARISTOTLE [21]). As regards the presence of heparin treatment in patients on dialysis, this information was absent or lacking details concerning the used protocol in the included studies.

The use of warfarin was associated with a major decrease in thromboembolic events (HR = 0.39; 95%CI 0.18-0.86; P < 0.00001) in patients with CKD. The effect was present in all studies but one (which revealed a strong trend for a benefit of warfarin) (Figure 3). Despite the overall favorable trend, a high heterogeneity, I^2 statistics of 91%, was observed driven by the differences in treatment effect. Only one study assessing the role of warfarin in the prevention of thromboembolism in patients on dialysis met the inclusion criteria for this meta-analysis. There, warfarin displayed a protective effect (HR = 0.44; 95%CI 0.26-0.74; P = 0.002). Also, the use of warfarin did not lead to an increased risk of bleeding (HR = 1.27; 95%CI 0.91-1.77; P = 0.15) [5].

In Table 1, data concerning renal function sub-analysis of 4 randomized controlled trials involving the use of the novel oral anticoagulants in patients with AF are shown. In AVERROES, aspirin was the treatment of the control arm and in the others, the *Randomized Evaluation of Long-Term Anticoagulation Therapy* (RE-LY), ROCKET-AF and *Apixaban for reduction in stroke and other ThromboembolLic events in atrial fibrillation* (ARISTOTLE) warfarin was used. Data concerning the effectiveness of the novel oral anticoagulants vs. warfarin and also vs. aspirin in patients with CKD (moderate / pre-terminal CKD) and AF are shown in Figure 4. A very low level of heterogeneity was found among the three selected trials (I^2=0%) showing an overall benefit of the novel oral anticoagulants compared to warfarin (HR = 0.80; 95%CI

0.66-0.96; P = 0.02). Apixaban, was more effective than aspirin in preventing stroke or systemic embolism in the non-endstage CKD population (HR = 0.32; 95%CI 0.19-0.55; P < 0.0001). In these novel oral anticoagulants trials, only a small minority of patients had eGFR <30ml/min [15, 21] and no patients on dialysis were included.

Discussion

The observed findings in this meta-analysis suggest an increased risk of thromboembolism when CKD is present among AF patients, with an incremental relation between the severity of renal dysfunction and the risk of thromboembolism. Anticoagulation seems to be effective in decreasing thromboembolic events in non-endstage CKD, with a particular benefit of novel oral anticoagulants in the moderate CKD population (eGFR 30 to 60ml/min) with AF. Regarding endstage CKD, data result from a single large National registry, and seem in favour of a benefit from warfarin. However, data on the novel oral anticoagulants in patients with endstage or severe CKD with eGFR < 25 to 30ml/min is currently lacking.

Preliminary evidence has suggested that adding CKD to the currently available risk stratification schemes for thromboembolism among AF patients may be worth further evaluation. In a sub-analysis of the *Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment* (AVERROES) trial, when adjusting for the $CHADS_2$ score in multivariate analysis, stage III CKD remained an independent predictor of stroke or systemic embolism (HR = 1.6; P < 0.01) [15].

Piccini and colleagues have tested the impact of adding CKD to the $CHADS_2$ score, and developed the R_2CHADS_2 score ($CHADS_2$ plus 2 points if creatinine clearance < 60ml/min). This was derived from the *Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With*

Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) cohort and validated in the *Anticoagulation and Risk Factors in Atrial Fibrillation* (ATRIA) study population. They found that, when using the R_2CHADS_2 score, almost 20% of patients were successfully reclassified into a more appropriate risk category (i.e., it improved the net reclassification index by 17.4% relative to $CHADS_2$; 95% CI 12.1-22.5%), even if c-statistics displayed similar values ($CHADS_2$ = 0.673 vs. R_2CHADS_2 = 0.672) [19].

A score comprising 8 variables (age, prior stroke, female gender, diabetes mellitus, heart failure, hypertension, proteinuria and eGFR < 45mL/min or end-stage renal disease) has been recently derived using data from the ATRIA cohort. Its external validation has shown promising results with higher c-statistics (0.70; 95%CI 0.67-0.72) than the $CHADS_2$ (0.66; 95%CI 0.64-0.69) or CHA_2DS_2-VASc (0.68; 95%CI 0.66-0.70) for the discrimination of all thromboembolic events [24]. The discriminative performance of this score was even better if only severe thromboembolic events were considered (c-statistic = 0.75; 95%CI 0.73-0.78), remaining better than $CHADS_2$ (c-statistic = 0.71; 95%CI 0.68-0.73) and CHA_2DS_2-VASc (c-statistic = 0.72; 95%CI 0.69-0.74). When assessing the net reclassification improvement obtained by the use of the new score, it was verified that 24% to 25% of patients were correctly reclassified into an adequate risk category, when compared to $CHADS_2$ and CHA_2DS_2-VASc, respectively (the percentage rose to 33% if only severe events were measured).

On the other hand, different findings were observed by Roldan et al. in a smaller population of patients with non-valvular AF stable on oral anticoagulation for more than 6 months, where adding eGFR (1 point to eGFR 30 to 59mL/min and 2 points to < 30mL/min) to the $CHADS_2$ and CHA_2DS_2-VASc scores resulted in no significant improvement in c-statistics or integrated discrimination improvement [10]. In addition, Banerjee et al. found that renal impairment and/or eGFR (codified as 3 different categories: <30, 30 to 59 and ≥ 60mL/min) did not increase the risk of ischemic stroke or systemic thromboembolism after adjustment for the

$CHADS_2$ risk factors. Thus, if added to $CHADS_2$ or CHA_2DS_2-VASc risk scores, eGFR did not independently add to the predictive value of any of these [12].

The increased risk of thromboembolism when CKD is present may be explained by the coexistent platelet dysfunction, a prothrombotic and inflammatory state and more severe vascular disease, frequently found in these patients [2]. It has also been proposed that the presence of CKD may be a marker of target-organ lesion [27]. Furthermore, an association of low eGFR with an increased prevalence of markers of left atrial stasis (dense spontaneous echocardiographic contrast and low flow velocities in the left atrial appendage) in AF patients on transesophageal echocardiogram may also account for this thromboembolic trend [28].

Oral anticoagulants were advantageous in the prevention of stroke or systemic embolism in patients with non-endstage CKD. Among patients on dialysis, the only study assessing the efficacy of warfarin in the prevention of thromboembolism demonstrated a benefit of this drug [5]. Besides scarcity of data, the increased risk of hemorrhagic stroke in this population when treated with warfarin [29] may deter the practicing physician from starting anticoagulation.

The observed advantage of the novel oral anticoagulants in the eGFR 30 to 60ml/min strata mimics the results observed in meta-analysis of the recent trials involving these agents [30], suggesting that their advantage concerning efficacy is maintained despite the presence of moderate CKD. Also, according to data from the sub-analysis of AVERROES in the class 3 CKD population, apixaban displays a higher efficacy compared with aspirin, with a similar bleeding risk [15]. However, only a minority of patients with eGFR 25 to 30ml/min and none with lower eGFR values have been included in these trials, which does not allow any firm conclusions concerning the use of these agents in those specific types of patients.

There are several limitations to this investigation, which are in part inherent to the meta-analysis methodology: some of the selected studies were small and the majority was

retrospective. Different methods for stroke definition have been used (e.g., with variable usage of imaging), and some uncertainties also remain concerning the chosen AF classification in some studies or even the reliability of its identification. Furthermore, a high heterogeneity of the assessed populations was illustrated by the relatively elevated I^2 score in most forest-plots.

Acknowledgements: none

Author, Ref	Study design, Acronym	Sample Size (pts)	Intervention or baseline anti-thrombotics	Dialysis pts (%) HD/PD	CKD pts (%) eGFR cutoff (ml/min)	Length of FUP (yrs)	Association of CKD with Stroke and/or SE			Anticoagulation in pts with CKD	
							Variable Outcome	HR 95%CI	Endpoint	Intervention Outcome	HR 95%CI
Roldan [10, 11]	Prospective Single-centre Observational	978	Acenocoumarol 100%	NA	eGFR 30-59 28% eGFR <30 3%	Median 2.4	eGFR NS	1.06 0.69-1.63	Stroke or SE	-	-
Banerjee [12]	Retrospective Regional (4 hospitals) Observational	5,912	VKA 52.5% Antiplatelet 30.8% None 26.0%	Baseline or FUP 2.2%	eGFR 30-59 20.2% eGFR < 30 5.8%	Mean 2.5	Renal impairment NS eGFR NS	1.06 0.75-1.49 1.09 0.84-1.41	Stroke or SE Stroke or SE	-	-
Olesen [5]	Retrospective Nationwide Observational	132,372	W 28.3% A 18.9% W+A 8.4%	Baseline RRT 0.7% FUP RRT 1.0% (78%HD/15%PD)	NA	Maximum 12	CKD (non-endstage) ↑ RRT ↑	1.49 1.38-1.59 1.83 1.57-2.14	Stroke or SE Stroke or SE	W NS ↓ trend W ↓	0.84 0.69-1.01 0.44 0.26-0.76
Friberg [13, 14]	Retrospective Nationwide Observational	170,291	W baseline 40% W baseline/FUP 47%	NA	renal disease ≈ 6.0%	Mean 1.5	Renal failure ↑	1.16 1.05-1.28	Ischemic stroke / US / TIA / SE	-	-
Eikelboom [15] Connolly [16]	RCT AVERROES	5,599	Apixa vs A (1:1) 5mg* bid vs 81-324mg od	Exclusion criteria	eGFR 30-60 30.3% eGFR ≤30 0.4%	Mean 1.1	Stage III CKD ↑	1.6 NA (P<0.01)	Stroke or SE	Apixa vs A ↓	0.32 0.18-0.55
Cha [17]	Retrospective Single-centre Observational	695	W 26.0% A 61.4% None 12.5%	NA	eGFR <60 20.8%	Median 5.5	eGFR < 60 ↑	3.63 1.57-8.42	Ischemic stroke / TIA / SE	W ↓	0.39 0.16-0.99
Patel [18] Piccini [19]	RCT ROCKET-AF	14,264	Riva vs W (1:1) 20mg* od	Exclusion criteria	eGFR <50 20.7%	Median 1.9	eGFR ↑	1.12 1.07-1.16	Stroke or SE	Riva vs W NS	0.88 0.65-1.19
Hart [20]	RCT SPAF-III	1,936	Low risk A 46.1% High risk 1:1 W vs low W+A** 53.9%	NA	eGFR 30-59 41.6% eGFR ≤30 1.5%	Low risk Mean 2 High risk Mean 1.1	Stage III CKD (pts treated with A) ↑	2.0 1.2-3.3	Ischemic stroke or SE	W vs A + low W ↓	0.24 0.10-0.38
Granger [21] Hohnloser [22]	RCT ARISTOTLE	18,201	Apixa vs W (1:1)	Exclusion criteria	eGFR ≤ 50 16.6% eGFR ≤30 1.5%	Median 1.8	-	-	Stroke or SE	Apixa vs W NS	0.79 0.55-1.14
Lai [23]	Retrospective Single-centre Observational	399	W 58.1% A 41.4%	23% HD	eGFR < 60 100% / 399 eGFR < 15 33.1% / 132	Mean W 2.6 No W 1.9	-	-	Ischemic stroke or SE	W ↓	0.28 0.16-0.50
Go [2] Singer [24]	Prospective Multicentric Observational ATRIA	10,908	W none	NA eGFR <15 0.9% ♂ 0.7% ♀	eGFR 45-59 18.5% / 2,499 eGFR <45 9.9% / 1,338	Pt-yrs 33,165	Proteinuria ↑ eGFR <45 ↑	1.54 1.29-1.85 1.39 1.13-1.71	Ischemic stroke or SE Ischemic stroke or SE	-	-
Connolly [25] Hijazi [36]	RCT RE-LY	17,951	High Dabi / Low Dabi vs W 150mg bid 110mg bid (1:1:1)	Exclusion criteria	eGFR < 50 18.8% / 3,374	Median 2.0	-	-	Stroke or SE	High Dabi vs W ↓ Low Dabi vs W NS	0.56 0.37-0.85 0.85 0.59-1.24

Table 1 – Selected studies for the systematic review: baseline information and main findings.

Legend: eGFR – estimated glomerular filtration rate; CKD – chronic kidney disease; FUP – follow-up; yrs – years; N.A. – not available; AF – atrial fibrillation; HR – hazard ratio; CI – confidence interval; pts – patients; W – warfarin; A – aspirin; Apixa – apixaban; Dabi – dabigatran; Riva – rivaroxaban; SE – systemic embolism; US – unspecified stroke; RRT – renal replacement therapy; TIA – transient ischemic attack; SPAF-III - Stroke Prevention in Atrial Fibrillation III; AVERROES - Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ROCKET-AF - Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RE-LY - Randomized Evaluation of Long-Term Anticoagulation Therapy; ARISTOTLE - Apixaban for reduction in stroke and other ThromboembоLic events in atrial fibrillation; ATRIA - Anticoagulation and Risk Factors in Atrial Fibrillation. Note: * Apixa (from 5mg bid to 2.5mg bid) and Riva (from 20mg od to 15mg od) presented dose-adjustment for patients with a certain degree of CKD. ** Target INR in all RCT was 2.0 to 3.0, except in the A + low dose W arm of the SPAF-III trial, where a mean INR of 1.3 was achieved as a result of the daily 1 to 3mg warfarin alongside with A 325mg od.

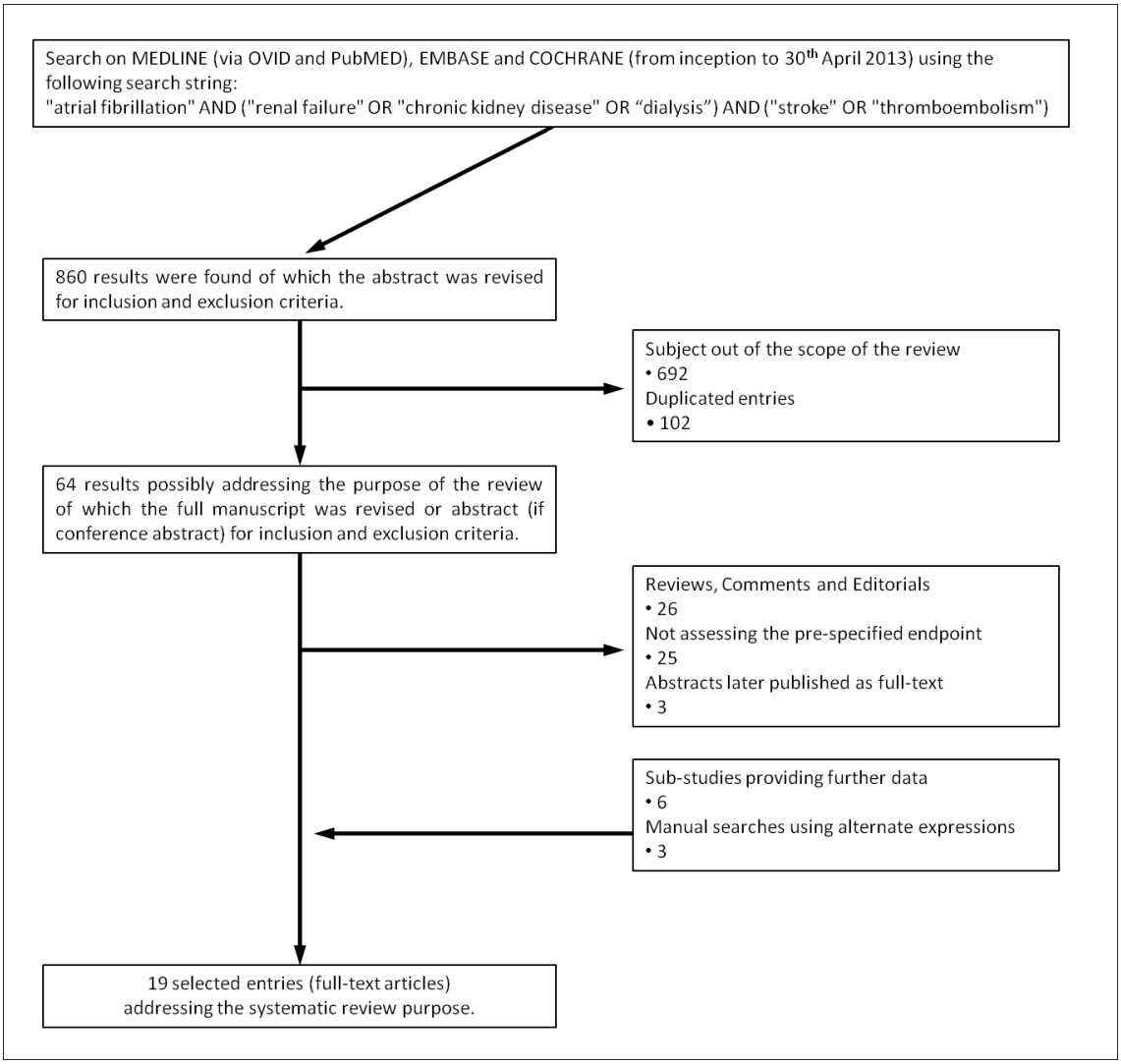

Figure 1 – Flow-chart diagram illustrating study selection.

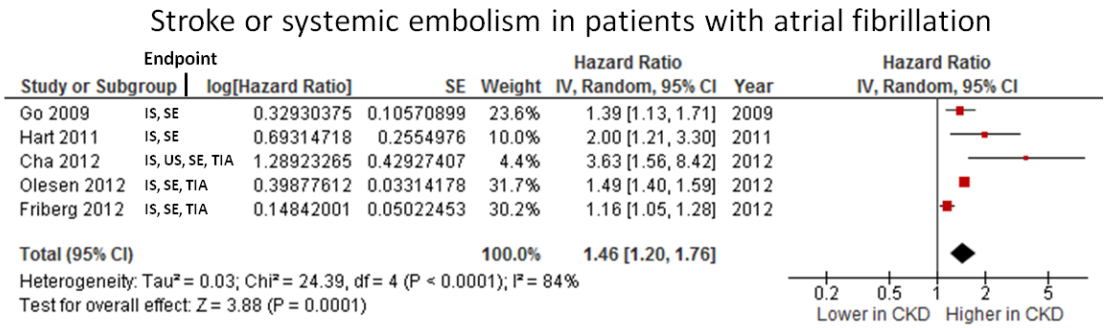

Figure 2 – Forest-plots illustrating the relation of stroke or systemic embolism in patients with AF with the presence/absence of chronic kidney disease.

Legend: CKD – chronic kidney disease; IS – ischemic stroke; US – stroke of uncertain origin; TIA – transient ischemic attack; SE – systemic embolism.

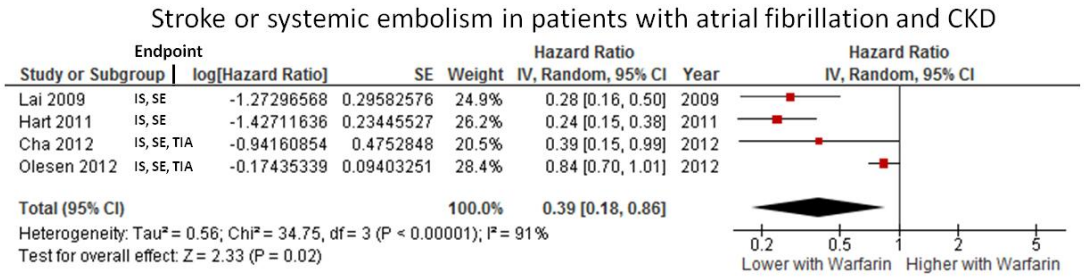

Figure 3 – Forest-plots illustrating the effect of anticoagulation in the incidence of stroke or systemic embolism in patients with atrial fibrillation and chronic kidney disease.

Legend: CKD – chronic kidney disease; IS – ischemic stroke; TIA – transient ischemic attack ; SE – systemic embolism .

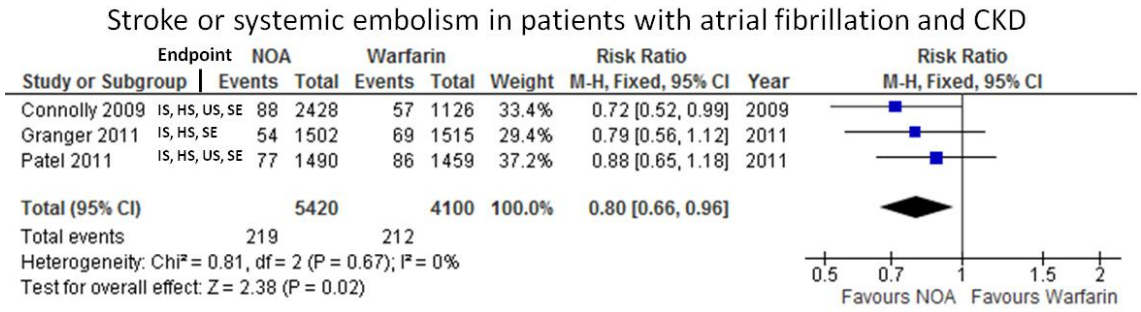

Figure 4 – Forest-plot illustrating the comparison of warfarin vs. the novel oral anticoagulants in the prevention of stroke or systemic embolism in patients with chronic kidney disease.

Legend: NOA – novel oral anticoagulants; CKD – chronic kidney disease; IS – ischemic stroke ; HS – hemorrhagic stroke ; US – stroke of uncertain origin ; TIA – transient ischemic attack ; SE – systemic embolism.

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II.C.3

Chronic kidney disease: One step further in the refinement of risk stratification of atrial fibrillation and impact on the choice of anticoagulant.

Rui Providência, Maria J Ferreira, Lino Gonçalves. Chronic kidney disease: one step further in the refinement of risk stratification of atrial fibrillation and impact on the choice of anticoagulant. Thromb Res 2013;132(2):e158-60. doi: 10.1016/j.thromres.2013.07.008.

Atrial fibrillation (AF) and chronic kidney disease (CKD) are very frequently associated. The observed prevalence of AF in a cohort of patients with CKD was 18% [1]. Conversely, in the AURICULA registry in Sweden, one 4.3 to 16.3% of individuals with AF showed moderate to severe CKD (estimated glomerular filtration rate < 45 and 30ml/min/1.73m2, respectively) [2].

In the ATRIA study, after adjustment for other confounding variables, a higher risk of ischemic stroke and other systemic embolism was observed in patients with AF and an estimated glomerular filtration rate under 45 mL/min [3].

Despite the fact that vascular disease is both more frequent and severe in the CKD population [4], the mechanism for this increased risk seems to be the higher prevalence of markers of atrial stasis and the prothrombotic milieu that can be found in the left atrium as glomerular filtration declines [5]. In a cohort of 372 patients with non-valvular AF evaluated by transesophageal echocardiogram, a gradual increase in the prevalence of dense spontaneous echocardiographic contrast, as eGFR deteriorated, was observed. Moreover, a low eGFR (<30 ml/min) independently predicted the presence of dense spontaneous echocardiographic contrast (adding information to congestive heart failure, stroke or transient ischemic attack and vascular disease) and low flow velocities (<20cm/s) in the left atrial appendage (independently of well known predictors of thromboembolism in AF like female gender, vascular disease).

Since thrombi in AF are mainly composed of fibrin, rather than platelets [3], anticoagulants would likely seem the most adequate therapy for stroke prevention. However, data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort showed that warfarin might be associated with an increased risk of stroke in hemodialysis patients, questioning some of this preliminary evidence [6].

Recently published data from a Danish registry comprising 132.372 patients with non-valvular AF confirmed the increased risk of stroke or systemic thromboembolism in patients with CKD (HR 1.49 95%CI 1.38-1.59 p<0.001) or requiring renal replacement therapy (RRT) (HR 1.83

95%CI 1.57-2.14 p<0.001) when compared to individuals with no renal disease [7]. Moreover, this risk was decreased with warfarin (HR 1.25 95%CI 1.07-1.47 p=0.01 in patients with non-end-stage CKD and HR 0.44 95%CI 0.26-0.74 p=0.002 in those with RRT). Aspirin failed to prevent or even increased these events (HR 1.25 95%CI 1.07-1.47 p=0.01 in non-end-stage CKD and HR 0.88 95%CI 0.59-1.32 p=0.54 in RRT), which seems to be according to the pathophysiologic mechanism that we have proposed for this association [5]. Conversely, the risk of bleeding was increased among all patients with renal disease (HR 2.24 95%CI 2.10-2.38 p<0.001 in CKD and HR 2.70 95%CI 2.38-3.07 p<0.001 in RRT), and further increased with all prophylactic therapies: warfarin (HR 1.33 95%CI 1.16-1.53 p<0.001), aspirin (HR 1.17 95%CI 1.02-1.34 p=0.03) or the combination of both (HR 1.61 95%CI 1.32-1.96 p<0.001) [7].

Strong proof in favor of the association of CKD with an increased risk of thromboembolism in non-valvular AF has been presented by *Piccini* and colleagues in a sub-analysis of the ROCKETAF trial. Furthermore, they have advanced one step further in the equation of risk stratification, by finding that the association between renal function and stroke was independent of and additive to the $CHADS_2$ score. Then, these authors have suggested a novel risk score, the R_2CHADS_2, which incorporated all variables from the $CHADS_2$ score and awarded 2 points to moderate chronic kidney disease (creatinine clearance < 60ml/min), leading to a net reclassification improvement of 17.4 to 22.6% in the assessment of the risk of stroke and systemic embolism when compared to $CHADS_2$ [8]. These findings are similar to those of ARISTOTLE renal sub-analysis, where an increase in thromboembolic events was demonstrated in the setting of compromised eGFR, after adjustment for other variables [9] and in a cohort study by Roldan and colleagues in patients under chronic anticoagulation with acenocumarol [10].

The theoretical possibility of incorporating creatinine clearance ("c") in the CHA_2DS_2-VASc score has already been considered by Marinigh et al [11], but its benefit needs yet to be assessed in clinical practice. Another problem that may merit consideration is which formula to

use for estimating GFR in this setting, since different ways have been used in the aforementioned studies (e.g., Modification of Diet in Renal Disease [3], Cockroft-Gault [8], Chronic Kidney Disease Epidemiology Collaboration, as well as cystatin-c measurements [9]).

Despite the apparent benefit of warfarin for preventing thromboembolic events, the associated bleeding risk leads to a lower net clinical benefit, which reinforces the need of individual case analysis for therapy tailoring and decision-making. The HAS-BLED score for assessing bleeding risk in this population will likely be an important piece in the decision process [12]. Additional precaution will be necessary if novel oral anticoagulants are chosen for patients with borderline renal function (e.g., stage 3 CKD; eGFR = 30 to 59ml/min) since eGFR levels may fluctuate during time, namely in the presence of infection, bleeding or other stressful events and these drugs are eliminated by this route (mainly dabigatran) [13].

Data from this Danish registry indirectly reinforces much of the enthusiasm concerning the novel oral anticoagulants, as data from the RE-LY [14], ARISTOTLE [8] and ROCKET-AF [15] subanalysis for patients with estimated creatinine clearance < 50ml/min shows superiority (dabigatran 150mg bid) or non-inferiority (dabigatran 110mg bid, rivaroxaban 15mg od and apixaban 2.5/5.0mg bid) for stroke prevention and comparable (dabigatran 110mg or 150mg bid and rivaroxaban 15mg od) or reduced (apixaban 2.5/5.0mg bid) major bleeding [16]. Despite this favorable evidence for individuals with stage 3 CKD, only 270 out of these 9.472 individuals (all from the ARISTOTLE trial) had stage 4 CKD (with clearance values ranging from 25 to 30ml/min) and none had end-stage renal disease, which leaves these two CKD stages (4 and 5) with no supporting evidence for therapy with the novel oral anticoagulants.

As for aspirin, its inadequateness seems now clear after the data from the Danish registry and the AVERROES [17] and SPAF III [18] trials. These trials compared oral anticoagulation (apixaban in the AVERROES and warfarin in the SPAF III) with aspirin and a sub-analysis of 2.213 patients with CKD shows clear reduction in the primary endpoint in favor of oral anticoagulation: HR 0.24 95%CI 0.10-0.38 p<0.001 in SPAF III for ischemic stroke and systemic

embolism (some patients in the aspirin arm also received under therapeutic doses of warfarin) and HR 0.32 95%CI 0.18-0.55 in the AVERROES. In the AVERROES trial no differences were found concerning major bleeding (HR=1.13 95%CI 0.74-1.75 p=0.57) [12].

In conclusion, warfarin treatment should be considered after net clinical benefit assessment (due to the increase in bleeding risk) in all patients with AF and CKD, as CKD independently increases the risk of thromboembolism (Figure 1). However, in patients in stage 3 CKD, the novel oral anticoagulants may be an option, as dabigatran 150mg bid seems to confer more effective protection, apixaban 2.5/5.0mg bid a higher safety profile and rivaroxaban 15mg od non-inferiority concerning efficacy and safety. At light of present data, no benefit exists for thromboembolic prevention with aspirin in patients with AF and CKD.

Patients with prohibitive bleeding risk contraindicating anticoagulant therapy may benefit from percutaneous left atrial appendage closure [19], since it has shown to be non-inferior to warfarin as far as effectiveness is concerned (RR 0.62 95%CI 0.35-1.25).

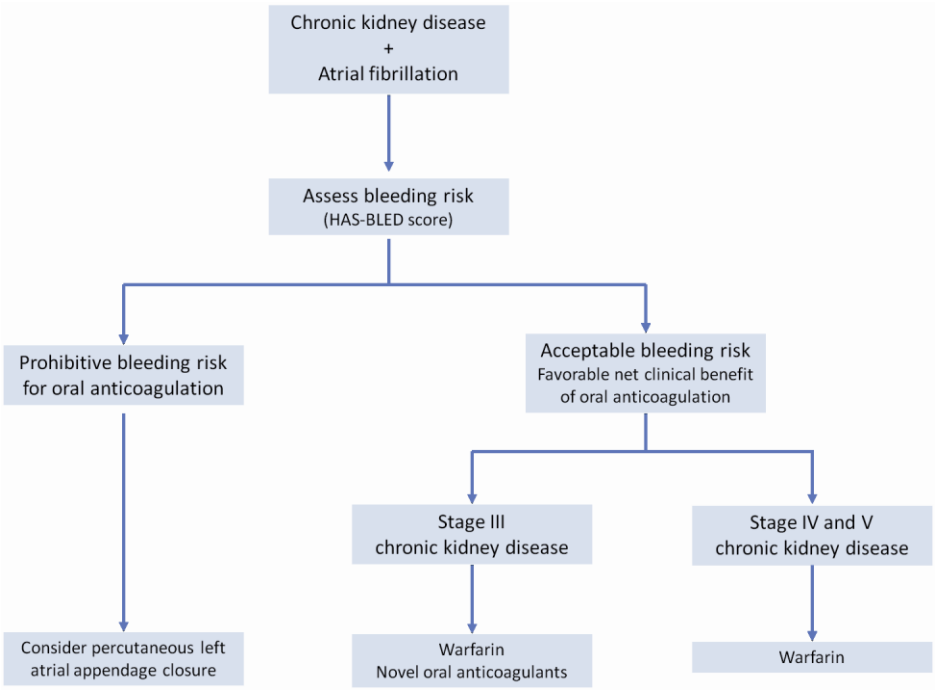

Figure 1 – Possible interpretation of recent trial results concerning the prophylaxis of thromboembolism in patients with atrial fibrillation and chronic kidney disease (CKD). Stages of CKD: Stage 3 – glomerular filtration rate (GFR) 30 to 59 ml/min/1.73m$_2$; Stage 4 – GFR 15 to 29 ml/min/1.73m$_2$; Stage 5 - <15 ml/min/1.73m$_2$ or on dialysis.

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Goal III.

The use of dagigatran in patients undergoing catheter ablation of atrial fibrillation

III.

Safety and Efficacy of Dabigatran versus Warfarin in Patients Undergoing Catheter Ablation of Atrial Fibrillation: a Systematic Review and Meta-analysis

Rui Providência, Jean-Paul Albenque, Stephane Combes, Abdeslam Bouzeman, Benjamin Casteigt, Nicolas Combes, Kumar Narayanan, Eloi Marijon, Serge Boveda. Safety and efficacy of Dabigatran versus warfarin in patients undergoing catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Heart 2014;100(4):324-35. doi: 10.1136/heartjnl-2013-304386.

Background: Dabigatran etexilate, a new thrombin inhibitor, has been shown to be comparable to warfarin in patients with atrial fibrillation (AF). However, there is a limited body of evidence on the efficacy and safety of using dabigatran among patients undergoing AF catheter ablation.

Objective: A random-effects meta-analysis was performed of controlled trials comparing dabigatran and warfarin in paroxysmal/persistent AF patients undergoing catheter ablation.

Methods: Data sources included MEDLINE, EMBASE and COCHRANE (from inception to April 2013). Three independent reviewers selected studies comparing Warfarin to Dabigatran. Descriptive and quantitative information was extracted from each selected study, regarding peri-procedural all-cause mortality, thromboembolic events and major bleeding, as well as modalities of peri-procedural anticoagulation bridging.

Results: After a detailed screening of 228 search results, 14 studies were identified enrolling a total of 4,782 patients (1,823 treated with dabigatran and 2,959 with warfarin). No deaths were reported. No significant differences were found between patients treated with dabigatran and warfarin as regards thromboembolic events (0.55% Dabigatran vs 0.17% Warfarin; RR=1.78; 95%CI 0.66-4.80; *P*=0.26) and major bleeding (1.48% Dabigatran vs 1.35% Warfarin; RR=1.07; 95%CI 0.51-2.26;*P*=0.86). No difference was found between the 110mg bid and 150mg bid dabigatran dosages concerning major bleeding (0% vs 1.62%, respectively; RR=0.19; 95%CI 0.01-3.18; *P*=0.25) and thromboembolism (0% vs 0.40%, respectively; RR=0.72; 95%CI 0.04-12.98; *P*=0.82).

Conclusions: In the specific setting of AF catheter ablation, this first pooled analysis suggests that patients treated with dabigatran have a similar incidence of thromboembolic events and major bleeding compared to warfarin, with low event rates overall.

Keywords: Anticoagulants; Stroke; Arrhythmias; Bleeding; Radiofrequency; Risk; Heterogeneity.

Introduction

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia and its prevalence is likely to rise steeply until 2050 [(1)]. Stroke and systemic embolism are among the most feared complications of AF and can be effectively tackled by anticoagulation [(2)].

Catheter ablation is currently recommended (class IIa, level of evidence C) as an interventional alternative for the treatment of patients with AF having symptomatic recurrences despite antiarrhythmic therapy [(3)]. Over the last 13 years this has became a very commonly performed procedure for the treatment of symptomatic AF patients [(4)].

Rigorous anticoagulation in the setting of AF catheter ablation has been demonstrated to be of prime importance. The recent large phase III trials involving the use of novel oral anticoagulants [(5-7)] confirmed the non-inferiority and even superiority, in some cases, of dabigatran, rivaroxaban and apixaban, compared to warfarin in AF patients. However, since a planned AF catheter ablation procedure was listed as an exclusion criteria in those trials, the efficacy and safety results cannot be extended to that setting. The 2012 Expert Consensus Statement on the management of patients with AF by the Heart Rhythm Society, European Heart Rhythm Association and European Cardiac Arrhythmia Society [(8)], highlights the limited clinical experience with the new anticoagulants in AF catheter ablation. Thus, even though dabigatran is being widely used and has been in vogue longer than the other new agents, strong evidence towards its utilization in patients undergoing AF ablation is lacking. Further, the presence of controversial results [(9)] in controlled trials with warfarin has lead cardiologists to question its safety and efficacy.

We therefore aimed to systematically evaluate, using a meta-analysis, all evidence concerning the use of dabigatran versus warfarin in catheter ablation for AF. The main objectives of this study were: (1) evaluate the efficacy and safety of dabigatran compared to warfarin; (2) determine whether there were significant differences between the 110 mg twice daily and 150

mg twice daily dosages of dabigatran; and (3) study the management of peri-procedural bridging anticoagulation.

Methods

I – Data Sources and Search strategy:

We performed a search on MEDLINE (via OVID and PubMED), EMBASE and COCHRANE (from inception to 13th April 2013) databases using the following search string: "atrial fibrillation" AND "ablation" AND "dabigatran".

The reference lists of the accessed full-text articles were further researched for sources of potential information relevant to this analysis. Experts in the field were contacted to ensure that all important studies in this area were covered. Abstract authors in congresses were also contacted by email in order to retrieve additional information. The databases were reassessed before the completion of the manuscript to find if any of the included abstracts had been published as full-text meanwhile.

II - Inclusion and Exclusion Criteria

The population, intervention, comparison and outcome (PICO) approach was used for conducting the meta-analysis [10]. The population of interest included patients with AF. The intervention was catheter ablation of AF and the associated peri-procedural anticoagulation. Comparisons were performed between the following groups: warfarin versus dabigatran; dabigatran 110mg bid versus 150mg bid. The primary outcomes were: major bleeding,

thromboembolism and all-cause mortality. The presence of minor bleeding, when reported, was also assessed.

Only controlled trials (full-text articles or conference abstracts) of patients undergoing catheter ablation of AF and treated either with warfarin or dabigatran before the procedure were selected.

The minimum necessary follow-up for study inclusion was until discharge after the procedure. Additionally, to be included, studies needed to provide information on assessment of all three major clinical outcome parameters: major bleeding, thromboembolism and death.

The following exclusion criteria were defined: trials with no comparator (i.e. warfarin), namely observational studies including only patients treated with dabigatran; starting of dabigatran treatment only after catheter ablation and evaluation of efficacy restricted to laboratory or imaging endpoints.

To ensure that trials met the pre-specified inclusion criteria, search results were reviewed by three investigators (RP, AB and BC), who needed to be in agreement for study selection.

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group [(11)].

Study quality was formally evaluated using the Delphi Consensus criteria for randomized controlled trials [(12)] and a modified Newcastle–Ottawa Quality Assessment Scale for Case Control Studies [(13)] by three reviewers (RP, AB and BC). An agreement, between the three reviewers was mandatory for the final classification of studies.

III - Endpoint definition for meta-analysis:

Classification of bleeding was based on previous reports and suggested recommendations [(14)].

The following endpoints were defined for the generation of forest-plots on meta-analysis.

- The primary endpoints were:

(i) All cause peri-procedural death

(ii) Thromboembolism – a composite of stroke, transient ischemic attack, systemic or pulmonary embolism. Asymptomatic cerebral embolism detected on routine or protocol magnetic resonance imaging or computed tomography (i.e. imaging endpoints with no clinical manifestation) was not included in the analysis.

(iii) Major bleeding – comprising cardiac tamponade, bleeding necessitating intervention or transfusion, massive haemoptysis, haemothorax, retroperitoneal bleeding or any other life-threatening bleed leading to prolongation of hospitalization.

- Secondary endpoint was:

- minor bleeding – defined as puncture site bleeding, thigh ecchymosis or hematoma, pericardial effusion with no haemodynamic compromise, minor gastrointestinal bleeding, epistaxis or any bleeding treated conservatively with no need for transfusion, surgery or prolonged hospitalization.

IV - Assessment of peri-procedural bridging of anticoagulation

The following data were extracted for assessing peri-procedural bridging anticoagulation: peri-procedural warfarin regimen (uninterrupted drug or discontinuation); timing of dabigatran interruption and restart; target activated clotting time (ACT).

V - Statistical Analysis

Data were pooled using random-effects, according to the Mantel-Haenszel model, through Review Manager (RevMan), Version 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The measurement of treatment effect was performed using

risk ratios (RR) and 95% CIs. Pairwise comparisons were performed for all endpoints between patients treated with dabigatran and warfarin and a separate sub-analysis (sensitivity analysis) was performed among patients treated with dabigatran, according to the dosage mentioned in the trials (150mg bid vs 110mg bid). Sensitivity analysis was also performed restricting the analysis of data to: trials whose patients were treated uninterrupted warfarin, prospective studies, investigations published as full-text articles, studies whose follow-up was at least 30 days and studies in which five of the nine items on the Delphi Consensus criteria for randomized controlled trials and a modified Newcastle–Ottawa Quality Assessment Scale for Case Control Studies were deemed satisfactory.

Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I^2 statistic, respectively. The presence of publication bias was evaluated by the use of funnel plots.

Results

I. Search Results

Overall, 228 entries were retrieved for title and abstract analysis. Of these, 169 were excluded as they did not meet inclusion criteria for the meta-analysis. The remaining 59 results were carefully screened, and after analysis of the full-text (in case of journal articles), only 14 studies (9 full text papers [9, 15-22] and 5 conference abstracts [23-27]) were deemed adequate for our review's purpose. The stepwise selection process is illustrated in Figure 1. There was a good agreement between investigators on the inclusion of the selected trials.

Baseline data and the design of selected trials are summarized in Tables I and II. The final population for this meta-analysis was composed of 4,782 patients (1,823 treated with dabigatran and 2,959 with warfarin). Table III illustrates the assessment of the included studies

through the Delphi criteria for randomized studies and Newcastle–Ottawa Scale for non-randomized case-controls studies.

The observed I^2 values showed a low to moderate heterogeneity in the main endpoint comparisons (I^2 = 0 for stroke and 41% for major bleeding).

II. Efficacy and Safety of Dabigatran vs. Warfarin

The main efficacy and safety outcomes (prevention of embolism and major bleeding) observed in the comparison between dabigatran and warfarin are displayed in Figure 2 and Table 4. The funnel-plot to ascertain publication bias is shown in Figure 3.

II.A. Death and Thromboembolism

No deaths were observed in any of the intervention groups. Thromboembolic events were reported in only 0.31% of patients (15 out of 4,782) and no significant differences were found between dabigatran and warfarin: 0.55% vs 0.17%, respectively (RR = 1.78; 95%CI 0.66-4.80; *P*=0.26).

II.B. Major Bleeding

Among all 14 studies, 67 events (accounting for an overall 1.40% incidence) of major bleeding were reported, with no significant differences observed between the 2 treatment arms (1.48% dabigatran vs 1.35% warfarin; RR= 1.07; 95%CI 0.51-2.26: *P*=0.86).

II.C. Minor Bleeding

Information on minor bleeding was not reported in one of the selected studies [24]. In the remaining, comprising 4,572 participants, 210 minor bleeding events (overall incidence 4.59%; 3.35% dabigatran versus 5.40% warfarin) were reported, with a relative risk reduction of 35% (95%CI 7-55%; *P*=0.02) in favor of dabigatran (Figure 4).

II.D. Sensitivity Analysis

Sensitivity analysis confirmed the lack of interference of uninterrupted warfarin, prospective studies, full-text articles, studies whose follow-up was at least 30 days and higher methodological quality studies (figures 5 to 7) in the overall results concerning the main endpoints: stroke and thromboembolism and major bleeding. However, as regards minor bleeding these analyses suggested a lack of significant differences.

III. Effect of Dabigatran Dosage: 150 mg bid versus 110 mg bid

Information on the dose of dabigatran used was available for 1,392 patients (155 with 110 mg bid and 1,237 with 150 mg bid). No significant differences were found between the two dosage groups (110mg bid versus 150mg bid, respectively) regarding major bleeding (0% vs 1.62%; RR = 0.19; 95%CI 0.01-3.18; *P*=0.25) and thromboembolism (0% vs 0.40%; RR = 0.72; 95%CI 0.04-12.98; *P*=0.82). Concerning minor bleeding, more events were observed with the 110mg bid dosage: 9.03% vs 2.51% (RR = 3.60; 95%CI 1.96-6.62; *P*<0.0001).

IV. Management of peri-procedural anticoagulation

The different peri-procedural regimens used in patients treated with dabigatran are displayed in Table II. The timing of the first withheld dose ranged from the morning of procedure (in 4 studies) to 48 hours before; the time interval for restarting ranged from 3 to 4 hours (in 6 studies) to 24 hours after ablation. In one study, uninterrupted dabigatran was used [19].

One third of all strokes or transient ischemic attacks (TIA) were associated with suspension of dabigatran for ≥ 24 hours before procedure (1 stroke in *Haines et al* [16] and 1 stroke and 1 TIA in *Rowley et al* [27]). Additionally, of all stroke and TIA in patients treated with dabigatran, 50% was related to a later timing (≥ 12 hours) for restarting the drug post-procedure (2 strokes and 2 TIAs [16, 27]). On the other hand, a higher incidence of major bleeding was reported by *Lakkireddy et al* [9], where dabigatran was stopped only in the morning of the procedure and restarted 3 hours post-procedure. Albeit suggesting a similar safety and efficacy profile, with

non-inferiority vs. warfarin, data concerning uninterrupted dabigatran results exclusively from one trial [19].

Among the patients of the warfarin group, safety and efficacy outcomes were similar irrespective of whether warfarin was continued or interrupted.

In addition, target ACT during procedure was 300 to 350 seconds in most studies, > 350 in 5 [9, 15, 19-21] and 250 to 300 seconds in one [26]. A higher value for target ACT [9, 15, 19-21] was not associated with a lower incidence of thromboembolic events. Furthermore, in the investigation by *Lakkireddy* and colleagues [9] a higher rate of cardiac tamponade in dabigatran treated patients (9/145) was observed. Importantly, a 3.7% rate of stroke was observed in the single study featuring a target ACT of 250 to 300 seconds [26]. However, due to the low number of participants, the possibility of a false positive association cannot be excluded.

Discussion:

The low rate of thromboembolic complications and major bleeding seen with dabigatran, (which was also similar to that observed with warfarin), seems to provide favorable support to its use, as an alternative to warfarin, in the setting of catheter ablation of AF. These results add important information on the use of dabigatran in this setting. They also serve to potentially alleviate some of the concerns raised by the rather unfavorable results in earlier studies (2.1% stroke or TIA and 6.2% major bleeds) [9], suggesting that dabigatran significantly increased the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy.

A very low rate of stroke and thromboembolic events was found in this meta-analysis among patients treated with dabigatran (0.55%), similar to what has been found in a recent analysis of

the Medicare beneficiaries (0.6 to 0.9%) [28]. A lower, but not significantly different, prevalence of embolism was found in the warfarin arm of this meta-analysis (0.17%), composed mainly of patients with uninterrupted treatment. This value is similar to the one described by *Hussein* and colleagues in patients with uninterrupted warfarin [29]. Therefore, we think that despite showing similar results compared to warfarin in this meta-analysis (and presenting values for thromboembolic complications similar to what has been reported in large registries of patients using anti-vitamin K agents [28]), validation of these results in future randomized controlled trials with blinded analysis may be justified. Furthermore, the use of uninterrupted dabigatran may also merit assessment, taking into account the promising results of the recently available study with this treatment regimen [19].

The proportion of patients referred for AF ablation who are on long-standing dabigatran therapy is progressively increasing. This is likely to pose new challenges for the practicing cardiologist, including the question of performing the procedure without discontinuation of dabigatran. The pooled data in this study from a large sample of patients provides an opportunity to address some of these issues.

In this meta-analysis comprising 14 controlled trials, dabigatran performed similarly to warfarin with regard to major bleeding and thromboembolism. Moreover, no deaths were observed in any of the treatment strategies. These results are in agreement with the favorable profile that was observed in an early observational non controlled trial by Winckle et al [30]. Furthermore, a recent analysis of the FDA Mini-Sentinel database for the period from October 19, 2010 (the date of dabigatran approval), to December 31, 2011, found that bleeding rates associated with dabigatran use during the period of interest did not appear to be higher than those associated with warfarin [31].

Though the present analysis suggests a lower rate of minor bleeding with dabigatran, there were marked differences in the reporting of this endpoint across the different studies. Furthermore, on sensitivity analysis these results did not remain significant. Thus, while this

result needs to be interpreted with caution, it seems, that at the very least, dabigatran is unlikely to be inferior to warfarin in this regard.

No significant differences in major bleeding and thromboembolism were observed between the two assigned dabigatran dosages. However, the low number of patients in each group (resulting from under-reporting of the dosage used in most selected studies) and the low rate of observed events, limit the extent to which firm conclusions can be drawn. The suggestion of less frequent minor bleeding with the 150mg bid dosage is hard to interpret due to the differences in reporting of this endpoint and in sample size.

The various transition regimens used in patients treated with dabigatran and the low number of observed events in each of those, renders difficult the task of establishing an ideal transition regimen in this setting. However, the great inter and sometimes intra-study variability notwithstanding, certain factors are likely to be important for decision-making.

The timing for drug interruption before the procedure must take into account the patient's renal function, as 80% of the drug is excreted by this pathway.

In patients with normal renal clearance, the best option may be drug suspension on the morning of the procedure, or the night before, but always less than 24 hours before the procedure.

If renal function is compromised, the drug should probably be interrupted sooner, depending on the degree of renal dysfunction.

There may be a rationale for restarting dabigatran 3 to 4 hours after assuring hemostasis, considering its short half-life and rapid onset of action.

The target ACT during catheter ablation in patients treated with dabigatran should be between 300 and 350 seconds, (similar to warfarin), as no additional benefits were found for higher values.

Finally, as there seems to be no inherent advantage of any of the studied dabigatran dosages, the creatinine clearance and bleeding risk (HAS-BLED score) should be taken into account for deciding the dosage to be used.

Limitations:

Important strengths of this study include the consistent reporting for thromboembolism (almost absent heterogeneity, I^2 = 0%) across studies. However, there are certain limitations, inherent to any meta-analysis.

First, heterogeneity was observed regarding major bleeding (I^2 = 41%; moderate heterogeneity). This may be explained by the marked diversity in ablation strategy, anticoagulation regimen, intra-procedural use of heparin and follow up between the incorporated studies. However, heterogeneity was low (I^2 = 12%) in the sensitivity analysis including only higher methodological quality studies, which confirms the small and similar incidence of major bleeding in both treatment arms already suggested by the forest-plot that included all studies.

Second, as already highlighted, certain comparisons are limited by the low number of subjects and low event rates. Third, in some cases of abstract-related data, even with the best attempts to gather information by directly contacting the authors, some data remained incomplete. However, these were mainly with regard to minor bleeding (a secondary endpoint) and details concerning peri-procedural drug transition; hence, missing data are unlikely to have significantly affected the primary results of the analysis. Fourth, only a minority of trials was randomized or prospective and a blinded analysis and/or central adjudication of endpoints was performed in none (i.e., the higher level of data quality). Therefore, these data must be considered preliminary and interpreted with some caution.

Conclusions:

The rate of thromboembolic complications and/or major bleeding in patients on dabigatran undergoing AF catheter ablation is low and similar to that seen with warfarin.

These results may suggest the feasibility and safety of AF catheter ablation in patients regularly treated with dabigatran. However, further prospective and randomized studies are still necessary to confirm these findings and clarify which peri-procedural regimen can minimize the risk of thromboembolic complications with dabigatran.

Table 1 – Baseline characteristics of included studies.

	Bassiouny et al. [15] 2013	Bernard et al. [23] 2013	Haines et al. [16] 2012	Ichiki et al. [24] 2012	Kaseno et al. [17] 2012	Kim et al. [18] 2012	Lakkireddy et al. [9] 2012	Maddox et al. [19] 2013	Mendoza et al. [25] 2012	Nin et al. [20] 2012	Pavaci et al. [26] 2012	Rowley et al. [27] 2012	Snipelisky et al. [21] 2012	Yamaji et al. [22] 2012
Source type	Journal article	Conference abstract	Journal article	Conference abstract	Journal article	Journal article	Journal article	Journal article	Conference abstract	Journal article	Conference abstract	Conference abstract	Journal article	Journal article
Study design	Prospective monocentric registry	Retrospective	Multicentric Retrospective case-match analysis	Prospective non-randomized	Retrospective	Retrospective	Multicentric Prospective non-randomized	Retrospective	Retrospective	Prospective randomized	Retrospective case-match analysis	Retrospective	Retrospective	Retrospective non-randomized and randomized*
Paroxysmal AF	57% D 55% W	46% D 50% W	53% D 48% W	53%	83% D 55% W	53% D 48% W	57% D 57% W	63% D 57% W	N.A.	76% D 71% W	N.A.	N.A.	68% D 46% W	65% D 62% W
Age	58.6 D 62.7 W	62.7 D 67.3 W	60.2 D 59.7 W	n.s.	59 D 62 W	61 D 61 W	60.4 D 60.3 W	62.3 D 62.5 W	62.9 D 64.0 W	61 D 61 W	N.A. Case-matched	63±10 similar	60.6 D 64.6 W	60 D 61 W
♀ Gender	25% D 26.6% W	N.A.	26% D 31% W	N.A.	25% D 21% W	20% D 26% W	21% D 21% W	24% D 33% W	10% D 12% W	16% D 20% W	N.A. Case matched	N.A.	19.4% D 25.6% W	25% D 24% W
Estimated thrombo-embolic risk	$CHADS_2$ Score = 0 42.6% D 29.1% W Score = 1 37.0% D 41.6% W Score ≥2 20.5% D 29.4% W	CHA_2DS_2-VASc 2.00 D 2.68 W	CHA_2DS_2-VASc 1.6±1.3 D 1.9±1.4 W	Values N.A. n.s. differences between treatment groups	$CHADS_2$ Score = 0 61% D 45% W Score = 1 31%D 41% W Score ≥ 2 8%D 14% W	CHA_2DS_2-VASc 1.6±1.3 D 1.7±1.3 W	$CHADS_2$ Score = 0 35% D 40% W Score = 1 43%D 41% W Score ≥2 23%D 19% W CHA_2DS_2-VASc 1.6±1.4 D 1.5±1.3 W	$CHADS_2$ 0.92±0.88 D 0.92±0.85 W CHA_2DS_2-VASc 1.73±1.45 D 1.69±1.33 W	$CHADS_2$ 1.32 D 1.29 W	$CHADS_2$ Score ≤ 1 82% D 80% W Score = 1 11%D 13% W Score ≥2 4%D 11% W	N.A.	$CHADS_2$ 1.3 ± 1	$CHADS_2$ 0.80 D 1.16 W	$CHADS_2$ Score = 0 36% D 33% W Score = 1 40%D 38% W Score ≥2 24%D 29% W CHA_2DS_2-VASc 1.8±1.6 D 1.7±1.6 W
Estimated bleeding risk	N.A.	N.A.	N.A.	N.A.	HAS-BLED 0.5±0.7 D 0.6±0.6 W	HAS-BLED 1.0±0.9 D 1.1±0.9 W	HAS-BLED 1.2±0.9 D 1.1±0.9 W	N.A.	HAS-BLED 1.47 D 1.63 W	N.A.	N.A.	N.A.	N.A.	N.A.
LV ejection fraction	55% D 55% W	60% D 58% W	56% D 57% W	N.A.	64% D 63% W	58% D 57% W	56% D 56% W	53% D 54% W	N.A.	61% D 62% W	N.A.	N.A.	N.A.	60% D 60% W
CKD / kidney function	Creat. 0.9 mg/dL D 0.9 mg/dL W	Creat. 1.0 mg/dL D 1.3 mg/dL W	Creat Clearence 93ml/min D 93ml/min W	N.A.	Creat. Clearence 97ml/min D 98ml/min W	Creat. 0.9 mg/dL D 0.9 mg/dLW	CKD 1% D 2% W	Creat. 1.0 mg/dL D 1.1 mg/dL W	N.A.	Creat. 0.9 mg/dL D 0.9 mg/dL W	N.A.	N.A.	N.A.	Exclusion of patients with renal clearence < 30mL/min

Legend: N.A. – not available; LV – left ventricle; CKD – chronic kidney disease; Creat. – creatinine.

* the first 291 patients were assigned to interrupted and non-interrupted warfarin in a non-randomized fashion and the last 212 patients were randomized to either uninterrupted warfarin or dabigatran.

Table 2 – Description of peri-procedural anticoagulation.

	Bassiouny et al. [15] 2013	Bernard et al. [23] 2013	Haines et al. [16] 2012	Ichiki et al. [24] 2012	Kaseno et al. [17] 2012	Kim et al. [18] 2012	Lakkireddy et al. [9] 2012	Maddox et al. [19] 2013	Mendoza et al. [25] 2012	Nin et al. [20] 2012	Pavaci et al. [26] 2012	Rowley et al. [27] 2012	Snipelisky et al. [21] 2012	Yamaji et al. [22] 2012
Patients treated with dabigatran	376	155	222	30	110	191	145	212	60	45	27	113	31	106
Dabigatran dosage	150mg bid	N.A.	150mg bid*	N.A.	110mg bid	150mg bid	150mg bid	150mg bid	150mg bid	110mg bid	N.A.	N.A.	150mg bid	110mg bid in 36 150mg bid in 70
Timing of first held dose of dabigatrain	Morning of the day of the procedure or the night before	24h	≤ 12h in 35 12-24h in 29 24-48h in 102 >48h in 18 Unknown in 18	morning of procedure	Morning of procedure	Night before procedure	Morning of procedure	Uninterrupted	Morning of procedure	Morning of the day before procedure	N.A.	Day before procedure	Morning of procedure	Morning of the day of the procedure
Time interval for restarting after procedure	After arousal from anesthesia/sedation	Within 24h	≤ 6h in 116 6-24h in 83 > 24h in 1 Unknown in 2	N.A.	Morning after procedure	4h	3h	Uninterrupted	immediately after sheath removal (144.3min)	4 hours after hemostasis at the puncture site	N.A.	> 24h (day following)	Evening of procedure	Single dose, 3 hours after the completion of the procedure
Patients treated with warfarin	623	44	222	180	101	572	145	251	58	45	27	169	125	397
Timing of first held dose of warfarin	uninterrupted	Uninterrupted	≤ 12h in 74 12-24h in 88 24-48h in 15 >48h in 25	uninterrupted	uninterrupted	uninterrupted	uninterrupted	Uninterrupted	uninterrupted	Morning of the day before procedure	uninterrupted	Day before procedure	Evening prior to the procedure	Uninterrupted in 203 patients. Interrupted 48h before in 194
Timing for restarting warfarin	uninterrupted	Uninterrupted	Day of the procedure	uninterrupted	uninterrupted	uninterrupted	uninterrupted	Uninterrupted	uninterrupted	4 hours after hemostasis at the puncture site	uninterrupted	Day after procedure	Evening of procedure	Day after procedure in patients who stopped warfarin
Target ACT (seconds) during procedure	350-450	N.A.	300-350 at least	N.A.	300-350	300-350	300-400	> 350-400	300-350	300-400	250-300	N.A.	> 350	300-350
Follow-up duration	1 month	1 month	Peri-procedural / hospital discharge	N.A.	At least 2 months	3 months	30 days	Peri-procedural / hospital discharge	1 month	2 weeks	N.A.	30 days	1 week	3 months

Legend: N.A. – not available; ACT – activated clotting time.

* Except for one elderly patient who took the 110mg bid dose.

Table 3 – Assessment of the quality of included studies: Delphi criteria for randomized studies and Newcastle-Ottawa Scale for non-randomized case-controls studies.

Study	Assessment	Classification*
Bassiouny et al. [15] 2013	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; groups controlled for baseline characteristics; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case/control status.	Attributable stars: 7
Bernard et al. [23] 2013	Adequate case definition; consecutive series of cases; controls were slightly older (3 years in average), had higher creatinine levels (1.3 vs 1.0 mg/dL) and a higher CHA_2DS_2-VASc (2.68 vs 2.00); information concerning the selection and definition of controls.	Attributable stars: 3
Haines et al. [16] 2012	Adequate case definition; consecutive series of cases; hospital controls, obtained by computer list generation; groups controlled for most baseline characteristics, except for slight differences in congestive heart failure, more prevalent in the dabigatran group and previous stroke, more prevalent in the warfarin group; a higher utilization of concomitant aspirin was observed in dabigatran patients and heparin/low molecular weight heparin was more used in the warfarin treatment arm; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case/control status.	Attributable stars: 6
Ichiki et al. [24] 2012	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; information concerning the selection and definition of controls.	Attributable stars: 4
Kaseno et al. [17] 2012	Adequate case definition; information concerning the selection and definition of controls; hospital controls; slight difference in baseline age (warfarin patients 3 years older), larger left atrial diameter (4mm difference in average) and higher prevalence of persistent AF in the warfarin group, requiring additional substrate modification; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case/control status.	Attributable stars: 4
Kim et al. [18] 2012	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; groups controlled for baseline characteristics, except for previous stroke, that was slightly more prevalent in the warfarin group; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; close monitoring of all patients during the 3 month follow-up period after the procedure; patients not blinded to case/control status.	Attributable stars: 6
Lakkireddy et al. [9] 2012	Adequate case definition; consecutive series of cases in the dabigatran treatment arm; controls matched for age, sex and type of AF; groups controlled for baseline characteristics; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case/control status.	Attributable stars: 6
Maddox et al. [19] 2013	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; groups controlled for most baseline characteristics, except for a slightly higher percentage of males in the dabigatran group; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case/control status.	Attributable stars: 6
Mendoza et al. [25] 2012	Adequate case definition; consecutive series of cases; hospital controls; information concerning the selection and definition of controls.	Attributable stars: 4
Nin et al. [20] 2012	Randomization performed; groups similar at baseline; eligibility criteria specified; point estimates and measures of variability presented for outcome measures; analysis of endpoints performed on an intention-to-treat basis.	Positive Delphi criteria: 5
Pavaci et al. [26] 2012	Adequate case definition; consecutive series of cases treated with dabigatran; case-matched hospital controls considering age, gender, body mass index, creatinine levels, left atrium dimensions and type of arrhythmia; information concerning the selection and definition of controls.	Attributable stars: 4
Rowley et al. [27] 2012	Adequate case definition; Series of cases treated with dabigatran, no information if the patients were consecutive; No information concerning the selection and definition of controls; Similar age and $CHADS_2$ score among treatment groups.	Attributable stars: 3
Snipelisky et al. [21] 2012	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; groups controlled for baseline characteristics, except for higher prevalence of persistent AF in the warfarin group; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case/control status; all patients had evidence for a completed medication profile with reconciliation.	Attributable stars: 7
Yamaji et al. [22] 2012	Adequate case definition; consecutive series of patients assigned to treatment groups in a non-randomized fashion in the first part of the study and with randomization to dabigatran or uninterrupted warfarin in the last 212 patients; adequate information concerning the selection and definition of controls; groups controlled for baseline characteristics; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; close monitoring of all patients during the 3 month follow-up period after the procedure; patients not blinded to case/control status.	Attributable stars: 7

Legend: * Number of criteria met out of a total of 9.

Table 4 – Comparison of endpoints across studies

	Bassiouny et al.[15] 2013	Bernard et al. [23] 2013	Haines et al. [16] 2012	Ichiki et al. [24] 2012	Kaseno et al. [17] 2012	Kim et al. [18] 2012	Lakkireddy et al. [9] 2012	Maddox et al. [19] 2013	Mendoza et al. [25] 2012	Nin et al. [20] 2012	Pavaci et al. [26] 2012	Rowley et al. [27] 2012	Snipelisky et al. [21] 2012	Yamaji et al. [22] 2012
Minor bleeding	7/376 D 16/623 W Groin hematoma 5/ 376 D 10/ 623 W GI bleed 1/376 D 2/623 W Minor Hemoptysis 1 /623 W Epistaxis 1/623 W PEff without tamponade 1/376 D 2/623 W	1/155 D 2/44 W	4/ 222 D 2/ 222 W Minor bleeding compications 2/ 222 D 1/ 222 W Vascular complication 2/222 D 1/222 W	N.A.	5/110 D 11/101 W Groin hematoma 5/110 D 11/101 W	5/191 D 19/572 W Groin hematoma 4/191 D 19/572 W PEff without tamponade 1/191 D	12/145 D 8/145 W Groin hematoma 6/145 D 5/145 W PEff without tamponade 6/145 D 4/145 W	1/212 D 3/251 W Groin hematoma 1/212 D 2/251 W Minor Hemoptysis 1/251 W	1/60 D 1/58 W Groin hematoma 1/58 W GI bleed 1/60 D	9/45 D 20/45 W Rebleeding from puncture site 9/45 D 20/45 W	2/27 D 4/27 W Groin hematoma 2/27 D 4/27 W	5/113 D 33/169 W Non-life threatening vascular complications 5/113 D 33/169 W	6/31 D 21/125 W Hematoma 1/31 D 4/125 W Rebleeding 5/31 D 10/125 W Echymosis 7/125 W	2/106 D 11/397 W Groin hematoma 1/106 D 4/397 W PEff without tamponade 1/106 D 7/397 W
Major bleeding	4/376 D 8/623 W PEff with need of pct. 3/ D 7/ W Hemoptysis* 1/ W Cerebral bleeding 1/ D †	2/155 D 2/44 W	3/222 D 3/222 W PEff with need of pct. 2/222 D 2/222 W Other major bleeding 1/222 D 1/222 W	4/30 D 4/180 W PEff with need of pct. 4/30 D 4/180 W	0/110 D 2/101 W Cardiac tamponade 2/101 W	4/191 D 12/572 W Cardiac tamponade 2/191 D 7/572 W Vascular complications 2/191 D 5/572 W	9/145 D 1/145 W Cardiac tamponade 9/145 D 1/145 W	1/212 D 3/251 W Cardiac tamponade 1/212 D 2/251 W Retroperitoneal hematoma 1/251 W	0	0	0	0/113 D 1/169 W Retroperitoneal bleed 1/169 W	0	0/106 D 4/397 W Cardiac tamponade 4/397 W
Thrombo-embolism	1/376 D 1/623 W Stroke 1/623 W Pulmonary embolism 1/376 D	0	2/222 D ‡ 0/222 W Stroke 1/222 D TIA 1/222 D	0	0	0	3/145 D 0/145 W Stroke or TIA 3/145D	1/212 D 0/251 TIA 1/212 D	0/60 D 1/58 W Stroke 1/58 W	0/45 D 1/45 W Mesenteric thrombosis 1/45 W	1/27 D 0/27 W Stroke 1/27 D	2/113 D 2/169 W Stroke 1/113 D 1/169 W TIA 1/113 D Pulmonary embolism 1/169 W	0	0

Legend: W – warfarin; D – dabigatran; N.A. – data not available; TIA – transient ischemic attack; PEff – pericardial effusion; GI – gastrointestinal; pct – pericardiocentesis; punct – puncture; N.A. – not available.

Comments: * Requiring transfusion. † Patient with a cerebral cavernous malformation. ‡The patients with stroke stopped dabigatran 36 hours before the procedure and the patient with TIA restarted the drug only 17 hours after the procedure.

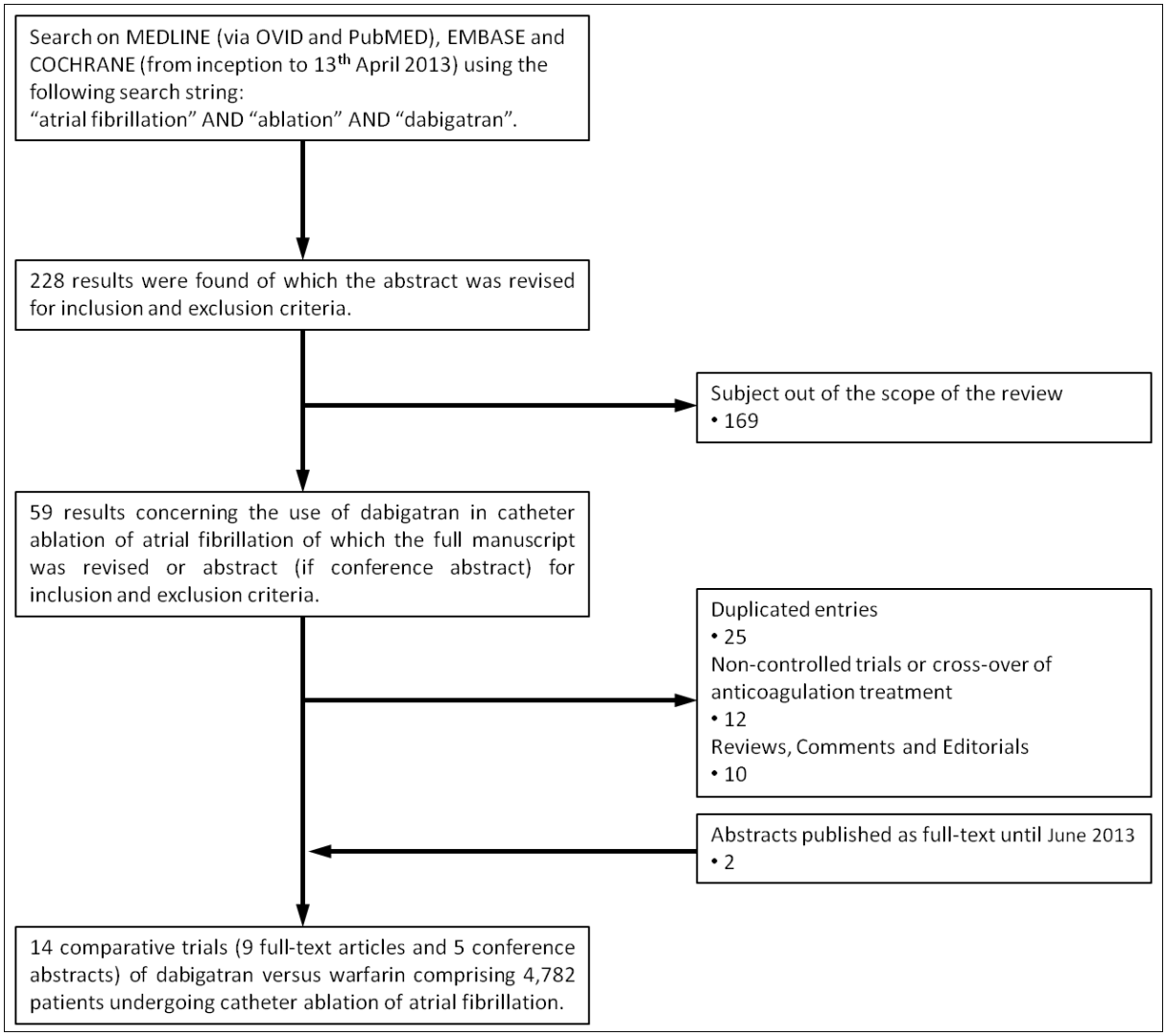

Figure 1 – Flow-chart diagram illustrating study selection.

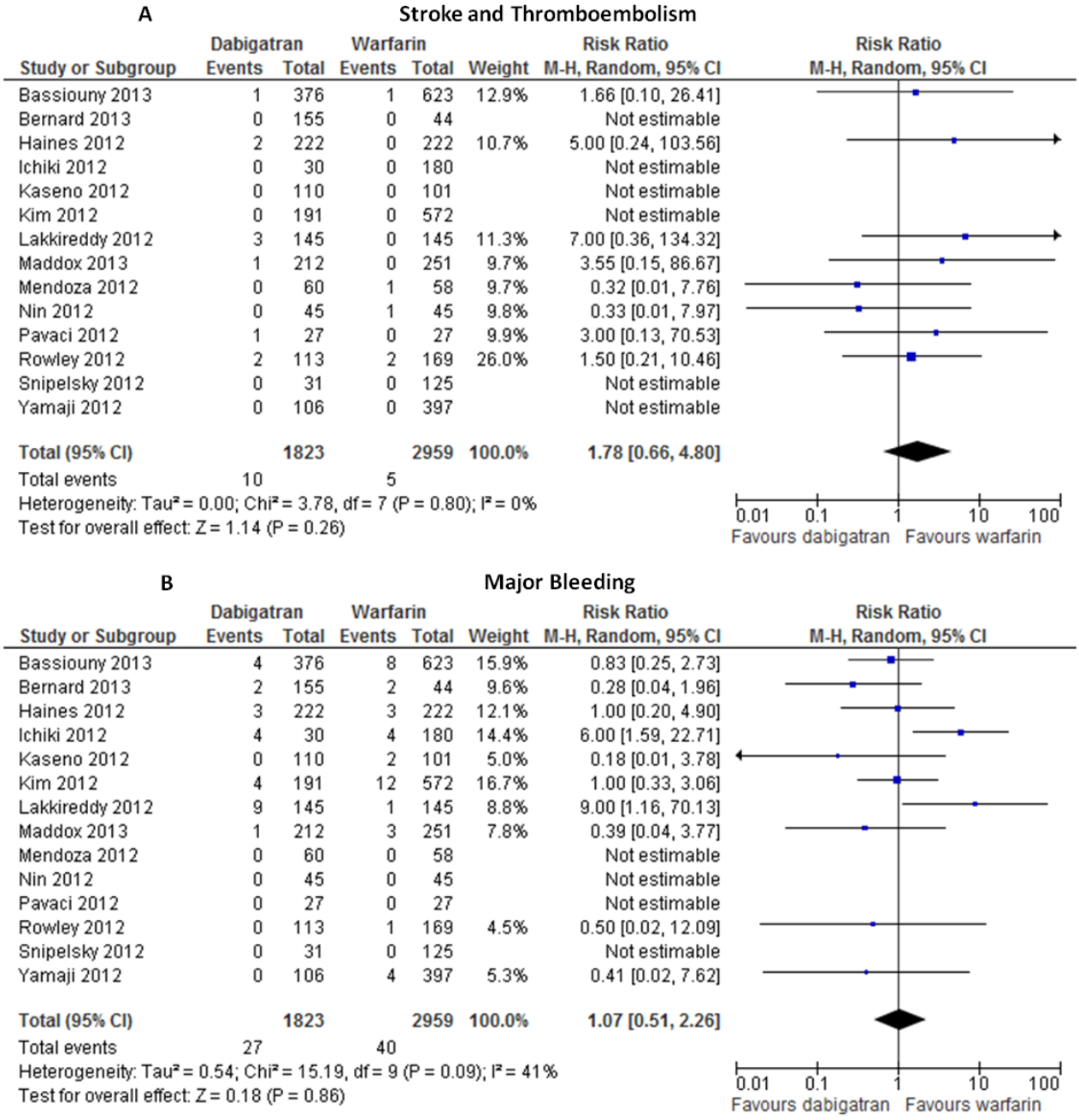

Figure 2 – Main efficacy and safety outcomes of the comparison of dabigatran versus warfarin among patients with atrial fibrillation treated with catheter ablation: A – Stroke and Thromboembolism; B – Major bleeding.

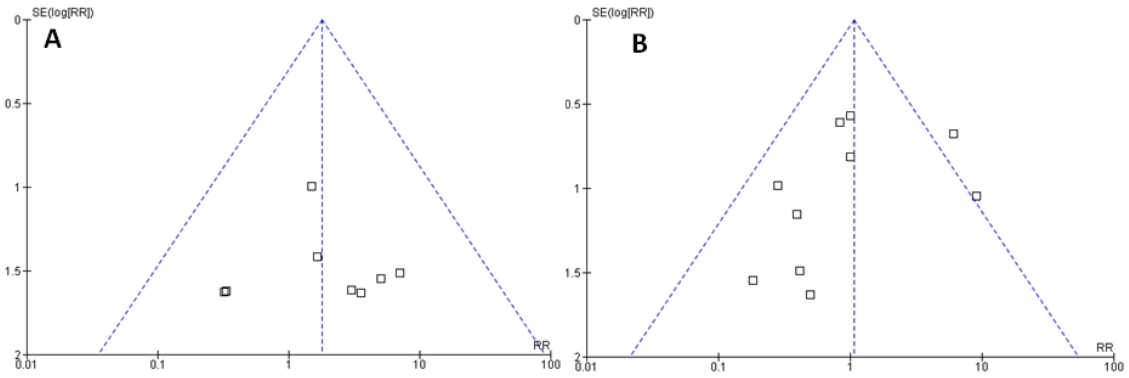

Figure 3 – Funnel-plots representing the studies used in the assessment of: A – Stroke and Thromboembolism. B – Major bleeding; The inverted and symmetrical funnel aspect can be observed for the assessed endpoints, with 95% of the studies lying within the confidence limit lines. This suggests that publication bias is not present among the selected studies for the meta-analysis.

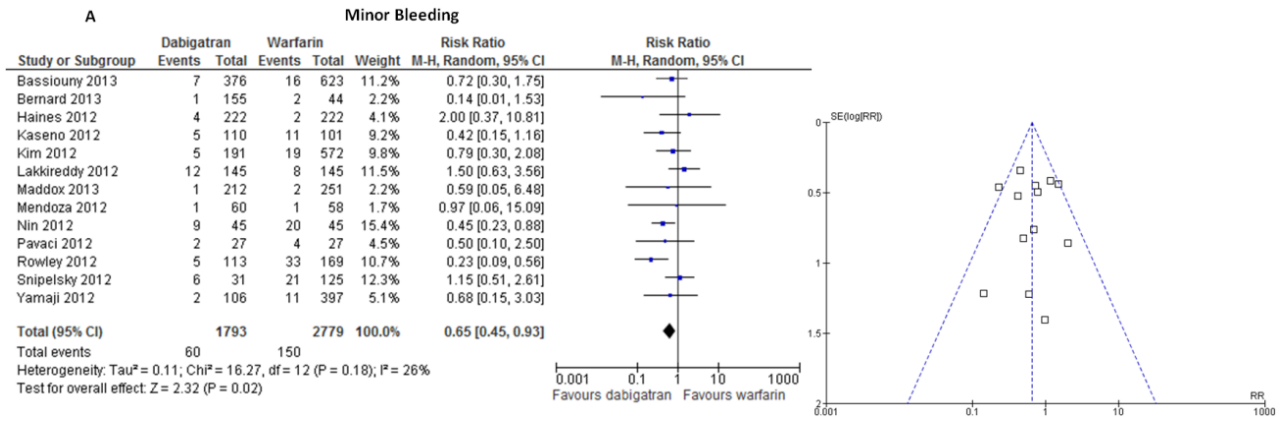

Figure 4 – Incidence of minor bleeding among patients treated with dabigatran or warfarin: A – Forest-plot. B – Funnel-plot.

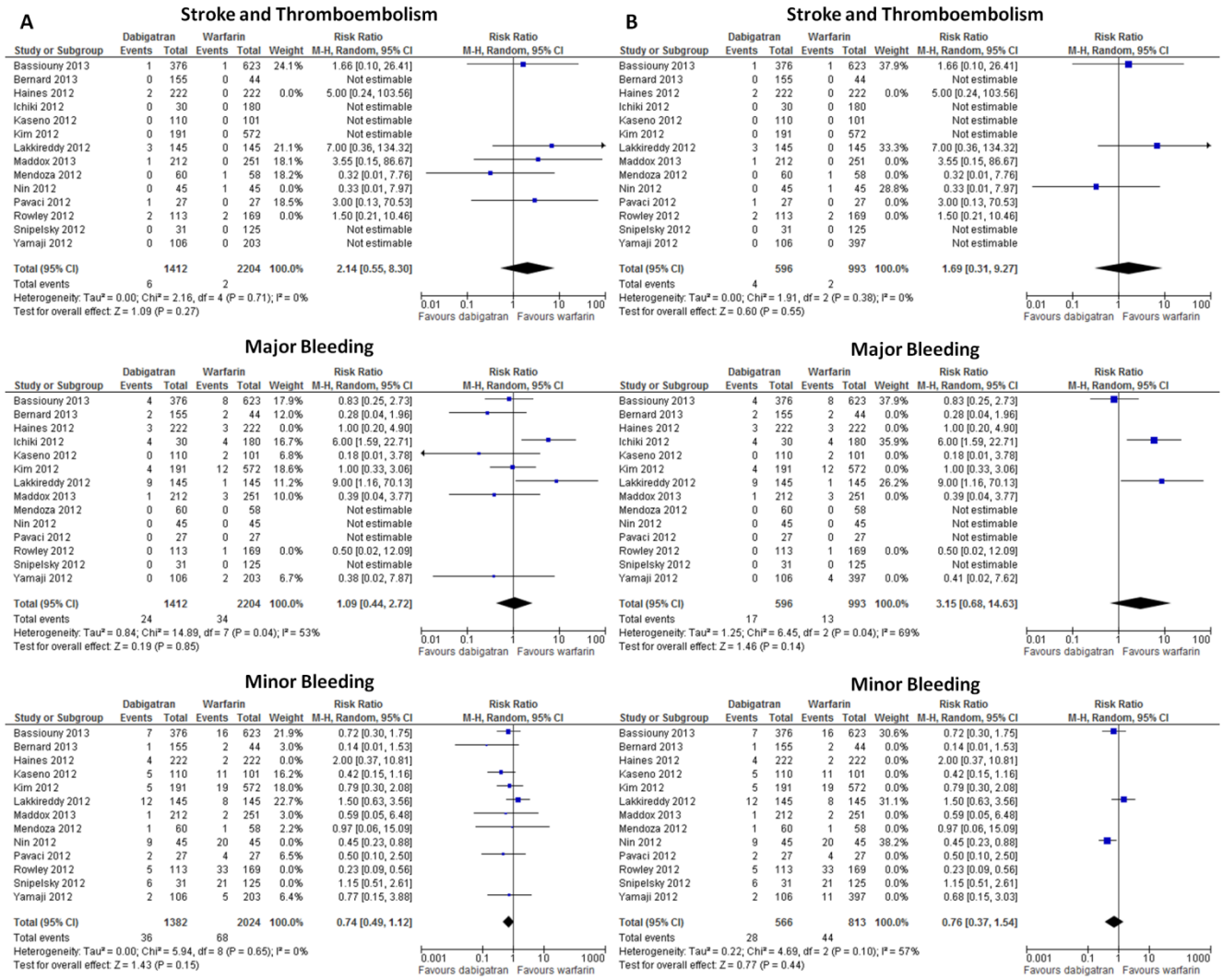

Figure 5 –Forest-plot illustrating the sensitivity analysis restricting data to: A - trials whose patients were treated uninterrupted warfarin; B - prospective studies.

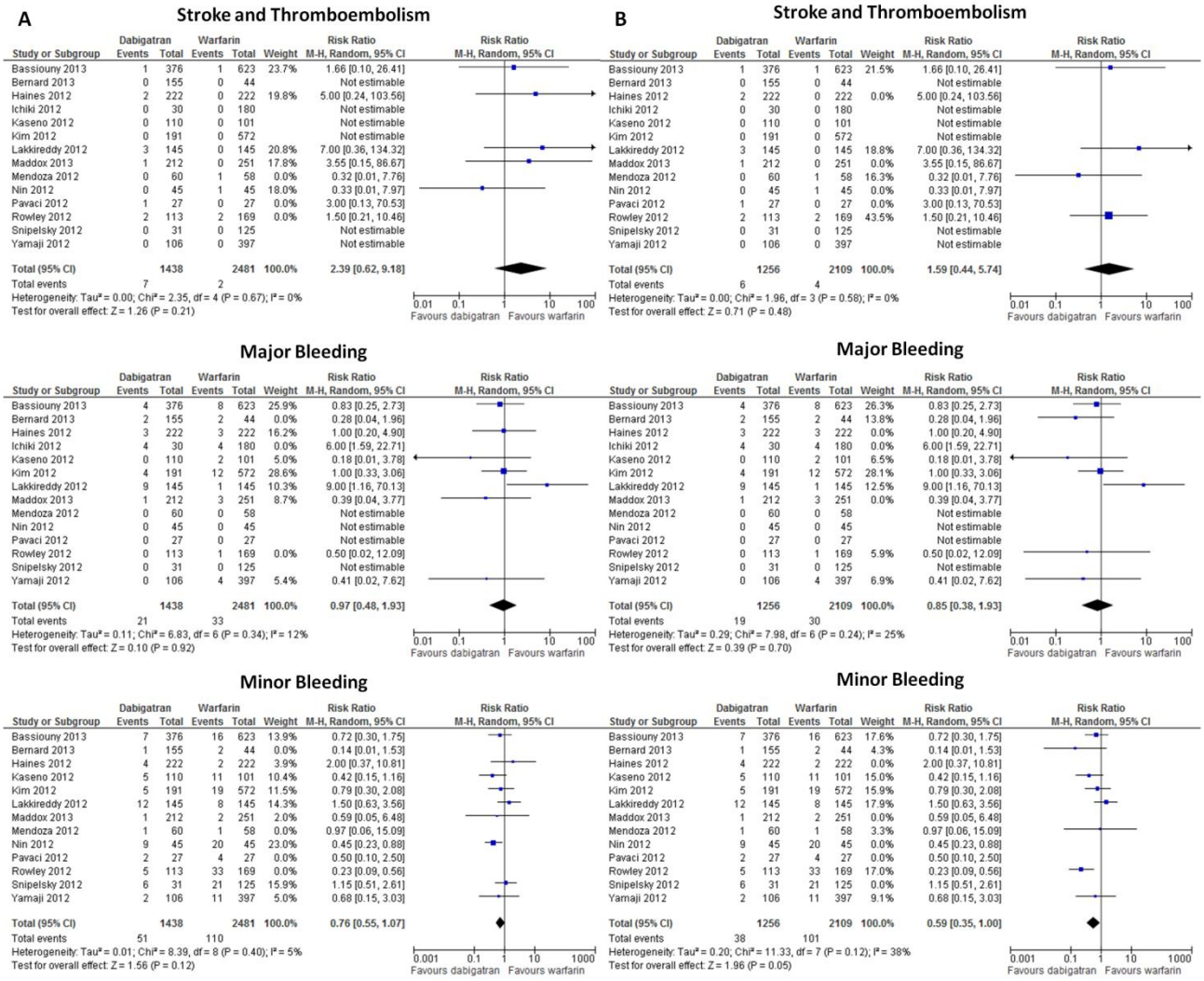

Figure 6 – Forest-plot illustrating the sensitivity analysis restricting data to: A - Investigations published as full-text articles; B - studies whose follow-up was at least 30 days.

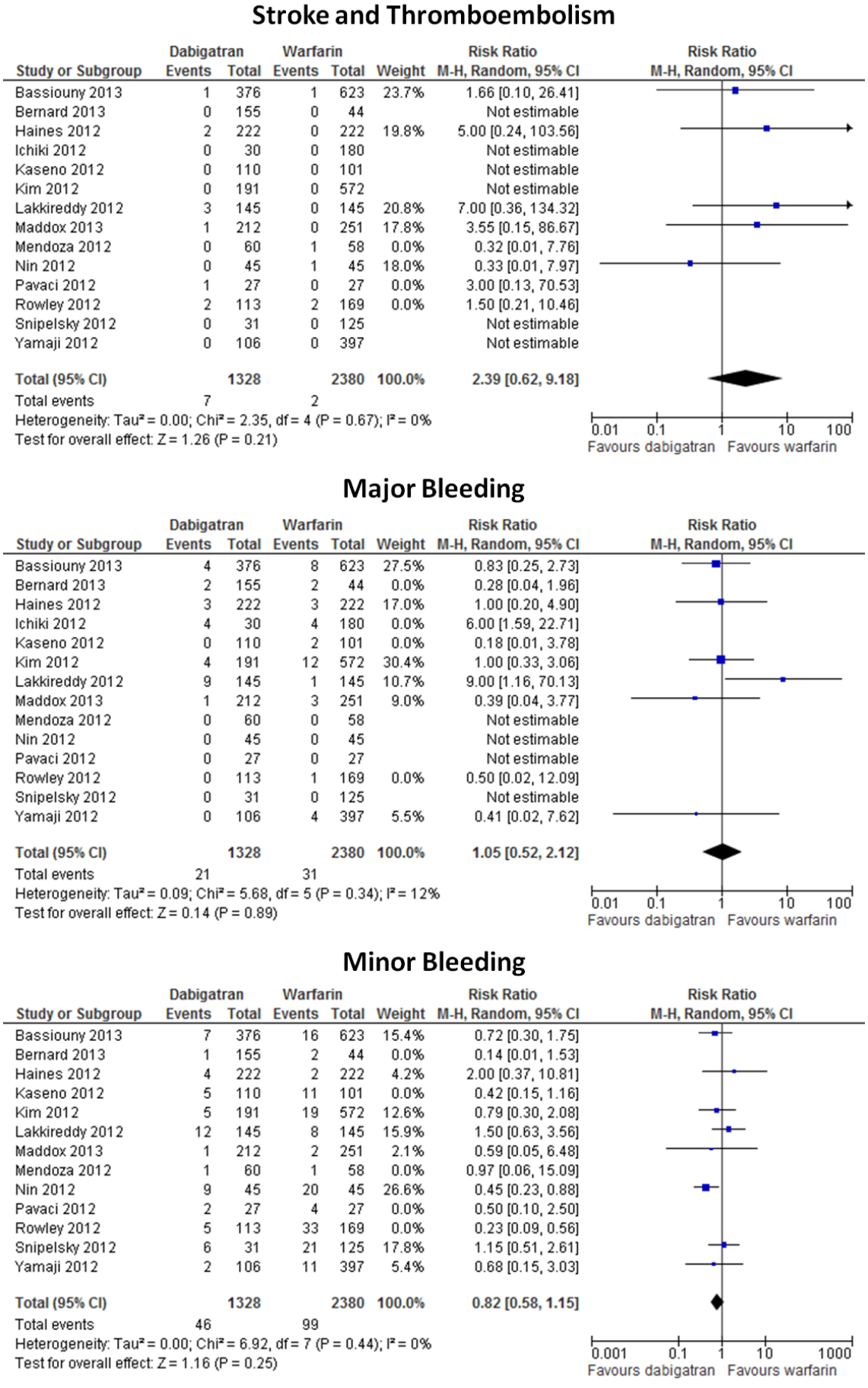

Figure 7 – Forest-plot illustrating the sensitivity analysis restricting data to higher quality full-text articles (Delphi criteria or Newcastle–Ottawa Scale ≥ 5).

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Goal IV.

Derivation of a risk score for the prediction of left atrial thrombi in patients with atrial fibrillation

IV.

Cardioversion safety in patients with non-valvular atrial fibrillation: which patients can be spared transesophageal echocardiography?

Rui Providência, Ana Faustino, Luís Paiva, Joana Trigo, Ana Botelho, José Nascimento, A.M. Leitão-Marques. Cardioversion safety in patients with non-valvular atrial fibrillation: which patients can be spared transesophageal echocardiography? Blood Coagul Fibrinolysis 2012;23(7):597-602

Abstract

Background/Objectives: To derive and test a score that can accurately predict the presence of left atrial or left atrial appendage thrombus (LAAT) in order to identify patients with non-valvular atrial fibrillation (AF) who can be spared transesophageal echocardiogram (TEE) and safely cardioverted.

Methods: Cross-sectional observational study including 180 subjects (37.2% women) undergoing clinical, echocardiographic and laboratory evaluation (including cardiac troponin I and C reactive protein - CRP) during an AF episode. LAAT was sought on TEE and predictors of this transesophageal echocardiographic finding were assessed. Based on predictors of LAAT (CRP, Atrial volume, Troponin, Episode duration and Stroke or embolism) we derived the CATES score and tested its accuracy through receiver operating curve analysis.

Results: LAAT was found in 9.4%. $CHADS_2$ and CHA_2DS_2-VASc had a modest performance in predicting these changes displaying a 0.620 (c-statistic) in average. Using CATES score displayed a higher area under the curve value: 0.816 for LAAT. No patients with LAAT were observed in patients with CATES scores ranging from “0” to “2”, which corresponded to 49.4% (n=89) of the sample.

Conclusions: We developed a score that presented a very good accuracy for the detection of LAAT in our sample. Further cross-validation using other population samples, namely with bigger dimensions, is needed to confirm the capability of selecting a very low risk group of patients that can be spared transesophageal echocardiography.

Keywords: atrial fibrillation; cardioversion; left atrial appendage thrombus; biomarkers; transesophageal echocardiography;

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia [1] and is a very common cause of admission to the emergency department (ED).

When the duration of the AF episode is unknown or longer that 48 hours and a rhythm control strategy is chosen, the European Society of Cardiology guidelines [2] recommend one of the following approaches: either effective anticoagulation for at least 3 weeks prior to cardioversion or a transesophageal echocardiogram (TEE) guided approach where cardioversion can be performed as soon as no thrombus is found in the left atrium of left atrial appendage. These approaches aim to avoid cardioversion-related stroke.

It is known that "AF begets AF" due to electroanatomical remodeling [3] and that total AF time is associated with relapse after cardioversion [4]. Therefore, the waiting time during the mandatory period of at least three weeks of effective anticoagulation period may be deleterious for the rhythm control strategy.

The absence of left atrial or left atrial appendage thrombus (LAAT) has been associated with safe cardioversion since the landmark trial Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) [5]. Still, TEE is an invasive and uncomfortable procedure.

Some predictors of LAAT have already been identified. Still, to best of our knowledge, no risk scores are currently available that allow us to detect patients that can be spared TEE and safely undergo cardioversion when the time of AF onset is unknown or over 48 hours.

Aim

To derive and test a score that can accurately predict the presence of LAAT in order to identify patients with non-valvular AF who can be spared TEE and safely cardioverted.

Methods

1. **Study population**

A cross-sectional study was conducted including all patients with AF of more than 48 hours evolution who underwent transesophageal echocardiogram (TEE) assessment for AF cardioversion from July 2009 to February 2011. All patients were wither out of or under suboptimal oral anticoagulation (INR <2.0 in the preceding 3 weeks, since all of them were medicated with vitamin K antagonists). A cardiac troponin I (cTnI) and C-reactive protein (CRP) measurement in the preceding 24 hours was a mandatory inclusion criterium. Out of a total of 282 subjects undergoing TEE assessment for AF cardioversion during that time period, 73.8% (n=208) had a cTnI and CRP measurement in the defined time window and were considered potentially eligible. Among these, 3 had thoracic pain complaints and a final diagnosis of non-ST elevation acute coronary syndrome, being therefore excluded from analysis. 14 had concomitant infections and were also ruled out. 11 of the remaining patients were also removed from analysis due to valvular AF (2 had mitral valve stenosis, 4 had moderate or severe aortic stenosis and 5 had prosthetic valves or previous valve repair). The remaining 180 patients were included for purpose of our research. All subjects provided their informed

consent to undergo the necessary investigations and to allow the usage of their data for research purposes, preserving their anonymity.

Baseline overall group characterization with demographic, anthropometric, clinical, laboratory and echocardiographic data, alongside with information on medication was obtained for all patients. Data was retrieved from clinical records (outpatient clinic evaluations, emergency department and hospital ward admissions).

2. Echocardiographic data

Transthoracic echocardiogram (TTE) and TEE were performed using a GE Vivid 7 echocardiograph alongside with M4S (1.5–4.0 MHz) and 6T phased array multiplane transoesophageal (2.9–7.0 MHz) probes. All examinations were performed by two cardiologists with accreditation in transthoracic and transesophageal echocardiography by the European Society of Cardiology. TEE was performed without anesthesia or sedation in more than 95% of patients. Images were later reanalysed using the GE Health Care EchoPac Dimension software, PC version 108.1.4. Left atrium volume was measured using the single-plane area length method [6, 7].

Left ventricle ejection fraction (LVEF) was qualitatively assessed and classified as normal (>55%), mildly (45 to 54%), moderately (30 to 44%), or severely (<30%) abnormal using the cutoff values defined in the guidelines [8, 9].

On TEE, the left atrium (LA) and left atrial appendage (LAA) were imaged in different tomographic planes to detect the presence of LAA T.

The cardiologists performing the TTE and TEE were blinded for the lab results and clinical information of the patients other than the fact that they were in AF and there was need for excluding TEE changes that could contraindicate cardioversion. TTE and TEE were performed after admission in the first 3 hours in 74.4% (n=134), 3 to 12 hours after in 17.8% (n=32) and 12 to 18 hours after admission in the remaining 7.8% (n=14).

3. Laboratory data

Blood samples were collected at admission in all patients. cTnI was measured using the Ortho-Clinical Diagnostics VITROS® Troponin I ES Assay. The lower limit of sensitivity and detection and the 99th percentile of this test were 0.012ng/mL and 0.034ng/mL, respectively. C-Reactive Protein (CRP) was measured using the CRP VITROS Chemistry Products assay. The lower limit of sensitivity was <0.5mg/dL and the reference interval for normal values was < 1.0mg/dL. A rise in cTnI and CRP was defined as the observed value over the lower limit of sensitivity (eg. 0. 1mg/dL was the observed rise in CRP in a patient with a value of 0.6mg/dl, assuming the 0.5mg/dL lower limit of sensitivity).

4. Statistics and Derivation of the CATES score

PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis. Comparisons were performed according to the presence/absence of LAAT. Chi-square was used for nominal variables and Student's t-test was used for comparison of continuous variables, where appropriate; the Levene test was used in order to check the homogeneity of

variance; equivalent non-parametric tests were used when Kolmogorov-Smirnov was in favor of absence of normal distribution. Results with $P < 0.05$ were regarded as significant.

Using the coordinates from the ROC curves we were able to define the optimal cutoff point (Youden index) for each parameter. Univariate analysis was then performed using the chi-square test. Continuous variables such as age, LVEF, indexed left atrial volume (iLAV), body mass index (BMI) and CRP and were converted into cathegorical variables and then used for univariate analysis (table II) and in the binary logistic regression analysis (table III).

Concerning cTnI, a detectable rise (≥ 0.001ng/mL) was used as a cutoff point due to recent data concerning this biomarker where minimal elevations were associated to embolic events [10] and left atrial stasis [11].

These data were used to estimate a logistic regression model with the backward stepwise method (likehood ratio; probability for stepwise = 0.1) to predict LAAT. The Hosmer-Lemeshow summary statistic was used to assess the goodness-of-fit of the models. Information regarding the wald and goodness of fit is shown on Table II.

A risk score was derived using the best combination of predictors on univariate analysis assessed by means of the best receiver operating characteristic (ROC) area under the curve (AUC) value for the detection of LAAT. The best combination included all univariate analysis predictors and each one was assigned with one point - CATES score: CRP, lef Atrial volume, Troponin, Episode duration and Stroke or embolism.

5. Evaluation of the derived model

The accuracy of the regression models was tested using ROC curves and the resulting AUC summary statistic (c statistic) for the prediction of LAAT. ROC curves were also traced for the $CHADS_2$, CHA_2DS_2-VASc score, cTnI, CRP and iLAV in order to assess the isolated contribution of clinical risk factors, biomarkers and echocardiographic parameters included in the model.

Cross-tabulation was performed to assess the prevalence of LAAT in each of the strata of the derived risk classification. The overall tendency of increasing event rates with increasing risk score was tested using chi-square for trend (gamma).

Results

The patients' baseline clinical, echocardiographic and analytic characteristics are shown on Table I. The following TEE endpoints were found: LAAT in 9.4% (n=17).

1. Observed differences according to changes found on TEE

Table I illustrates comparisons performed between patients according to the presence of LAAT. Patients with LAAT had higher prevalence of previous stroke or TIA, more frequently AF

lasting for over a week, higher values of $CHADS_2$ and CHA_2DS_2-VASc, higher rises of cTnI and more frequent dilatation of the LA and LV.

2. Predictors of LAAT

On univariate analysis, previous Stroke or TIA, estimated AF episode duration of more than 1 week, iLAV ≥ 60.0ml/m^2, positive cTnI and CRP rise ≥ 0.2mg/dL were predictors of LAAT (Table II). Only positive troponin, iLAV ≥ 60.0 ml/m^2 and previous stroke or TIA were independent predictors on multivariate analysis (Table III).

3. Assessment of the CATES score

ROC curves obtained with the CATES score and comparisons with other variables and clinical scores for the prediction of LAAT can be seen on Figure I.

The use of cTnI and iLAV by themselves provided higher values of AUC than the clinical risk scores $CHADS_2$ and CHA_2DS_2-VASc. Still, the best performance was observed with the CATES score with very good accuracy for detecting LAAT (Figure I).

No patients with LAAT were observed in CATES scores ranging from “0” to “2”, which corresponded to 49.4% (n=89) of the sample.

The prevalence of LAAT gradually increased with rising values of the CATES score, as it is illustrated by the Gamma for trend value. The association was not so strong with the $CHADS_2$ and CHA_2DS_2-VASc scores, which presented a lower and non-significant Gamma for trend as far as LAAT is concerned.

Conversely, according to the $CHADS_2$ classification, a prevalence of LAAT ranging from 4.3% to 9.7% were observed in patients classified as "0" to "2". No patients with LAAT were found under CHA_2DS_2-VASc of zero. Still, patients under this category represented only 3.3% (n=6) of the sample.

Discussion

We have derived a risk score composed of predictors of LAAT (namely clinical risk factors, biomarkers and echocardiographic parameters) that could very accurately detect the presence of LAAT. Moreover, a sample of patients (accounting for 49.4% of the total study population) whose CATES score value was ≤ 2 presented no LAAT on TEE and could have therefore been spared this procedure before undergoing cardioversion.

Evidence of an association between LAAT and the duration of AF [12, 13] and $CHADS_2$ [12, 14, 15] score with LAAT, like we observed in our sample, has been previously documented. Habara et al. have also identified history of recent embolic events as a predictor of LAAT [(14)]. A recent paper by Tang et al. [12] has shown a role for BMI, that we could not confirm in our data.

Rises in cTnI [11] and CRP [16] and a dilated LA [17, 18] have been previously identified as predictors of left atrial stasis on TEE and were also observed in our sample.

As far as compromised LVEF [17, 19, 20] is concerned, as association with LAAT has also been described but was not clear in our sample, probably due to its small size.

The role of left atrial size and low LVEF for the detection of LAAT in patients with a low (0 or 1) $CHADS_2$ score has been illustrated by Kleeman et al. [19]. Unlike these authors, Puwanant et al found an association between LAAT and the $CHADS_2$ score, with no or almost no changes in patients with a score of zero [20].

Other biomarkers have also shown to be related to the presence of LAAT, like NTproBNP [18] and D-dimers [13].

In a multivariate analysis model for the prediction of LAAT, AF duration, echocardiographic parameters and some clinical risk factors that composed the $CHADS_2$ score (DM, Stroke e CHF) were included [21]. This model had an excellent diagnostic performance (AUC 0.90). Still, since the presence of spontaneous echocardiographic contrast was among the included predictors, in order to use this model a TEE was needed. These authors have also found data supporting the role of the $CHADS_2$ score as a predictor of LAAT.

In the paper by Deftereos et al. [13] the independent value of adding biomarkers to echocardiographic (LA diameter) and clinical data (CHA_2DS_2-VASc) was also demonstrated. Still, they did not use c-statistic to test the accuracy of such type of model to predict these changes.

Limitations:

Our patients composed a high risk population, with a high prevalence of clinical risk factors. This may be due to the fact that since we are a tertiary hospital, patients with higher cardiovascular risk and previous cardiovascular events are more frequently referred to us or already under follow-up in our center. This also explains the very high observed prevalence of

statin and ACEi / ARB-II treatment. Medication with oral anticoagulants was lower than observed in the Euro Heart Survey on AF [22]. We underline that more than a third of the patients presented to the emergency department with their first symptomatic AF episode and may partly contribute to this low prevalence of oral anticoagulation.

We think that no selection bias can be found in this sample due to the exclusive selection of patients with cTnI measurement. The decision to measure cTnI was taken only according to the assistant cardiologist way of practice in the ED. This had nothing to do with the patient's profile. Some cardiologists in the ED decided not to request cTnI to any of the patients due to lack of evidence. Conversely, other cardiologists measured cTnI in every AF patient since it is part of the ED "cardiology lab panel". Therefore, since ED shifts and days changed arbitrarily every week we can assume that over the follow-up period any type of possible selection bias could be dismissed.

Recent evidence has shown that in some ED's troponin utilization may be as high as 86% in patients with AF and only 4.9% are treated for acute coronary syndrome [23].

Unfortunately, due to financial constraints NTproBNP and D-dimer are not part of our ED "cardiology lab panel" and therefore are not frequently measured in these patients. For their measurement to be done, some additional requests had to be made. This is time consuming and therefore leads to their underutilization.

Even though the $CHADS_2$ and CHA_2DS_2-VASc have not been developed for predicting changes on TEE, their predictive capability (or of some of the risk factors that compose them) is widely known and has been demonstrated in the literature.

We have used single plane apical 4-chamber view iLAV. This method was shown to be almost as accurate as the 2 plane method but is less technically demanding and time-consuming [6, 7]. Moreover, previous studies have shown that the additional accuracy of the two plane

method is very small and therefore doesn't support its usage. Hence, the single plane method seems more suitable for wide usage.

Conclusions

We have developed a score, named CATES, that presented a very good accuracy for the detection of left atrial and left atrial appendage thrombus in our sample. Nevertheless, these findings still need further cross-validation using other population samples, namely with bigger dimensions, in order to confirm the capability of selecting a very low risk group of patients that can be spared transesophageal echocardiography.

Table I - Population baseline characteristics and sub-analysis according to the presence of left atrium or left atrial appendage thrombus.

	Overall (n=180)	**LAAT** (n=17)	**No LAAT** (n=163)	**P**
Demographics				
Age	67.16±11.71	69.88±10.86	66.87±11.79	0.178
♀	37.2% (67)	41.2%(7)	36.8% (60)	0.362
Body Mass Index (Kg/m^2)	28.98±4.58	27.66±4.21	29.12±4.61	0.252
Clinical Data				
Congestive heart failure	52.2% (94)	52.9% (9)	52.1% (85)	0.475
Hypertension	79.4% (143)	76.5% (13)	79.8% (130)	0.375
Diabetes mellitus	25.6% (43)	23.5% (4)	25.8% (42)	0.420
Stroke or TIA	12.2% (22)	41.2% (7)	9.2% (15)	<0.001
Vascular disease[a]	45.6% (82)	47.1% (8)	45.4% (74)	0.448
AF episode duration >1 week	73% (132)	100% (17)	71.0% (115)	0.005
$CHADS_2$ score	2.10±1.26	2.65±1.50	2.04±1.22	0.046
CHA_2DS_2-VASc score	3.60±1.71	4.29±1.53	3.53±1.72	0.051
Medication				
Vitamin K Antagonists	34.4% (62)	47.1% (8)	33.1% (54)	0.250
Antiplatelet agents	48.9% (88)	35.3% (6)	50.3% (82)	0.120
ACE-i or ARB-II	72.8% (131)	70.6% (12)	73.0% (119)	0.831
Statin	39.4% (71)	35.3% (6)	39.9% (65)	0.713
Laboratory Assessment				
Haemoglobin (g/dL)	13.86±1.81	13.56±1.71	13.90±1.82	0.232
Platelets (10^3/uL)	217.22±88.05	230.59±78.84	215.81±89.07	0.263
INR	1.39±0.66	1.39±0.64	1.38±0.67	0.294
Rise in cTnI (ng/mL)	0.027±0.076	0.091±0.225	0.020±0.030	0.008
Rise in CRP (mg/dL)	1.13±2.99	0.94±1.07	1.15±3.12	0.087
Estimated GFR using MDRD (ml/min)	73.72±27.22	78.73±22.95	73.19±27.65	0.382
Echocardiographic characterization				
Indexed left atrial volume (ml/m^2)	59.34±22.79	66.44±16.20	58.60±23.28	0.023
Indexed LV diastolic diameter (mm/m^2)	30.22±5.43	33.85±4.73	29.80±5.36	0.001
LV ejection fraction < 55%	25.6% (46)	29.4% (5)	25.2% (41)	0.351

Legend: LAAT – left atrium or left atrial appendage thrombus; TIA – transient ischemic attack; AF – atrial fibrillation; ACE-i - angiotensin converting enzyme inhibitor; ARB-II - angiotensin II receptor blocker; INR - international normalized ratio; cTnI – cardiac Troponin I; CRP – C reactive protein; GFR – glomerular filtration rate; MDRD - modified diet in renal disease formula; LV – left ventricle.
[a] vascular disease is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque.

Table II – Predictors of left atrial or left atrial appendage thrombus (LAAT) on univariate analysis.

	LAAT	
Variable	**Odds ratio** (95%CI)	**p**
Congestive heart failure	1.032 (0.380-2.808)	0.950
Hypertension	0.825 (0.252-2.696)	0.750
Age ≥ 55	3.306 (0.386-23.904)	0.269
Diabetes mellitus	0.886 (0.274-2.869)	0.840
Stroke / TIA	6.907 (2.294-20.796)	<0.001
Vascular disease [a]	1.069 (0.393-2.909)	0.896
Female	1.202 (0.435-3.322)	0.723
Body mass index ≥ 30.0	0.690 (0.231-2.057)	0.503
AF episode duration > 1 week	N.A.	0.010
iLAV ≥ 60.0ml/m^2	2.764 (0.974-7.843)	0.049
LV ejection fraction < 55%	1.240 (0.412-3.731)	0.702
Detectable rise in Troponin I (≥ 0.001ng/mL)	5.368 (1.188-24.250)	0.016
Rise in C reactive protein ≥ 0.2mg/dL	4.498 (1.245-16.246)	0.013

Legend: LAAT - left atrial and left atrial appendage thrombus; TIA – transient ischemic attack; AF – atrial fibrillation; iLAV – indexed left atrial volume.

N.A. – not applicable due to lack of subjects with LAAT in the < 1 week duration AF episode group.

[a] - vascular disease is defined as having at least one of the following: myocardial infarction, peripheral artery disease and complex aortic plaque.

Table III – Multivariate analysis models for the prediction of left atrial or left atrial appendage thrombus (LAAT).

Model	Variable	Wald	B	Exp β	$CI_{95\%}$	P	Hosmer and Lemeshow test
LAAT	Rise in Troponin	3.665	1.549	4.706	0.964-22.979	0.056	$\chi^2 = 6.250$ df = 4 p = 0.181
	iLAV ≥ 60ml/m^2	3.354	1.096	2.993	0.926-9.673	0.067	
	Stroke or TIA	12.259	2.185	8.887	2.616-30.190	<0.001	
	Constant	0.235	-0.300	0.741		0.628	

Legend: LAAT - left atrial and left atrial appendage thrombus; iLAV – indexed left atrial volume; TIA – transient ischemic attack.

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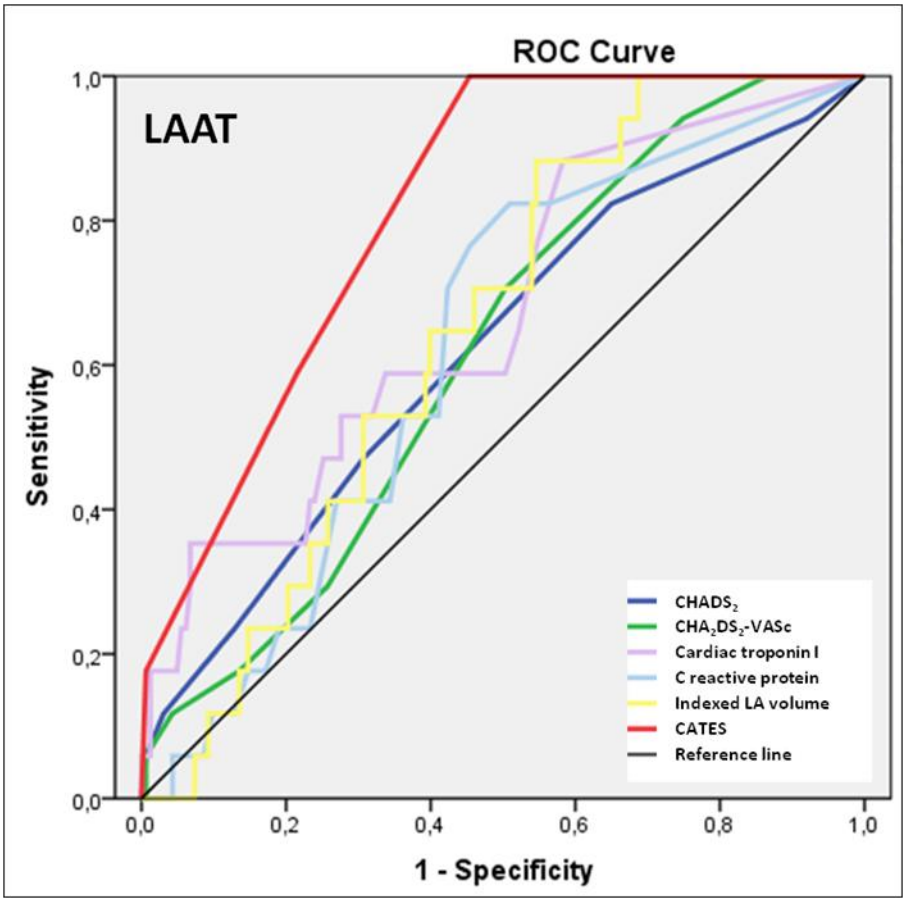
Table IV – Presence of left atrial and left atrial appendage thrombus according to the $CHADS_2$, CHA_2DS_2-VASc and CATES scores.

$CHADS_2$ Score			**CHA_2DS_2-VASc Score**			**CATES score**		
Score	No.	**LAAT**	**Score**	**No.**	**LAAT**	**Score**	No.	**LAAT**
0	14 (7.8%)[a]	1 (7.1%)[b]	0	6 (3.3%)	0	0	11 (6.1%)	0
1	46 (25.6%)	2 (4.3%)	1	16 (8.9%)	0	1	41 (10.2%)	0
2	62 (34.4%)	6 (9.7%)	2	20 (11.1%)	1 (5.0%)	2	37 (22.8%)	0
3	33 (18.3%)	4 (12.1%)	3	44 (24.4%)	4 (9.1%)	3	46 (26.7%)	7 (15.2%)
4	18 (10.0%)	2 (11.1%)	4	47 (26.1%)	7 (14.9%)	4	41 (22.8%)	7 (17.1%)
5	5 (2.8%)	1 (20.0%)	5	22 (12.2%)	2 (9.1%)	5	4 (2.2%)	3 (75.0%)
6	2 (1.1%)	1 (50%)	6	16 (8.9%)	1 (6.3%)	Total:	180	17
Total:	180	17	7	7 (3.9%)	1 (14.3%)	Gamma (Chi-Square for trend)		0.78
Gamma (Chi-Square for trend)		0.31	8	1 (0.6%)	1 (100%)	P		<0.001
P		0.104	9	1 (0.6%)	0			
			Total:	180	17			
			Gamma (Chi-Square for trend)		0.29			
			P		0.065			

Legend: LAAT - left atrial and left atrial appendage thrombus;
[a] corresponds to the percentage of the study sample; [b] corresponds to the percentage of patients that receive a score of zero.

Figure I – ROC Curve analysis* for the prediction of left atrial appendage thrombus (LAAT).



Legend: Area under the curve (AUC) and 95% confidence interval (CI) concerning LAAT prediction using: $CHADS_2$ – AUC 0.620 ($_{95\%}$CI 0.479-0.762; p=0.103); CHA_2DS_2-VASc – AUC 0.619 ($_{95\%}$CI 0.498-0.739; p=0.108); Cardiac Troponin I – AUC 0.672 ($_{95\%}$CI 0.537-0.806; p=0.020); C reactive protein – AUC 0.622 ($_{95\%}$CI 0.501-0.742; p=0.099); Indexed left atrial volume – AUC 0.648 ($_{95\%}$CI 0.543-0.753; p=0.045); CATES score – AUC 0.816 ($_{95\%}$CI 0.737-0.896; p<0.001).

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Discussion.

I. The role of atrial fibrillation in cerebrovascular mortality in Portugal

Despite all the changes in the treatment of arterial hypertension (earlier treatment, achievement of better control levels, better selection of drugs, less patients left untreated and even changes in legislation for controlling the amount of salt in bread), cerebrovascular disease remains the main cause of death in Portugal [1]. The high prevalence of atrial fibrillation in stroke units [2], suggests that this arrhythmia may play an important role in the national situation. Still, data from other institutions are needed, in order to confirm these data and provide more precise information concerning the involvement of this arrhythmia as a culprit of cerebrovascular morbidity and mortality at National level.

Data from the "*prevalência de Fibrilhação Auricular na população portuguesa com 40 ou Mais Anos*" (FAMA) study, suggest that only 40% of patients with known atrial fibrillation were treated with anticoagulants and a 40% of the patients with the arrhythmia had not been previously diagnosed [3]. Therefore, three measures may have a high impact in lowering the amount of strokes attributable to this arrhythmia: (i) education of the population concerning the benefits of pulse palpation, the underlying risks of atrial fibrillation and the benefits of anticoagulation; (ii) strict application of the risk stratification schemes and adherence to the European Society of Cardiology guidelines as regards use of anticoagulation; (iii) screening high risk populations, namely individuals over 65 years of age, who have some of the known risk factors for thromboembolism, which are also known to signal risk for developing the arrhythmia.

II. Mechanisms involved in thrombogenesis in patients with atrial fibrillation

Our investigations have allowed us to identify several factors that seem to play an important role in thrombogenesis among patients with atrial fibrillation (e.g. cardiac troponin I, renal function assessed through estimated glomerular filtration rate, mean platelet volume and mean corpuscular volume, red cell distribution width, left atrial size assessed through area and volume and left atrial deformation measured through strain rate obtained with speckle tracking).

II.A. Echocardiographic parameters and risk stratification

By using transesophageal echocardiogram findings as endpoints, we have found promising results concerning left atrial size and left atrial deformation as predictors of a thrombogenic state in patients with atrial fibrillation.

The addition of left atrial area and left ventricular ejection fraction to the $CHADS_2$ and CHA_2DS_2-VASc scores significantly improved the discriminative capability of these scores in about 0.1 (c-statistics of 0.62 and 0.63, respectively, increased to 0.73 and 0.74; both P <0.01) [4]. These are highly used and easy to measure parameters, whose incorporation in risk stratification (left ventricle ejection fraction is used in CHA_2DS_2-VASc, but only with the < 40% cutoff, as a surrogate of congestive heart failure) would be simple and quick. However, the benefits of this score must be shown using clinical endpoints, namely thromboembolic events, before implementation. Until now, the role of left atrial size in risk stratification has been insufficiently addressed and its three dimensional nature was very frequently overlooked [5].

The use of speckle tracking as a technique for evaluating cardiac deformation is more recent, and most studies have focused on its use for assessing the left ventricle [6]. Our proof of concept study has shown that compromised deformation of the left atrium may provide an

important input concerning the presence of a thrombotic status. On multivariate analysis logistic regression, atrial fibrillation episode duration, peak negative strain rate and time-to-peak positive strain were independent predictors of left atrial appendage thrombi or sludge. The area under the curve for the estimated probabilities using this model was high: 0.89; 95%CI 0.81-0.96; *P* <0.001 [7].

Interestingly, on mulvariate analysis, left atrial deformation parameters, but not left atrial volume, were predictors of thrombi. These may reflect the fact that compromised atrial function and fibrosis (measured by speckle tracking) may play an important role in the development of left atrial stasis and eventually thrombus formation. Also, some dilated left atria, may still preserve a certain degree of contractility and endothelial integrity, which may prevent thrombi formation. Therefore, these data suggest that using left atrial function may be more accurate than the mere use of its dimensions, even if assessed with appropriate methods like measurement of volume.

II.B. Novel biomarkers for risk stratification

Our investigation focusing on cardiac troponin I [8] has suggested a direct relation between rising concentrations of cardiac troponin I and a higher prevalence of transesophageal echocardiogram stasis-related changes: the higher the rise in troponin I, the higher the prevalence of these markers of left atrial stasis. Furthermore, the addition of cardiac troponin I to $CHADS_2$ and CHA_2DS_2-VASc scores improved their discriminative ability concerning transesophageal findings, both through received operator characteristic curve analysis and net reclassification improvement.

We have recently proposed several mechanisms for explaining this association [9]:

- Embolization of dense spontaneous echocardiographic contrast into the coronary tree; coexistence of left atrial fibrosis, which may be either thrombogenic or associated to

atrial ischemia; the fast atrial rate that exists during atrial fibrillation may lead to demand-supply imbalance in the left atrium and eventually dilation, fibrosis and ischemia; positive troponin may be a result of endothelial dysfunction or platelet and coagulation activation.

Troponin seems to be a pivotal marker in this field, since it added incremental predictive value to other biomarkers, namely mean platelet volume and C-reactive protein [10]. Also, the role of this biomarker has been later confirmed for predicting thromboembolic events and adverse outcome in post-hoc analysis of two phase-III mega-trials of the novel oral anticoagulants in atrial fibrillation: the *"Randomised Evaluation of Long Term Anticoagulant Therapy"* (RE-LY) [11] and the *"Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation"* (ARISTOTLE) trials [12].

It is interesting to note that most investigation on thromboembolic risk concentrates on the hemodynamics of the left atrium rather than on the components forming the thrombus. It has been known, for long, that dense spontaneous echocardiographic contrast, a precursor and strong predictor of the formation of thrombi in left atrium or left atrial appendage, seems to be composed of erythrocyte [13], platelet and leukocyte aggregates [14]. Therefore, there is a strong rationale for assessing the relationship of blood cells with the prothrombotic status in non-valvular atrial fibrillation.

While focusing on data available from a simple complete-blood count with standard morphologic index assessment, we have found that mean corpuscular volume, red cell distribution width [15] and mean platelet volume [16] could be involved in the development of left atrial appendage thrombus and dense spontaneous echocardiographic contrast. However, when analyzing the red blood cell indexes separately, despite adding incremental predictive value to each other, when clinical risk factors from $CHADS_2$ and CHA_2DS_2VASc classifications and left ventricle ejection fraction were added to the models, only mean corpuscular volume remained an independent predictor of these endpoints [15]. As regards, mean platelet volume,

it is important to underline its capability to associate with the presence of left atrial thrombi, alongside with variables such as previous stroke or transient ischemic attack and troponin I. Mean platelet volume was also incorporated in the predictive models of dense spontaneous echocardiographic contrast, low flow velocities and left atrial stasis, adding predictive value to clinical, echocardiographic and laboratory variables [16].

C-reactive protein was also briefly assessed for the derivation of a scheme, whose aim was displaying a good accuracy for predicting the presence of left atrial appendage thrombus [10], and its association of left atrial thrombogenesis had already been shown by other group [17].

II.C. The role of chronic kidney disease and the choice of anticoagulant in patients with atrial fibrillation and chronic kidney disease

Regarding the role of chronic kidney disease in thrombogenesis in atrial fibrillation patients, our findings have shown that estimated glomerular filtration rate, as assessed through the Chronic kidney disease epidemiology collaboration equation (CKD-EPI), shows an inverse association with the prevalence of dense spontaneous echocardiographic contrast: in patients with lower estimated glomerular filtration rate (<45 ml/min) smoke is present twice more frequently than in patients with normal values (≥90 ml/min). On multivariate analysis, a predictive value was found for estimated glomerular filtration rate, even when adjusting to clinical parameters from $CHADS_2$ and CHA_2DS_2-VASc [18].

Interestingly, the association was also confirmed for clinical endpoints, in a meta-analysis that included hazard ratio already adjusted for known risk factors, reinforcing that the presence of kidney disease associated with thromboembolism also just by itself, and not only due to the higher prevalence of comorbidities. The presence of chronic kidney disease led to a 46%

increase in the risk of thromboembolism in patients with moderate kidney disease, doubling to up to 83% in cases of terminal disease [19].

Despite the increased risk of thromboembolic events in chronic kidney disease, these patients are also at higher risk of bleeding events [20].

Nevertheless, anticoagulation is an effective option, even according to this limitation, the analysis of the pooled data from our meta-analysis has shown that warfarin decreased the incidence of thromboembolic events in patients with non-endstage chronic kidney disease and atrial fibrillation by 61% [19]. In patients on dialysis there seems to be also a beneficial effect (translated by a 56% decrease in thromboembolic events) [19], contradicting some of the results of the first studies that may have been caused by: (i) focusing on hemorrhagic stroke or a combined endpoint of hemorrhagic and ischemic stroke, rather than stroke and systemic embolism; (ii) use of a retrospective design; (iii) absent data concerning the use and posology of heparin; (iv) lack of information concerning the INR time in therapeutic range.

In addition, when analysing studies comparing the novel oral anticoagulants with warfarin, the newer drugs demonstrated higher efficacy (HR = 0.77; 95%CI 0.64-0.93, P=0.006) among patients with non-endstage chronic kidney disease. The same was observed in a comparison with aspirin (HR = 0.32; 95%CI 0.19-0.55, P<0.0001). The use of the novel oral anticoagulants in patients with atrial fibrillation and endstage kidney disease, and the eventual need of dose-adjustment still needs to be tested.

When, despite the increased thromboembolic risk, there seems to be a prohibitive bleeding risk (as suggested by a high HAS-BLED score), percutaneous closure of the left atrial appendage may be an option to consider, in face of the results of the "*Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF"* (PROTECT-AF) trial [21]. Still, no specific sub-studies of this therapy have focused in the context of endstage renal disease.

III. Role of dabigatran in patients undergoing catheter ablation of atrial fibrillation

Due to high and acutely increased thromboembolic risk in the setting of catheter ablation of atrial fibrillation, and the exclusion of these patients from the phase III RE-LY trial [22], strong support towards the use of dabigatran in these patients was still lacking. We have gathered data from a total of 4,782 patients (1,823 treated with dabigatran and 2,959 with warfarin) which confirms the safety and efficacy of dabigatran in the context of catheter ablation of atrial fibrillation [23]. However, due to the high variation in the posology of the drug (different timings for stopping and restarting treatment), missing data concernin the used dosage and almost absence of investigations with uninterrupted dabigatran, it is still difficult to propose an ideal regimen.

As far as the other novel oral anticoagulants are concerned, evidence regardin apixaban is still scarce and preliminary results are now becoming available with rivaroxaban [24]. However, *"A Study Exploring Two Treatment Strategies in Patients with Atrial Fibrillation Who Undergo Catheter Ablation Therapy"* (VENTURE-AF) [25], a prospective randomized trial comparing rivaroxaban with warfarin in this context will probably provide the definite answer and support towards its applicability.

IV. Towards a novel thrombotic risk scheme for patients undergoing cardioversion or catheter ablation of atrial fibrillation

For a long time, transesophageal echocardioram has been used before cardioversion of AF due to the need of excluding the presence of thrombi, which are associated with a high risk of peri-procedural thromboembolism if the cardioversion is not deferred [26]. This results in a high number of rather uncomfortable and invasive procedures, which are most frequently negative,

since usually only about 10% of patients have a left atrial appendage thrombus [27]. The prevalence of left atrial appendage thrombus is even lower in patients undergoing catheter ablation, as they are usually under oral anticoagulation, but its presence prohibits the performance of such procedure.

Therefore, the creation of a non-invasive tool that could detect patients with a very low likelihood of possessing a left atrial appendage thrombus and therefore be spared transesophageal echocardiography, seems to be a crying need. This could avoid examinations in specific patients subgroups where the very low probability of findings may in some cases be outweighed by the risk of transesophageal echocardiography associated major complications of 0.2 to 0.5% [28].

We have described a new classification, the CATES score (C-reactive protein, left Atrial volume, Troponin I, Episode duration and Stroke or embolism), that displayed a good discriminative capability for the presence of left atrial appendage thrombus (area under the curve value = 0.816, which was far better than the performance of $CHADS_2$ and CHA_2DS_2-VASc, that displayed an average of 0.620) [10]. These results are promising, specifically if we take into account that patients whose score ranged "0" to "2", which corresponded to 49.4% (n=89) of the sample. However, and despite showing for the first time in clinical practice the positive interaction of echocardiographic, clinical and laboratory data for predicting this specific endpoint, these results need yet to be confirmed through an external validation in a different population.

Very recently, another alternative has become available: *Doukky* and colleagues [29] have validated the ratio of left ventricular ejection fraction (LVEF) to left atrial volume index (LAVI) of < 1.5 as a predictor of the absence of left atrial appendage thrombus, obviating the need for transesophageal echocardiography before certain procedures (cardioversion of atrial fibrillation, implantable cardioversor defibrillator testing and AF ablation).

The usefulness of this algorithm in the setting of patients undergoing catheter ablation of AF may be even higher, since the only alternative, the cardiac computer tomography (CT) scan, despite the present data on sensitivity and specificity (97% and 100%, respectively) [30], is not devoid of radiation exposure.

Nonetheless, we think that due to the similarity of results with the ratio of LVEF/LAVI (See Table I) it would be interesting to compare the acuity of the two scores in a future head-to-head trial. Despite the fact that the ratio of LVEF/LAVI may have the advantage of simplicity, the CATES score may benefit from a more global evaluation of the patient, due to the inclusion of clinical, laboratory and echocardiographic parameters.

V. The unmet needs of risk stratification and thrombo-prophylatic treatment of patients with atrial fibrillation

The current risk schemes ($CHADS_2$ and CHA_2DS_2-VASc) [31, 32] are based on clinical risk factors and an echocardiographic parameter (left ventricle ejection fraction < 40%) was introduced in the most recent one, as an alternative to the presence of congestive heart failure (Figure 1).
However, as discussed throughout this thesis, these scores possess a low c-statistic value and consequently a very low discriminative power [33]. It is known that a c-statistic of 0.5 translates mere chance. When the c-statistic value rises to 1.0 it means that the test is a perfect discriminator. This way, we can clearly observe that the performance of these scores resembles much closer to mere chance than to perfection. We think that probably, that is why the evolution of risk stratification is being made towards almost anticoagulation: using the $CHADS_2$ score only about 20% of individuals were classified as low risk and received no anticoagulant treatment. With the CHA_2DS_2-VASc risk score, the number of patients with an indication for anticoagulation has raised to more than 90 to 95% [34].

If we carefully evaluate the performance of these scores, the yearly risk of not having a thromboembolic event is higher than the risk of a sustained one, for every risk category: a $CHADS_2$ score of 0 (low risk) translates into a 1.9% yearly risk of thromboembolic events and a 98.1% year risk of not sustaining embolism. For patients in the higher risk category, risk score of 6, the yearly risk of thromboembolism is 18.2%, meaning that 81.8% of patients will not be affected by the feared complication [31]. The same seems to occur with the CHA_2DS_2-VASc score: Individuals with low risk (score of 0) have a 0.7% yearly risk of thromboembolism, i.e. 99.3% probability of no events, and those with the higher score (score of 9) have a 15.9% annual incidence of thromboembolism, meaning that 84.1% of patients in this risk category will not have events [32]. It is true that if we extend the time interval of surveillance of these patients, the number of events in each risk score would increase and the final figures would seem more appropriate. However, this seems to occur always at the expense of an excessive number of patients that are put under oral anticoagulation, and at risk of bleeding, without immediate benefit as far as thromboembolism protection is concerned.

The great advantage of these scores is their simplicity and ease of use, that has allowed their widely application all around the World. We acknowledge that this was an important step in the field, since it reinforced the message of high thromboembolic risk in specific subsets of patients with AF and allowed a great number of patients at risk to start receiving the appropriate therapy. However, despite the fact that they are the most effective scores at present time, this doesn't mean that we should not try to improve our practice and develop more appropriate alternatives.

If we consider the XIXth century Virchow Triad (Figure 2) [35], it seems reasonable to think that, even at the light of such an ancient pathophysiologic theory, probably the presently included risk factors in these scores can provide only an oversimplified view of the matter and seem to aim insufficiently at the mechanisms involved in thrombogenesis.

In current days, more and more complex pathways involved in coagulation are being discovered. Therefore, from a mechanistic point of view the $CHADS_2$ and CHA_2DS_2-VASc seem rather outdated, which may justify its low performance. In different areas of cardiology, the available risk scores are much more comprehensive and like the *"Global Registry of Acute Coronary Events"* (GRACE) risk score, include a whole set of variables, from clinical data, imaging to biomarkers [36].

Another point that may merit future consideration is the impersonalized thromboembolic prophylaxis that is used in these patients. It seems strange to us that patients at different levels of risk should receive the same treatment. Besides the insufficient discriminative performance of these scores, the existence of bleeding scores that are not directly incorporated in the former, in order to adjust treatment, may be a part of the explanation.

Also, it is worrisome that risk factors like hypertension, age and prior stroke are currently part of antagonic risk classifications, signaling both bleeding and embolic risk. Finding new markers of cardioembolism that are not associated with bleeding should be a challenge for the next years in cardiovascular research in order to minimize aggressive anticoagulation in patients where bleeding risk exceeds the probability of cardiac embolism.

Tailoring treatment to the patient's needs would be difficult and sometimes even dangerous using the elderly vitamin-K antagonists. However, that seems a likely and achievable goal with the novel oral anticoagulants, which provide a much more predictable dose-response and lower rate of interactions, allowing a better therapeutic level control.

By showing the possible role of biomarkers and echocardiographic parameters we hope to draw attention into a possible new way of improving risk stratification. We acknowledge that our work has focused in the specific scenario of left atrial stasis and some of these markers should still be tested for more solid endpoints. However, as discussed along this thesis and as illustrated (Figure 3) the relationship between the markers of left atrial stasis and clinical thromboembolism or adverse outcomes, both at short and long term, has already been shown

to be a very close one [37-9]. Furthermore, some of these markers have already demonstrated to be effective in the prediction of thromboembolic events [40, 41].

The framework below (figure 4) illustrates the most recent findings in the field of risk stratification of patients with atrial fibrillation, showing some possible candidates for future inclusion in new risk schemes.

These newly identified pathways may also draw attention to other possible ways of decreasing thromboembolic risk: avoiding the deterioration of estimated glomerular filtration rate, or the decrease of left atrial contractility and synchronism, delaying left atrial fibrosis, preserving the left atrial endothelium anti-thrombotic function, preventing left atrial regional ischemia and interfering with the metabolism and activation of red blood cells and platelets, in order to avoid their activation and expression of adhesion molecules.

Despite being merely hypothetical, the involvement of these pathways may suggest that there may be more than anticoagulation or left atrial appendage closure to offer to these patients in order to grant them with a better prognosis.

The road to thromboembolic protection in atrial fibrillation is only in its beginning but, we think that some of the markers identified in our investigations may allow us to approach the final aimed destination: providing the appropriate treatment to the right patient.

VI. Future Directions

Our findings aim to contribute to the advance of knowledge in the field. However, they also raise further issues that need yet to be clarified.

VI.A. Improving thromboembolic risk stratification

a. Future scores aiming to risk stratify patients with atrial fibrillation should try to simultaneous discriminate thromboembolic and bleeding risk. Since these are two extremes that very frequently coexit, it would be of the utmost importance to develop scores which could place patients under thromboembolic risk categories adjusted to their bleeding risk. In this way, probably we would be able to treat patients with high thromboembolic + low bleeding risk more aggressively and those with low thromboembolic + high bleeding risk, which would justify in a more conservative approach, or eventually the use of non-pharmacologic options.

b. The currently existing risk schemes do not allow a personalized anticoagulant treatment for patients with an indication for anticoagulation. Adjustment of target INR or anticoagulant dosage according to the level of risk of the patient (using vitamin-K antagonists), according to the $CHADS_2$ score has failed to translate into any advantage to the patient [42]. We wonder if the future risk stratification scores, with higher discriminative capability may allow a better tailoring of therapy.

c. Validation of our findings concerning biomarkers and echocardiographic parameters using thromboembolic endpoints is still warranted. Also, assessing the additive predictive value of all these new predictors alltogheter should be the goal of future studies. Severall ongoing or recently terminated trials may shed a light into the role of these new predictors: possibly data from the new anticoagulants mega-trials on AF can be used in the future for this purpose, since a relevant part of the participants have been included in biomarkers (RE-LY [43] and the *"Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48"* - ENGAGE-AF TIMI 48) [44] and echocardiographic sub-studies [44].

d. In other fields of cardiology, despite having become more complex and sophisticated, risk scores can now very effectively and accurately predict outcomes. Grace risk score, for example, combines the use of clinical data, laboratory and electrocardiogram data. It requires the use of a calculator for correct assessment, but has become the gold standard for risk stratification of patients with acute coronary syndrome [36]. Risk models combining clinical and echocardiographic alongside with biomarkers have not yet been developed for the prediction of thromboembolism in AF. Still, we believe that this may be an effective way of fine-tuning the currently available AF clinical risk stratification schemes, further improving their predictive capability. Due to their complexity, if this type of models ever reaches clinical practice, calculators will be needed to correctly assess the TE risk. This is what currently happens with the Grace risk score, where free calculators are currently available online for global usage [45]. Despite its higher complexity, the fact that Grace risk scores provides very valuable and accurate information regarding the prognosis of subjects with acute coronary syndrome, and the fact that it can be easily calculated through web applications or calculators, has led to its broad usage worldwide.

e. Thromboembolic risk needs a systematic revaluation and regular adjustment (e.g. annually), unlike what happens in other clinical risk scores where the patient either has the risk factor or not, and once he acquires it, he will preserve it for its entire life. The immediate cost of the laboratory and echocardiographic assessment for the estimation of the risk using combined risk scores, can eventually be compensated by the high number of patients that can be spared to lifelong anticoagulation due to reclassification into lower risk groups. Moreover, some patients will be reclassified into higher risk classes, which can lead to additional prevention of events.

VI.B. Knowledge gaps in anti-thrombotic treatment

a. Studies with the novel oral anticoagulants among patients with atrial fibrillation and dialytic kidney disease are still lacking.
b. Confirmation of the suggestion of benefit of warfarin in terminal kidney disease among patients with atrial fibrillation is still needed. Also, methodological aspects that need monitoring in this population are the use of heparin and respective dosage, and the target INR or used drug dosage (should it be the same one that is used in patients with normal glomerular filtration rate? Should it be adjusted to kidney function?)
c. The best posology for dabigatran in the setting of catheter ablation of atrial fibrillation needs yet to be elucidated. Will uninterrupted dabigatran provide a benefit similar to uninterrupted warfarin? Which dabigatran dosage is advantageous? Should it be chosen according to the thromboembolic risk of the patient or the type of procedure?
d. Apixaban, rivaroxaban and, possibly, edoxaban still need to be tested in the context of atrial fibrillation ablation.
e. The safety and efficacy of apixaban and edoxaban in patients undergoing cardioversion of atrial fibrillation has not yet been demonstrated.

VI.C. An alternative to transesophageal echocardiography

a. Further knowledge of the mechanisms underlying thrombus formation in patients with atrial fibrillation can be obtained through the evaluation of the contribution of all the identified new predictors in a sample of sufficient size to allow the estimation of the contribution of each of these and also the clarification of the addictive value of these

new predictors when used ensemble. Do these variables add incremental information and render possible a very high discriminative capability due to the gathering of information from several of the involved pathways in thrombogenesis? Or, if used togheter, does a plateau state with a moderate discriminative capability develop, due to the fact that they signal changes similar pathways?

b. Concerning left atrial deformation, it is still not known if segmentar (and which segment) or global (the average of all segments) provides the most valid information concerning left atrial stasis. Also, it remains to be assessed if all the currently available techniques for assessing deformation (speckle-tracking, vector velocity imaging or tissue doppler derived) have the same accuracy concerning this endpoint.

c. The CATES score should be prospectively validated in an independent population, ideally in a head-to-head comparison with the ratio of LVEF/LAVI, in order to assess its possible usefulness in current clinical practice. Since more predictors of thrombi formation have been recently identified, the ultimate and most accurate score (combination of these factors) for predicting this transesophageal finding remains yet to be determined.

Table I – General overview of two currently available tools to predict the presence of left atrial appendage thrombus.

	Ratio of LVEF/LAVI Doukky et al. [29] (n=215)	**CATES score** Providência et al. [10] (n=180)
Requirements for estimating the index / score	Transthoracic echocardiogram to measure LVEF and LAVI	Transthoracic echocardiogram to measure LAV Laboratory tests: C-reactive protein and cardiac troponin I Clinical data: previous stroke or TIA and duration of AF episode
$CHADS_2$ score	2.5±1.3	2.10±1.26
Indication of TEE	Cardioversion – 42.3% AF ablation – 29.8% ICD implantation – 19.5% ICD revision and testing – 8.4%	Cardioversion – 100%
Oral anticoagulation	63.3%	34.4%
Prevalence of LAAT	8.8%	9.4%
Cutoff value **Sensitivity and specificity**	< 1.5 Sensitivity 100% Specificity 55.6%	>2 Sensitivity 100% Specificity 54.6%
Area under the curve	0.83	0.816
Amout of patients who could obviate the need of TEE	50.7% (those with a ratio ≥ 1.5)	49.4% (those with a score ≤ 2)
External validation	Performed by Doukky et al. [(1)]	Not yet performed

Legend: TIA – transient ischemic attack; ICD – implantable cardioversor defibrillator; TEE – transesophageal echocardiogram; LAAT – left atrial appendage thrombus.

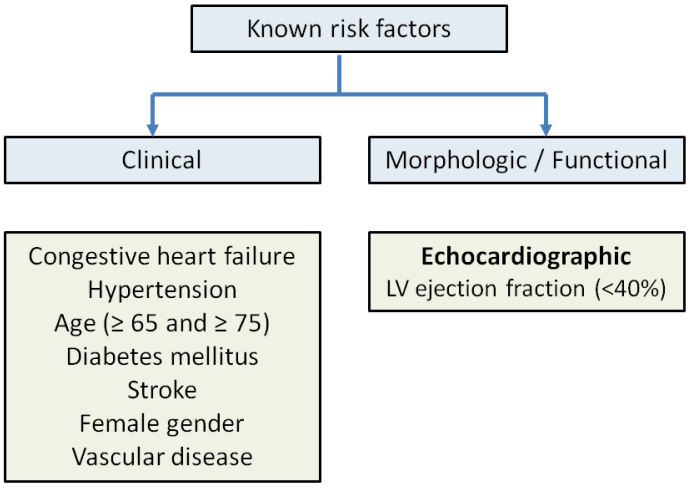

Figure 1 – Risk factors for thromboembolism in patients with atrial fibrillation that have been incorporated in the $CHADS_2$ and CHA_2DS_2-VASc risk scores. Legend: LV – left ventricle.

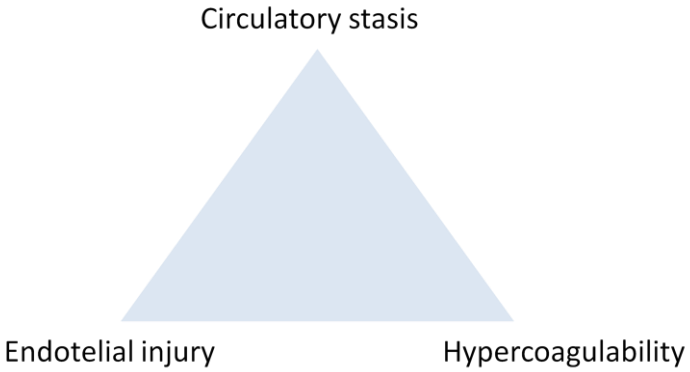

Figure 2 – Virchow Triad.

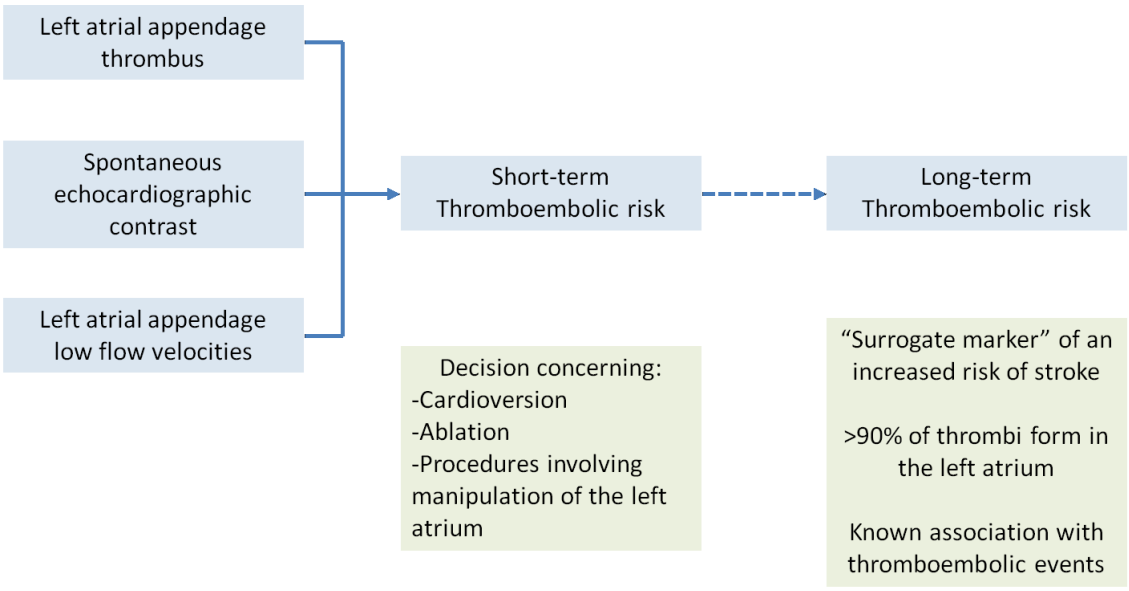

Figure 3 – Flowchart elucidating the association of markers of left atrial stasis with short and long-term thromboembolic risk.

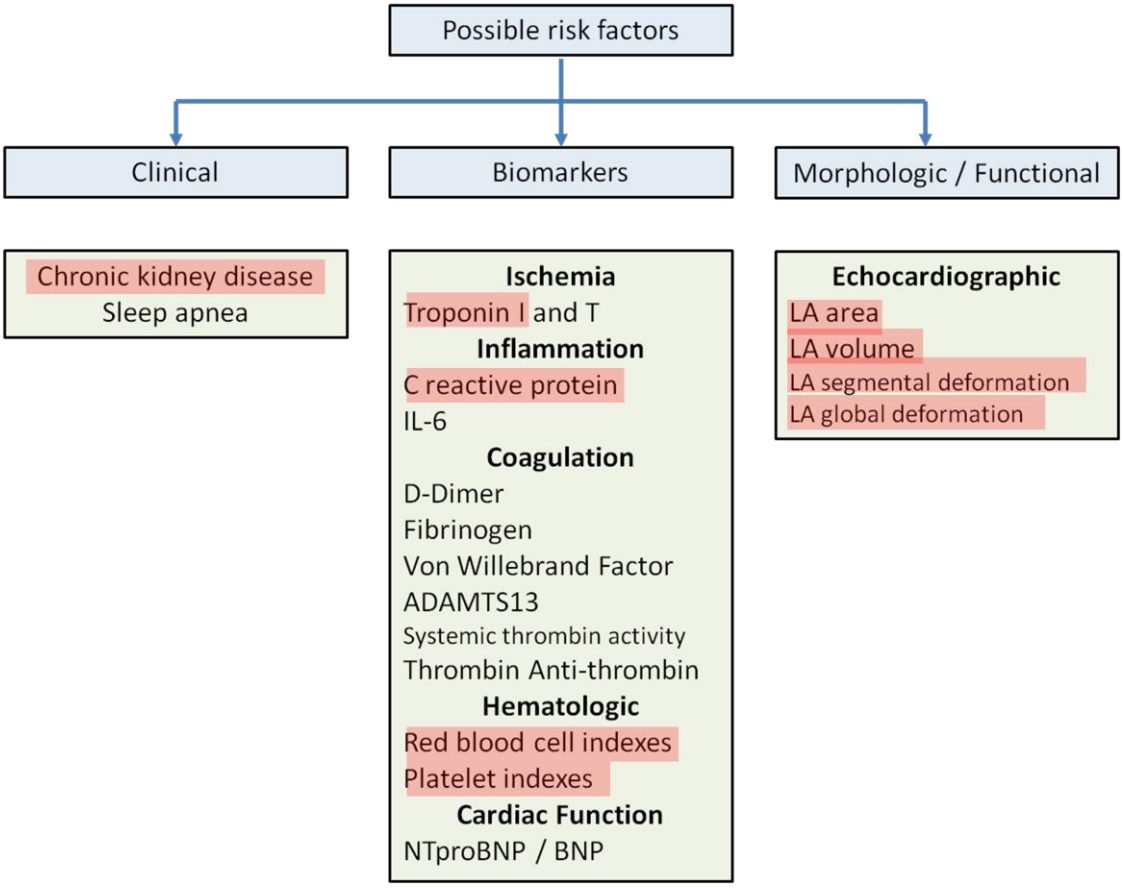

Figure 4 – Recently identified candidates for possible inclusion in risk stratification schemes of patients with atrial fibrillation.

Legend: IL – interleukin; BNP – brain natriuretic peptide, LA – left atrial. Highlighted in red are some of the risk factors resulting from the investigations included in this thesis.

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Conclusion.

The role of atrial fibrillation in cerebrovascular mortality at national (and also international) level should not be misjudged. Accurately identifying and treating individuals at risk must be a priority of XXIst Century Medicine.

We have found new markers and pathways that seem to be involved in thrombogenesis in atrial fibrillation patients that may merit validation using clinical endpoints: clinical variables (chronic kidney disease as assessed through the estimated glomerular filtration rate), biomarkers (mean platelet volume, mean corpuscular volume, cardiac troponin I and C reactive protein) and echocardiographic parameters (left atrial size - area and volume - and deformation). These variables seem to independently increment the discriminative of the clinical variables currently used in risk scores ($CHADS_2$ and CHA_2DS_2-VASc).

Our meta-analysis provides strong clinical evidence concerning the use of chronic kidney disease for risk stratification and its incremental value to the existing stratification schemes. In the context of moderate chronic kidney disease, the novel oral anticoagulants performed favourably, when compared with warfarin. However, in end-stage kidney disease, no data exists concerning the use of these agents. Also, our results seem to ease some of the concerns regarding the use of warfarin in these patients. Nevertheless, further studies may be needed to provide robust evidence to this high risk thrombotic and bleeding scenario.

Despite not clarifying the best regimen for dabigatran in the setting of catheter ablation of atrial fibrillation, our meta-analysis confirms the efficacy and safety of this drug.

According to the new classification we have derived, the CATES scheme, almost 50% of patients can be spared transesophageal echocardiogram before cardioversion (and eventual catheter ablation) if the appropriate conditions are met. However, external valiation of this score is still warranted.