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

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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 CHADS2 and CHA2DS2-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.

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

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RISK STRATIFICATION OF ATRIAL FIBRILLATION: WHERE DO WE STAND?

Stroke and thromboembolism are among the most severe complications of atrial fibrillation (AF). Risk stratification is currently based on clinical risk scores: either the CHADS2 or the CHA2DS2-VASc score are recommended (Table 1).

The CHADS2 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. The recently developed CHA2DS2-VASc score has succeeded in identifying a truly low risk group of patients: annual stroke risk of 0%5,10. 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 CHA2DS2-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. In the CHA2DS2-VASc validation cohort (1,084 patients from the Euro
Congestive heart failure (or left ventricular systolic dysfunction) - CHF
Hypertension - HTN
Risk factor - Risk factor
Diabetes mellitus - DM
Hypertension
Stroke or transient ischemic attack - TIA
Risk factor

June 26, 2012
Diabetes mellitus
- DM

Previous myocardial infarction, peripheral arterial disease or aortic plaque
Stroke or transient ischemic attack

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

| 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          | Age 65 to 74 yr                       |
| A2         | Age ≥ 75 yr                           | A          | Age ≥ 75 yr                           |
| D          | Diabetes mellitus                     | D          | Diabetes mellitus                     |
| Si         | Stroke or transient ischemic attack   | Si         | Stroke or transient ischemic attack   |
| VASc       | Previous myocardial infarction, peripheral arterial disease or aortic plaqueFemale |

All variables are assigned one point, when present, except those marked with ( ), which receive two points. Subjects with a CHADS2 score of 0 (low risk) should be placed under antplatelet therapy, those with a score of 1 (intermediate risk) can either undergo oral anticoagulation or antplatelet therapy and the remaining (high risk) have clear benefit with oral anticoagulation, unless contraindicated. Using the CHADS2 score, individuals with a score of zero (truly low risk) should be placed under no treatment (preferably) or, as an option, medicated with an antplatelet agent. Intermediate risk individuals (score of 1) should be placed under oral anticoagulation (preferably) or antplatelet agents (as an alternative). The remaining patients (score ≥ 2) should be anticoagulated.

Table 1: Explaining the CHADS2 and CHA2DS2-VASc risk scores

Heart Survey of AF, the calculated C-statistics suggested a modest predictive value of CHA2DS2-VASc (C-statistic = 0.606) and CHADS2 (C-statistic = 0.561) for predicting thromboembolism.

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 CHA2DS2-VASc and the HAS-BLED score. Thus, those individuals classified as high risk for thromboembolism using the CHADS2 or CHA2DS2-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 CHADS2 score value[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 CHADS2 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%
Cl. 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)\(^2\).

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\(^3\).

Rates of stroke were independently related to the levels of cTnI (2.09%/year in patients with cTnI \(\geq 0.040\) 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 \(\geq 0.040\) 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 \(\geq 0.040\) 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:DS\(-\)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\(^3\).

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:DS\(-\)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\(^\[20\]\) (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:DS\(-\)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\(^\[21\]\) which is known to represent LA size grossly.
Left ventricle systolic dysfunction has long been known to be associated with thromboembolism in atrial fibrillation. We have recently demonstrated that by adding echocardiographic parameters (LA area and LV systolic function) to CHADS2 or CHA2DS2-VASc we could achieve a significant improvement in the prediction of transesophageal markers of LA stasis. An ongoing echocardiographic sub-study from the ENGAGE-TI-MI-48 trial will probably clarify this matter using clinical endpoints (Table 4).

Other methods like apical 4-chamber LA area or LA volume (the current gold standard) have been proposed as more accurate. We have recently demonstrated that by adding echocardiographic parameters (LA area and LV systolic function) to CHADS2 or CHA2DS2-VASc we could achieve a significant improvement in the prediction of transesophageal markers of LA stasis. An ongoing echocardiographic sub-study from the ENGAGE-TI-MI-48 trial will probably clarify this matter using clinical endpoints (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. 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. 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 reevaluation 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) 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.

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### Table 3 Biomarkers associated with thromboembolism in atrial fibrillation

| Biomarker | Association |
|-----------|-------------|
| cTnI and NT-proBNP | Independently associated with the rate of stroke |
| CRP and IL-6 | Added prognostic information to the CHADS2 and CHA2DS2-VASc scores |
| D-dimers | Elevated levels were predictive of stroke and major bleeding |

C-TnI: 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

| Parameter | Association |
|-----------|-------------|
| Left ventricle systolic dysfunction | Associated with thromboembolism in atrial fibrillation and is currently used in the CHADS2-VASc score |
| Left atrial diameter | Associated with thromboembolism in old studies. Nowadays, diameter is not considered an appropriate way of assessing left atrial size |
| Left atrial area and volume | Associated with thromboembolism |
| Left atrial deformation assessment (strain and strain rate) | Associated with thromboembolism |
| Left atrial appendage thrombus, spontaneous echocardiographic contrast and low flow velocities in the left atrial appendage | Associated with a high risk of thromboembolic events and an adverse prognosis |

Other methods like apical 4-chamber LA area or LA volume (the current gold standard) have been proposed as more accurate. We have recently demonstrated that by adding echocardiographic parameters (LA area and LV systolic function) to CHADS2 or CHA2DS2-VASc we could achieve a significant improvement in the prediction of transesophageal markers of LA stasis. An ongoing echocardiographic sub-study from the ENGAGE-TI-MI-48 trial will probably clarify this matter using clinical endpoints.

The invasive nature of this technique makes it inadequate for wide usage in AF patients.
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Providência R et al. Future perspectives in AF risk stratification

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