World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/1949-8462office
wjc@wjgnet.com
doi:10.4330/wjc.v4.i6.195

World J Cardiol 2012 June 26; 4(6): 195-200
ISSN 1949-8462 (online)

FIELD OF VISION

Risk stratification of patients with atrial fibrillation: Biomarkers and other future perspectives

Rui Providência, Luís Paiva, Sérgio Barra

Rui Providência, Luís Paiva, Sérgio Barra, Department of Cardiology, Coimbra's Hospital Centre and University, 3041-801 S.Martinho do Bispo, Coimbra, Portugal
Rui Providência, Coimbra's Medical School, University of Coimbra, 3041-801 S.Martinho do Bispo, Coimbra, Portugal
Author contributions: Providência R wrote the draft version of the paper; Paiva L and Barra S provided further ideas for improving the paper; and all authors wrote the final version of the paper.
Correspondence to: Rui Providência, MD, MSc, Department of Cardiology, Coimbra's Hospital Centre and University, Quinta dos Vales, 3041-801 S.Martinho do Bispo, Coimbra, Portugal. rui_providencia@yahoo.com
Telephone: +351-239-800100 Fax: +351-239-445737
Received: June 6, 2012 Revised: June 9, 2012
Accepted: June 16, 2012
Published online: June 26, 2012

Abstract

Risk stratification of atrial fibrillation (AF) and adequate thromboembolism prophylaxis is the cornerstone of treatment in patients with AF. Current risk stratification schemes such as the $CHADS_2$ and CHA_2DS_2-VASc scores are based on clinical risk factors and suboptimally weight the risk/benefit of anticoagulation. Recently, the potential of biomarkers (troponin and NT-proBNP) in the RE-LY biomarker sub-analysis has been demonstrated. Echocardiography is also being evaluated as a possible approach to improve risk score performance. The authors present an overview on AF risk stratification and discuss future potential developments that may be introduced into our current risk stratification schemes.

Key words: Anticoagulation; Atrial fibrillation; Risk stratification; Stroke; Thromboembolism

Peer reviewers: Dr. Richard G Trohman, Professor of Medicine, Rush University Medical Center, 1653 West Congress Parkway, Room 983 Jelke, Chicago, IL 60612, United States; Dr. Mamas Mamas, Manchester Heart Centre, Central Manchester NHS Foundation Trust, Oxford Road, Manchester, M13 9WL, United Kingdom

Providência R, Paiva L, Barra S. Risk stratification of patients with atrial fibrillation: Biomarkers and other future perspectives. *World J Cardiol* 2012; 4(6): 195-200 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i6/195.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i6.195

RISK STRATIFICATION OF ATRIAL FIBRILLATION: WHERE DO WE STAND?

Stroke and thromboembolism are among the most severe complications of atrial fibrillation (AF)[1]. Risk stratification is currently based on clinical risk scores: either the $CHADS_2$[2] or the CHA_2DS_2-VASc score[1] are recommended (Table 1).

The $CHADS_2$ score has an issue with the identification of low risk patients (those with a score of zero), who cannot be truly classified as low risk, since their annual risk of thromboembolic events is around 1.9% a year[3]. The recently developed CHA_2DS_2-VASc score has succeeded in identifying a truly low risk group of patients: annual stroke risk of 0%[4,5]. Unfortunately, it tends to be over-inclusive, referring a very high percentage of subjects to oral anticoagulation. This is worrying since some of these subjects would never experience an event even if they remained untreated and using the CHA_2DS_2-VASc score they become exposed to an increased risk of bleeding (BL).

Despite being easy to use and the best currently available option for decision making concerning antithrombotic therapy in AF, risk scores have shown limited capability in predicting thromboembolic events, with low values for area under the curve[4,6,7]. In the CHA_2DS_2-VASc validation cohort (1.084 patients from the Euro

Table 1 Explaining the CHADS$_2$ and CHA$_2$DS$_2$-VASc risk scores

Risk score	Risk factor	Risk score	Risk factor
C	Congestive heart failure	C	Congestive heart failure (or left ventricular systolic dysfunction)
H	Hypertension	H	Hypertension
A	Age ≥ 75 yr	A_2	Age 65 to 74 yr Age ≥ 75 yr[1]
D	Diabetes mellitus	D	Diabetes mellitus
S_2	Stroke or transient ischemic attack[1]	S_2	Stroke or transient ischemic attack[1]
		VASc	Previous myocardial infarction, peripheral arterial disease or aortic plaque Female

All variables are assigned one point, when present, except those marked with ([1]), which receive two points. Subjects with a CHADS$_2$ score of 0 (low risk) should be placed under antiplatelet therapy, those with a score of 1 (intermediate risk) can either undergo oral anticoagulation or antiplatelet therapy and the remaining (high risk) have clear benefit with oral anticoagulation, unless contraindicated. Using the CHA$_2$DS$_2$-VASc score, individuals with a score of zero (truly low risk) should be placed under no treatment (preferably) or, as an option, medicated with an antiplatelet agent. Intermediate risk individuals (score of 1) should be placed under oral anticoagulation (preferably) or antiplatelet agents (as an alternative). The remaining patients (score ≥ 2) should be anticoagulated.

Table 2 Clinical risk stratification scores for patients with atrial fibrillation: pros and cons

In favour
Very simple to understand
Easy to use
Solid evidence supporting the use of these classifications
Patients classified as low risk according to the CHA$_2$DS$_2$-VASc score are truly low risk (annual risk of events 0%)
Against
Limited capability to detect patients at risk of thromboembolism
Patients with a high thromboembolic risk are also bound to present a high bleeding risk
Patients classified as high risk present no additional benefit when treated more aggressively
Individuals classified as low risk with the CHADS$_2$ score are not truly low risk: 19% risk at ten years
According to the CHA$_2$DS$_2$-VASc score, almost all individuals should be placed under oral anticoagulation (only 8.4% of subjects were classified as having a score of 0 in the validation cohort of this score[5]) and, even in the highest risk score, with a CHA$_2$DS$_2$-VASc score of 9, most patients experienced no events after 5 and 10 yr of follow-up

Heart Survey of AF), the calculated C-statistics suggested a modest predictive value of CHA$_2$DS$_2$-VASc (C-statistic = 0.606) and CHADS$_2$ (C-statistic = 0.561) for predicting thromboembolism[4].

Another issue with these scores is the fact that they share a large number of risk factors with other scores developed to assess BL risk, namely hypertension, stroke history and age ≥ 65 years, which are variables shared both by the CHA$_2$DS$_2$-VASc and the HAS-BLED score[8]. Thus, those individuals classified as high risk for thromboembolism using the CHADS$_2$ or CHA$_2$DS$_2$-VASc scores, who are referred for anticoagulation, may also have a high risk of BL.

This may have been one of the reasons, in the RE-LY trial sub-analysis, for the failure in finding an incremental benefit of higher doses of dabigatran (150 mg *bid*) *vs* dabigatran 110 mg *bid* using warfarin as the common comparator, in patients with higher CHADS$_2$ score values[9].

If we had a score that could discriminate both thromboembolic (TE) and BL risk, placing patients in different categories, we would probably be able to treat patients with high TE + low BL risk more aggressively, and those with low TE + high BL risk in a more conservative way (Table 2).

Other risk classifications (like the CRUSADE bleeding score) have been widely used for predicting BL risk in other situations, such as coronary artery disease[10]. However, at the present time, besides HAS-BLED, only the HEMORR2HAGES score[11] has been tested in patients with AF, which makes assessment of such BL risk scores and comparison with the HAS-BLED a worthy field of research in the next few years.

Major issues concerning these clinical risk stratification scores are addressed in Table 2.

FIRST FAVORABLE EVIDENCE FOR BIOMARKERS

The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) was a non-inferiority trial that aimed to evaluate dabigatran (a direct thrombin inhibitor) *vs* warfarin for the prevention of stroke or systemic embolism. The trial comprised 18113 patients with AF and a risk of stroke (average CHADS$_2$ was 2.1 ± 1.1) and demonstrated that dabigatran 110 mg *bid* was noninferior to warfarin concerning stroke or systemic embolism (1.69% per year with warfarin *vs* 1.53% with dabigatran; $P < 0.001$ for noninferiority) and resulted in less major bleeding (3.36% *vs* 2.71%, $P = 0.003$). As far as the 150 mg *bid* dose was concerned, dabigatran was more effective in preventing stroke or thromboembolism (relative risk 0.66, 95%

CI: 0.53-0.82, $P < 0.001$) and displayed a similar rate of major bleeds (3.11%, $P = 0.31$) when compared to warfarin. Both dabigatran doses were less frequently associated with hemorrhagic stroke (0.12% for 110 mg *bid*, 0.10% for 150 mg *bid* and 0.38% for warfarin; both comparisons, $P < 0.001$)[12].

In a recently published biomarker sub-study of this trial which included 6189 patients followed for a median of 2.2 years, the prevalence of NT-proBNP and cardiac troponin I (cTnI) elevation and their role in risk stratification were assessed[13].

Rates of stroke were independently related to the levels of cTnI (2.09%/year in patients with cTnI ≥ 0.040 μg/L *vs* 0.84%/year in those with cTnI < 0.010 μg/L; HR = 1.99, 95% CI: 1.17-3.39) and NT-proBNP (2.30%/year in the highest *vs* 0.92%/year in the lowest quartile group; HR = 2.40, 95% CI: 1.41-4.07). The same was also observed concerning vascular mortality both for cTnI (6.56%/year in patients with cTnI ≥ 0.040 μg/L *vs* 1.04%/year in those with cTnI < 0.01 μg/L; HR = 4.38, 95% CI: 3.05-6.29) and for NT-proBNP (5.00%/year in the highest *vs* 0.61%/year in the lowest quartile group; HR = 6.73, 95% CI: 3.95-11.49). Only cTnI was significantly associated with major bleeding. The annual rate of major bleeds was 1.72% in patients with undetectable cTnI and rose to 4.38% in those with cTnI ≥ 0.040 μg/L (HR 2.01, 95% CI: 1.39-2.90). No significant association was found between NT-proBNP levels and major bleeding.

Levels of cTnI and NT-proBNP added prognostic information to the $CHADS_2$ and CHA_2DS_2-VASc scores, with a significant increase in C-statistics both for the prediction of stroke and systemic embolism, and for the prediction of the composite TE outcome (stroke, systemic embolism, pulmonary embolism, myocardial infarction and vascular death, excluding hemorrhagic death). According to this refinement in risk stratification, a group of patients with $CHADS_2$ score of 0-1 and elevated biomarkers had a higher annual rate of a composite of TE events than those with higher $CHADS_2$ scores and undetectable biomarkers. Moreover, some patients with higher $CHADS_2$ scores and undetectable cTnI could also be correctly reclassified as low risk. Lastly, a group of patients with high clinical risk of TE events and positive biomarkers was found to be in the highest category of risk. Therefore, the authors proposed that additional therapy might be necessary for this high TE risk group. Some of the suggested options were: intensified pharmacologic treatment (angiotensin converting enzyme inhibitors, angiotensin receptor blockers or statins), left atrial (LA) appendage closure and LA volume reduction. Furthermore, risk stratification of coronary artery disease also seemed advisable for this very high group[13].

With respect to troponin, we propose some explanations for its role in risk stratification: First, embolization of small particles that compose dense spontaneous echocardiographic contrast into the peripheral circulation, namely the coronary tree (causing microvascular ischemia, which leads to raised troponin values) and cerebral circulation. Second, raised troponin may be a result of LA dysfunction due to a more fibrosed left atrium predisposing to thrombosis. Fibrosis may be related to ischemia of the left atrium wall, and since the atria are thin structures, only small rises in troponin are usually detected. Third, troponin elevation may also be a manifestation of endothelial dysfunction or platelet and coagulation activation leading both to microemboli into the coronary tree and to the development of prothrombotic changes in the left atrium. Finally, it is possible that the raised values might be revealing underlying coronary artery disease that is partially responsible for the adverse prognosis.

Hijazi *et al*[13] proposed that the level of NTproBNP in AF may reflect some degree of atrial dysfunction, which is known to be a marker of atrial thrombus formation and may provide a plausible explanation for the prognostic significance of raised NTproBNP levels.

This was the first published study concerning the putative role of biomarkers in the risk stratification of AF. Preliminary data exist concerning other plausible biomarkers. Some have been evaluated using transesophageal echocardiography in order to measure their association with markers of LA stasis: C reactive protein (CRP)[14] and cTnI[15] have been shown to be associated with LA appendage thrombus (LAAT) and dense spontaneous echocardiographic contrast. Thus, they have been shown to increment the predictive power of $CHADS_2$ and CHA_2DS_2-VASc to predict these transesophageal changes. Other biomarkers have also been shown to be related to the presence of LAAT, such as NTproBNP[16] and D-dimers[17].

Preliminary data from the RE-LY trial in favor of a relationship between some of these markers and clinical events is already available for D-dimers[18], CRP and interleukin-6 (IL-6)[19]. Baseline D-dimer levels were significantly associated with the risk of stroke, cardiovascular death and major bleeding. This positive association was independent of $CHADS_2$ score risk factors.

IL-6 was predictive of stroke and both IL-6 and CRP have been associated with an increased risk of vascular death and cardiovascular events. Only IL-6 was significantly associated with major bleeding[19] (Table 3).

A small prospective observational study has confirmed the capability of D-dimers for predicting cardiovascular events in patients with AF[20].

POSSIBLE BENEFIT OF ADDING ECHOCARDIOGRAPHIC PARAMETERS

Transthoracic echocardiography provides a large number of parameters that can be used for improving risk stratification in patients with AF. It is of note that CHA_2DS_2-VASc already includes left ventricle systolic dysfunction as part of the "C"- congestive heart failure[4].

Most studies concerning the role of LA size as a predictor of TE events have been based on outdated parameters. The mostly widely studied has been LA diameter[21,22] which is known to represent LA size grossly.

Table 3 Biomarkers associated with thromboembolism in atrial fibrillation

cTnI and NT-proBNP[11]	cTnI and NT-proBNP were independently associated with the rate of stroke Both markers were also associated with vascular mortality Only cTnI was associated with bleeding risk cTnI and NT-proBNP added prognostic information to the $CHADS_2$ and CHA_2DS_2-VASc scores
CRP and IL-6[17]	CRP and IL-6 have been associated with an increased risk of vascular death and cardiovascular events IL-6 levels were predictive of stroke and major bleeding
D-dimers[16,18]	D-dimers are independently associated with the risk of stroke and cardiovascular death Raised D-dimer levels were associated with major bleeding

cTnI: Cardiac troponin I; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; CRP: C reactive protein; IL–6: Interleukin-6.

Table 4 Echocardiographic parameters associated with thromboembolism in atrial fibrillation

Transthoracic echocardiogram	Left ventricle systolic dysfunction has long been known to be associated with thromboembolism in atrial fibrillation and is currently used in the CHA_2DS_2-VASc score[4] Left atrial diameter was shown to be associated with thromboembolism in old studies. Nowadays, diameter is not considered an appropriate way of assessing left atrial size[21] Left atrial area and volume have been shown to be associated with the presence of left atrial appendage thrombus and other markers of left atrial stasis[22]. Studies concerning hard clinical endpoints are still lacking[23] Left atrial deformation assessment (strain and strain rate) holds promise in this field, since it translates changes in atrial kinetics and function
Transesophageal echocardiogram	Left atrial appendage thrombus, spontaneous echocardiographic contrast and low flow velocities in the left atrial appendage have been associated with a high risk of thromboembolic events and an adverse prognosis[22] The invasive nature of this technique makes it inadequate for wide usage in AF patients

Other methods like apical 4-chamber LA area or LA volume (the current gold standard) have been proposed as more accurate[23]. We have recently demonstrated that by adding echocardiographic parameters (LA area and LV systolic function) to $CHADS_2$ or CHA_2DS_2-VASc we could achieve a significant improvement in the prediction of transesophageal markers of LA stasis[24]. An ongoing echocardiographic sub-study from the ENGAGE-TI-MI-48 trial will probably clarify this matter using clinical endpoints[25] (Table 4).

FUTURE PERSPECTIVES

In other fields of cardiology, despite having become more complex and sophisticated, risk scores can now very effectively and accurately predict outcomes. The Grace risk score (GRS), for example, combines the use of clinical, laboratory and ECG data. It requires the use of a calculator for correct assessment, but has become the gold standard for risk stratification in patients with acute coronary syndrome[26]. Risk models combining clinical and echocardiographic data with biomarkers have not yet been developed for the prediction of thromboembolism in AF. However, 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 model ever reaches clinical practice, calculators will be needed to correctly assess the TE risk. This is what currently happens with the GRS, where free calculators are currently available online for global usage[27]. Despite its higher complexity, the fact that GRS 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.

Furthermore, TE 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 his entire life.

The immediate cost of the laboratory and echocardiographic assessment for the estimation of risk using combined risk scores can eventually be compensated by the high number of patients that can be spared lifelong anticoagulation due to reclassification into lower risk groups. Moreover, some patients will be reclassified into higher risk classes. If upper reclassified individuals, due to their higher TE risk, are subsequently divided according to their BL risk, we would also likely achieve more net clinical benefit by providing them with more aggressive anticoagulant therapy if they have low BL risk. This may be accomplished either by including risk factors that are only associated with TE events (and have no association with bleeding) or by applying a special adjustment for BL risk (by merging a BL risk score to this tool). Despite the expected increase in complexity, this may lead to a lower incidence of ischemic and bleeding events, and a subsequent decrease in associated costs.

Possibly data from the new anticoagulants mega-trials on AF can be used in the future for this purpose, since a relevant number of the participants have been included in biomarkers (RE-LY and ENGAGE)[12,25] and echocar-

diographic sub-studies[25].

CONCLUSION

The $CHADS_2$ and CHA_2DS_2-VASc scores are extremely useful and simple to use clinical tools for risk stratifying patients with AF. However, they have shown limited power in predicting thromboembolic events.

The incorporation of echocardiographic parameters and biomarkers may be used to further improve these scores. Including variables that could correctly discriminate between TE and BL risk (or adjusting the results according to a BL risk stratification that could be part of the main score) would likely overcome some of the limitations of $CHADS_2$ and CHA_2DS_2-VASc.

In order to be more accurate, future risk classification schemes may become more sophisticated and complex. A calculator for computing the score will eventually become necessary. Nevertheless, some improvements may arise with complexity, namely the possibility of personalizing treatment and the clear definition of risk groups that can benefit from different therapeutic intensities: a low risk group with less aggressive or nil anticoagulation, an intermediate risk group with standard anticoagulation and a higher risk strata in need of more aggressive therapy (possibly percutaneous closure of the LA appendage alongside standard or higher dosage anticoagulation).

REFERENCES

1 **Camm AJ**, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; **31**: 2369-2429

2 **Wann LS**, Curtis AB, Ellenbogen KA, Estes NA, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Stevenson WG, Tracy CM, Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Heuzey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS, Jacobs AK, Anderson JL, Albert N, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on Dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2011; **123**: 1144-1150

3 **Gage BF**, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285**: 2864-2870

4 **Lip GY**, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; **137**: 263-272

5 **Olesen JB**, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011; **342**: d124

6 **Fang MC**, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2008; **51**: 810-815

7 **Van Staa TP**, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. *J Thromb Haemost* 2011; **9**: 39-48

8 **Pisters R**, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; **138**: 1093-1100

9 **Oldgren J**, Alings M, Darius H, Diener HC, Eikelboom J, Ezekowitz MD, Kamensky G, Reilly PA, Yang S, Yusuf S, Wallentin L, Connolly SJ. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. *Ann Intern Med* 2011; **155**: 660-667, W204

10 **Subherwal S**, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV, Peterson ED, Alexander KP. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation* 2009; **119**: 1873-1882

11 **Gage BF**, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006; **151**: 713-719

12 **Connolly SJ**, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151

13 **Hijazi Z**, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Vinereanu D, Siegbahn A, Yusuf S, Wallentin L. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation* 2012; **125**: 1605-1616

14 **Ederhy S**, Di Angelantonio E, Dufaitre G, Meuleman C, Masliah J, Boyer-Chatenet L, Boccara F, Cohen A. C-reactive protein and transesophageal echocardiographic markers of thromboembolism in patients with atrial fibrillation. *Int J Cardiol* 2011 Mar 12; Epub ahead of print

15 **Providência R**, Paiva L, Faustino A, Botelho A, Trigo J, Casalta-Lopes J, Nascimento J, Leitão-Marques AM. Cardiac troponin I: Prothrombotic risk marker in non-valvular atrial fibrillation. *Int J Cardiol* 2012 Feb 19; Epub ahead of print

16 **Deftereos S**, Giannopoulos G, Kossyvakis C, Raisakis K, Kaoukis A, Aggeli C, Toli K, Theodorakis A, Panagopoulou V, Driva M, Mantas I, Pyrgakis V, Rentoukas I, Stefanadis C. Estimation of atrial fibrillation recency of onset and safety of cardioversion using NTproBNP levels in patients with unknown time of onset. *Heart* 2011; **97**: 914-917

17 **Habara S**, Dote K, Kato M, Sasaki S, Goto K, Takemoto H, Hasegawa D, Matsuda O. Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation. *Eur Heart J* 2007; **28**: 2217-2222

18 **Eikelboom J**, Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Reilly PA, Yusuf S, Wallentin L, Siegbahn A. D-dimer is Prognostic for Stroke, Major Bleeding and Death During Anticoagulation of Atrial Fibrillation - a RELY Sub-

study. *Circulation* 2010; **122**: A18321
19 **Aulin JK**, Ezekowitz MD, Andersson U, Connolly SJ, Huber K, Reilly PA, Siegbahn A, Wallentin L, Yusuf S, Oldgren J. Interleukin-6 and C-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation. *J Am Coll Cardiol* 2011; **57**: E91
20 **Mahé I**, Bergmann JF, Chassany O, Dit-Sollier CB, Simoneau G, Drouet L. A multicentric prospective study in usual care: D-dimer and cardiovascular events in patients with atrial fibrillation. *Thromb Res* 2012; **129**: 693-699
21 **Aronow WS**, Gutstein H, Hsieh FY. Risk factors for thromboembolic stroke in elderly patients with chronic atrial fibrillation. *Am J Cardiol* 1989; **63**: 366-367
22 **Pearce LA**. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. The Stroke Prevention in Atrial Fibrillation Investigators. *Ann Intern Med* 1992; **116**: 6-12
23 **Lang RM**, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440-1463
24 **Providência R**, Botelho A, Trigo J, Quintal N, Nascimento J, Mota P, Leitão-Marques A. Possible refinement of clinical thromboembolism assessment in patients with atrial fibrillation using echocardiographic parameters. *Europace* 2012; **14**: 36-45
25 **Ruff CT**, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, Hanyok J, Patel I, Shi M, Salazar D, McCabe CH, Braunwald E. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010; **160**: 635-641
26 **Bradshaw PJ**, Ko DT, Newman AM, Donovan LR, Tu JV. Validity of the GRACE (Global Registry of Acute Coronary Events) acute coronary syndrome prediction model for six month post-discharge death in an independent data set. *Heart* 2006; **92**: 905-909
27 Available from: URL: http: //www.outcomes-umassmed.org/grace/. Assessed 29th May 2012

S- Editor Cheng JX **L- Editor** Webster JR **E- Editor** Zheng XM