

## Novel therapeutic concepts

# Biomarkers in atrial fibrillation: a clinical review

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Assessment of atrial fibrillation (AF)-associated stroke risk is at present mainly based on clinical risk scores such as CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc, although these scores provide only modest discrimination of risk for individual patients. Biomarkers derived from the blood may help refine risk assessment in AF for stroke outcomes and for mortality. Recent studies of biomarkers in AF have shown that they can substantially improve risk stratification. Cardiac biomarkers, such as troponin and natriuretic peptides, significantly improve risk stratification in addition to current clinical risk stratification models. Similar findings have recently been described for markers of renal function, coagulation, and inflammation in AF populations based on large randomized prospective clinical trials or large community-based cohorts. These new findings may enable development of novel tools to improve clinical risk assessment in AF. Biomarkers in AF may also improve the understanding of the pathophysiology of AF further as well as potentially elucidate novel treatment targets. This review will highlight novel associations of biomarkers and outcomes in AF as well as recent progress in the use of biomarkers for risk stratification.

### Keywords

Biomarkers • Atrial fibrillation • Stroke risk • Troponin • BNP • GFR • cystatin C • D-dimer • CRP • IL-6  
• Review • Risk stratification • Coagulation • Inflammation

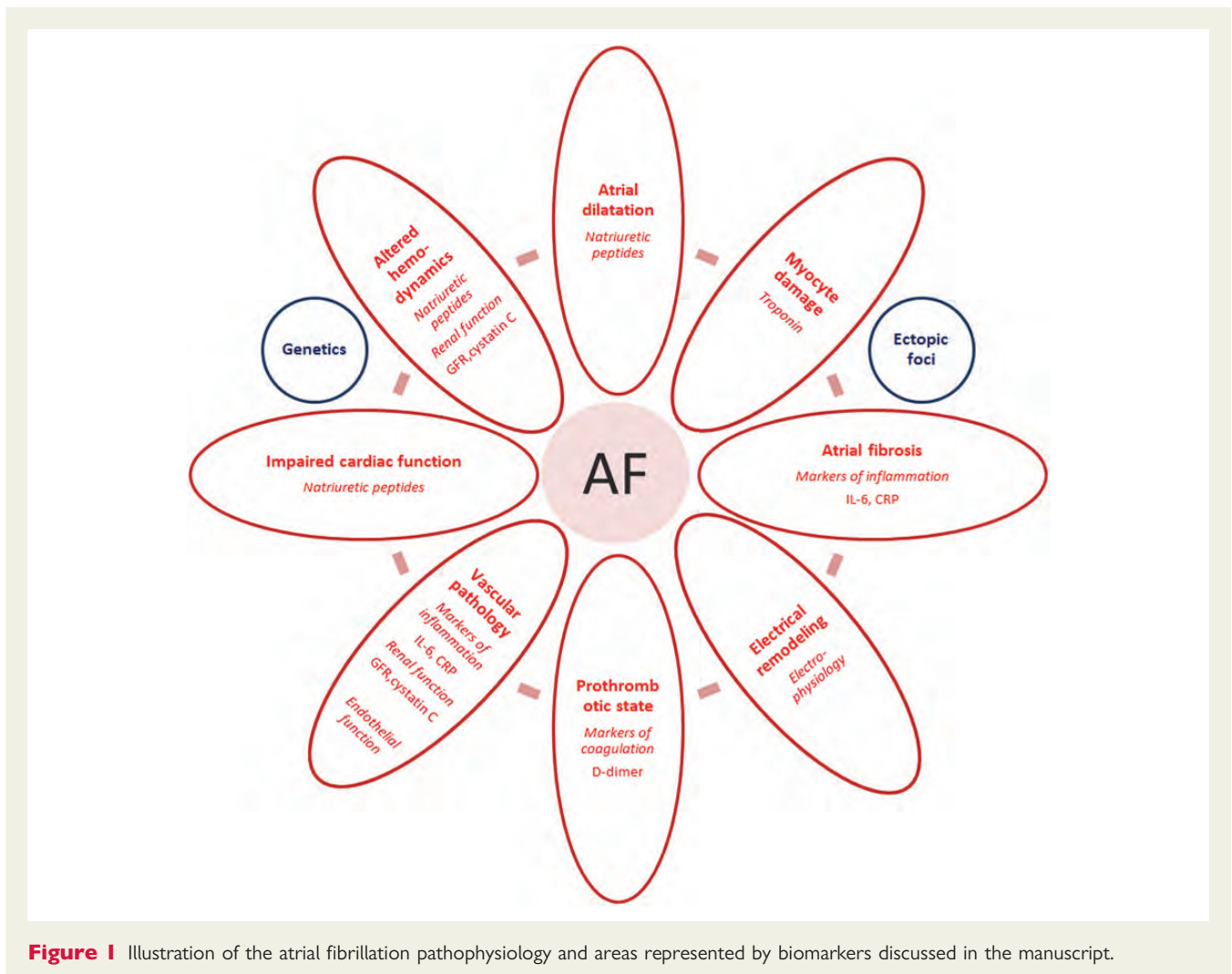
## Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and confers an independent increased risk of stroke and death.<sup>1,2</sup> The prevalence of AF increases with age, is doubled for every decade after the age of 50 years, and reaches ~10% in persons ≥80 years. Furthermore, it is projected to increase in the coming decades.<sup>3,4</sup> Although the exact mechanisms behind AF are not completely elucidated, the underlying pathophysiological changes have been well described. For the most common type of atrial fibrillation related to aging, the process involves a structural remodelling in which connective tissue deposition and fibrosis are the hallmarks, as well as altered atrial electrophysiological properties facilitating the initiation and perpetuation of AF.<sup>5,6</sup> In addition, left ventricular dysfunction and elevated ventricular filling pressures contribute to atrial remodelling and may produce a substrate and a trigger for AF as well.<sup>7,8</sup> Moreover, the significant role of the pulmonary veins as one of the key trigger sites for the onset of AF has also been well described.<sup>9</sup> Despite clinical differences in presentation, duration, and AF type, the corner stone of the management of patients focuses on

relief of symptoms and prevention of AF-associated stroke. Several clinical and echocardiographic risk factors have been identified that predict risk of stroke in AF. Systematic reviews have identified prior stroke/transient ischaemic attack/thromboembolism, older age, hypertension, diabetes, and structural heart disease as important risk factors.<sup>10,11</sup> Recently, vascular disease, age ≥65 years, and female gender were also added and now constitute the variables in the widely used CHA<sub>2</sub>DS<sub>2</sub>-VASc score [which assigns 1 point each to a history of congestive heart failure, hypertension, diabetes mellitus, vascular disease, age ≥65 years, and sex category (female gender) and 2 points to age ≥75 years and prior stroke/TIA].<sup>12,13</sup> Although easy to apply, the clinical risk scores including the CHA<sub>2</sub>DS<sub>2</sub>-VASc only seem to offer a modest discriminating value for the individual patients with C-statistic that range from 0.549 to 0.638,<sup>13</sup> where 1.0 is perfect discrimination and 0.5 is no better than random chance. Biomarkers derived from the blood, such as markers of inflammation, coagulation activity, cardiovascular stress, myocardial injury, and cardiac and renal dysfunction, have an increasing body of evidence showing association with clinical events and may help refine risk assessment in AF patients (Figure 1).

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**Figure 1** Illustration of the atrial fibrillation pathophysiology and areas represented by biomarkers discussed in the manuscript.

## Cardiac biomarkers

### Myocyte injury

Cardiac troponin, an intracellular protein involved in heart muscle contraction, was initially identified as a sensitive indicator of myocardial damage and myocardial infarction.<sup>14,15</sup> Subsequent reports displayed cardiac troponin as an indicator of increased risk of reinfarction and mortality in patients with acute coronary syndromes.<sup>16,17</sup> Slight elevations in troponin level were then observed in a proportion of patients with stable coronary artery disease, heart failure, and also in elderly apparently healthy individuals and associated with worse outcomes and increased mortality independent of conventional major coronary risk factors.<sup>18–20</sup> The continuous development of more sensitive troponin methods has made it possible to detect and measure troponin level in almost all individuals when utilizing the most sensitive methods currently available.<sup>21,22</sup> The importance of troponin in an AF population was first reported from the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) biomarker substudy performed in 6189 patients with AF and treated with either warfarin or dabigatran because of a raised risk of stroke.<sup>23</sup> The results

indicated, first, that detectable levels of troponin I ( $\geq 0.01 \mu\text{g/L}$ ) were common and seen in  $\sim 55\%$  of the patients with AF and at least one risk factor for stroke. Secondly, troponin was significantly and independently associated with increased risk of stroke or systemic embolism. Moreover, in comparison with CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc, when adding information about troponin measurements to a predictive model for stroke outcomes, the troponin I level provided significant incremental prognostic information. Thirdly, it was shown that risk assessment concerning cardiovascular death was improved by the use of troponin, both independently and when adding troponin I to the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc risk scores. These results were recently confirmed in the even larger Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) biomarker study, in which blood samples were collected and analysed for high-sensitivity troponin T in 14 892 patients with AF and treated with either apixaban or warfarin because of a raised risk of stroke.<sup>24</sup> By using a high-sensitivity troponin assay, it was possible to detect even lower levels of circulating troponin (lower limit of detection 1.5 ng/L). Consequently, an even larger proportion of patients, 73%, were identified to have detectable levels. The ARISTOTLE troponin

substudy results verified that the troponin levels were related to the risk of stroke and death, in a continuous fashion, independent of base-line characteristics and other biomarkers. These two studies, therefore, provide firm evidence that patients classified as having elevated troponin levels based on the 99th percentile upper reference limit for healthy subjects (troponin I  $\geq 0.04$   $\mu\text{g/L}$ , high-sensitivity troponin T  $\geq 13$  ng/L for the respective assays) had the highest rates of thrombo-embolic events and cardiovascular death independent of adjustments for clinical characteristics and other powerful biomarkers. Similar findings have also recently been reported from a registry cohort of stable chronically anticoagulated AF patients.<sup>25</sup> Patients with levels above the 50th percentile of the troponin distribution in an AF population had an increased risk of stroke, other ischaemic events, and a higher mortality regardless of their risk as estimated by the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc-scores.

The origin behind elevated cardiac troponin in patients with AF requires further study. It may be due to mechanisms such as increased ventricular rate causing oxygen demand/mismatch and myocardial ischaemia, volume and pressure overload, changes in microvascular blood flow, atrial calcium overload, oxidative stress, or alterations in tissue structure.<sup>26–30</sup> Even without a complete understanding of the mechanism, the firm evidence and the general availability of cardiac troponin measurements for routine care in most hospitals worldwide makes it a very attractive candidate for use to improve prognostication of patients with AF, in addition to the currently recommended clinical risk stratification.

## Myocyte stress

B-type natriuretic peptide (BNP) is a neurohormone secreted from the myocytes mainly in response to increased wall tension such as volume or pressure overload. The levels also increase during states of haemodynamic stress, e.g. left ventricular hypertrophy, ventricular dilatation, in heart failure, acute coronary syndromes and AF as well as with ageing, renal dysfunction, and female gender.<sup>23,31–33</sup> B-type natriuretic peptide is synthesized as an inactive prohormone. It is cleaved in equimolar amounts into the bioactive hormone, BNP, which has an important role in cardiovascular remodelling and volume homeostasis, and the inactive N-terminal fragment (NT-proBNP).<sup>34</sup> Initial studies described elevated levels of natriuretic peptides in patients with AF compared with matched controls in sinus rhythm.<sup>35–37</sup> It was thereafter reported that levels of natriuretic peptides fall rapidly following restoration of sinus rhythm.<sup>38–40</sup> The usefulness of levels of natriuretic peptides to predict maintenance of sinus rhythm after successful cardioversion so far is controversial.<sup>41–43</sup> However, from a community-based population of older adults it was recently shown that elevated NT-proBNP levels predict an increased risk of development of AF independent of other risk factors including echocardiographic parameters.<sup>44</sup>

The role of natriuretic peptides as powerful prognostic markers for cardiovascular outcomes and mortality was initially established in heart failure cohorts, thereafter in patients with acute coronary syndromes and later in stable coronary artery populations and in asymptomatic community-based elderly subjects.<sup>45–49</sup> The use of natriuretic peptides for risk prediction in anticoagulated AF

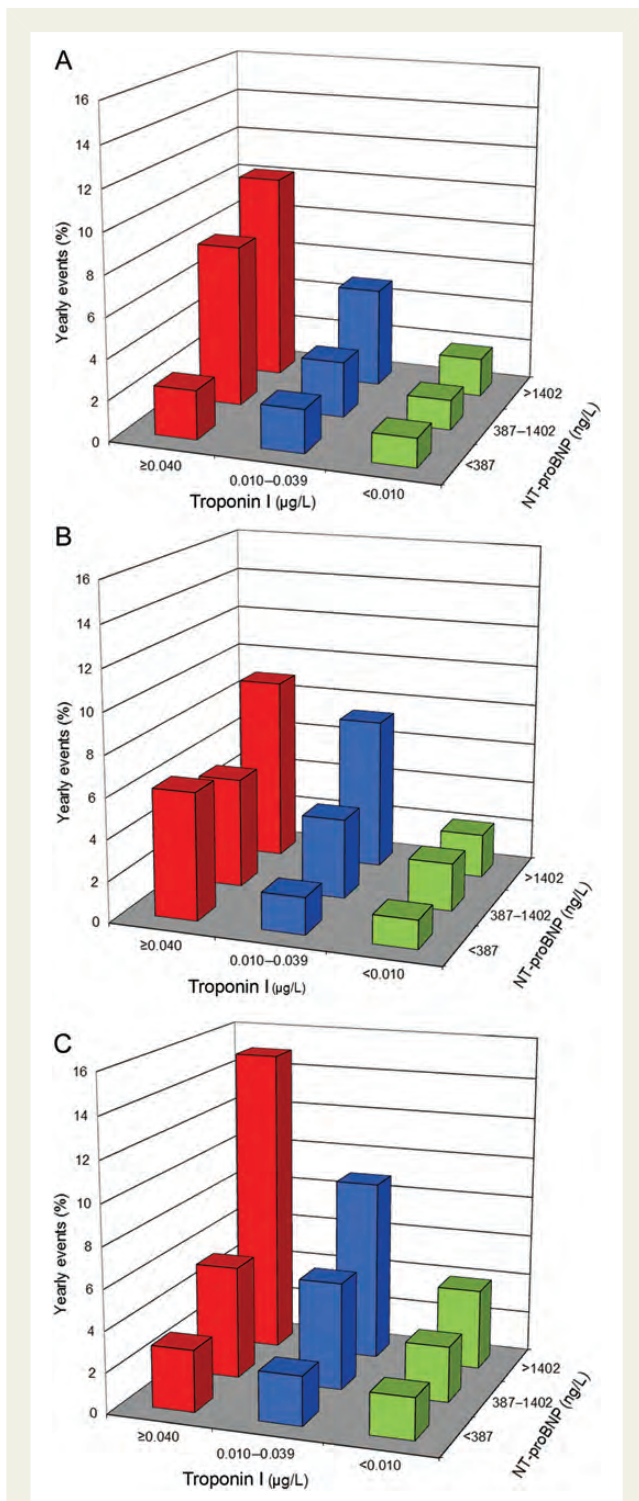
patients was first reported from the 6189 patients with AF in the RE-LY biomarker study.<sup>23</sup> Although previous studies had described elevated natriuretic peptide levels in AF patients, it was not until the RE-LY results that the prognostic value of this information was highlighted. In the RELY substudy, the level of NT-proBNP correlated with the risk of thrombo-embolic events and cardiovascular mortality with higher risk at rising levels. Despite adjustment for known risk factors, the risk of stroke or systemic embolism was doubled and for cardiovascular mortality five-fold higher in patients with the highest quartile levels of NT-proBNP in comparison with patients with normal NT-proBNP levels. The addition of NT-proBNP to the CHADS<sub>2</sub> and CHA<sub>2</sub>-DS<sub>2</sub>-VASc risk stratification models resulted in significant improvements in the discrimination performance for both outcomes as well. The results from the larger ARISTOTLE biomarker study verified and extended these findings to several events and subgroups.<sup>50</sup> Thereby in the ARISTOTLE cohort the NT-proBNP level was related also to both subtypes of stroke (ischaemic or haemorrhagic). There was an especially strong association between elevated risk of ischaemic stroke and rising NT-proBNP levels.

B-type natriuretic peptide levels have also been found to predict likelihood of subsequent identification of atrial fibrillation for patients with cryptogenic stroke.<sup>51,52</sup> For patients with low BNP levels, identification of AF with subsequent monitoring was found to be very unlikely.

Apart from constituting a reliable marker of ventricular dysfunction in heart failure patients, there are arguments for NT-proBNP being of atrial origin in AF due to myocyte stress in the atria and thus reflecting atrial dysfunction.<sup>53–55</sup> The proposed model is appealing, since atrial dysfunction is an established risk factor of thrombus formation in atrial fibrillation and thereby represents a plausible pathophysiologic mechanism for the relation between natriuretic peptides and thrombo-embolic events in AF.<sup>56</sup> The improved risk prediction by adding natriuretic peptides to clinical risk stratification models is substantial and the availability of the analysis is widespread and easy accessible. Therefore, the opportunity to use measurement of NT-proBNP to improve risk stratification of AF patients in routine clinical practice is very attractive. *Figure 2* illustrates the information provided by cardiac biomarkers in regard to annual rates of a composite outcome in each CHADS<sub>2</sub>-class based on data from the RE-LY substudy.

## Cardiac biomarkers as a complement to echocardiography in atrial fibrillation

Regarding prediction of incident AF, results from the Cardiovascular Health Study displayed NT-proBNP levels to be a considerably stronger marker than any other clinical covariate as well as echocardiographic assessment which included parameters such as left ventricular dimensions, left atrial dimension, percent fractional shortening, and left ventricular mass.<sup>44</sup> Further, when a risk score was constructed to predict individuals' absolute risk of developing AF based on participants in the Framingham study, the addition of echocardiographic parameters to clinical covariates did not result in clinically meaningful changes in risk category (i.e. shifting between low, intermediate, or high risk) according to net



**Figure 2** (A) Outcomes according to biomarker levels in patients in the RE-LY trial with a CHADS<sub>2</sub> score of 0–1. (B) Outcomes according to biomarker levels in patients in the RE-LY trial with a CHADS<sub>2</sub> score of 2. (C) Outcomes according to biomarker levels in patients in the RE-LY trial with a CHADS<sub>2</sub> score of  $\geq 3$ . Annual event rate for a composite outcome consisting of stroke, systemic embolism, pulmonary embolism, myocardial infarction, and vascular death (excluding haemorrhagic death).

reclassification analysis.<sup>57</sup> Concerning the risk of thrombo-embolic and cardiovascular events in AF patients, there are several echocardiographic risk factors identified. The use of transoesophageal echocardiography provides information of variables associated with thromboembolism such as atrial dense spontaneous echo contrast, low flow velocities in the left atrial appendage, or the presence of left atrial thrombus.<sup>56</sup> These parameters have in small studies been linked to elevated levels of natriuretic peptides and may contribute to the prognostic properties of natriuretic peptides in AF.<sup>58–60</sup> However, based on transthoracic echocardiography, there seem to be no close association between the degree of impaired left ventricular ejection fraction and risk of thrombo-embolic events in patients with atrial fibrillation and heart failure.<sup>10,61</sup> Further, available information on left ventricular function based on echocardiography or other imaging was adjusted for in both the RE-LY and ARISTOTLE biomarkers substudy analysis, in which NT-proBNP and troponin, among others, still provided significant improvements in risk prediction. At present, guidelines recommend screening of newly detected AF patients with echocardiography in order to identify underlying structural pathologies and potential reversible causes of AF and also for tailoring of treatments.<sup>12</sup> New techniques in the field of echocardiography such as three-dimensional echocardiography, tissue Doppler imaging, or speckle tracking echocardiography may in the future add complementary information.

## Markers of renal function

### Glomerular filtration rate

Glomerular filtration rate (GFR) is accepted as a useful index of renal function. The gold standard measurement for GFR is complex and difficult to perform in daily clinical practice and requires urinary or plasma clearance of exogenous markers. Therefore, GFR is usually estimated from serum levels of endogenous filtration markers such as creatinine. Several equations exist that incorporate demographic variables such as age, gender, body size, and ethnicity along with serum creatinine to estimate GFR. Reduced GFR has been associated with an increased risk of death, adverse cardiovascular events, and bleeding events in patients with coronary artery disease as well as in the general population.<sup>62–64</sup> The prevalence of AF is higher in end stage renal disease populations compared with the general population, and the AF prevalence increases when GFR decreases in general chronic kidney disease cohorts.<sup>65–69</sup> Impaired renal function is also associated with an increased risk of short- and long-term AF recurrence after successful electrical cardioversion as well as poorer maintenance of sinus rhythm after AF ablation therapy.<sup>70–73</sup> Concerning renal function and stroke outcomes in AF, Go *et al.*<sup>74</sup> reported an independent risk increase with reduced GFR or if proteinuria was present. These results were based on estimated GFR calculated according to the Modification of Diet in Renal Disease equation. Hohnloser *et al.*<sup>75</sup> reported similar findings based on the ARISTOTLE trial population, in which increased rates of stroke and bleedings occurred as renal function deteriorated estimated with the Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration equations.

## Cystatin C

Cystatin C is a small protein, synthesized at a constant rate in all nucleated cells.<sup>76</sup> It is freely filtered by the glomerulus, does not return to the blood flow, is minimally influenced by disease states, and is therefore believed to be a better endogenous marker of GFR than creatinine.<sup>77</sup> Cystatin C has been proposed as a more reliable marker of renal function than serum creatinine, in particular for the detection of small reductions in GFR.<sup>77,78</sup> Chronic kidney disease is associated with a prothrombotic state and progressive vascular atherosclerosis.<sup>79,80</sup> Cystatin C is considered to reflect microvascular renal dysfunction and has been linked to elevated levels of markers of coagulation, raised levels of inflammatory markers, and severity of coronary artery disease.<sup>78,81–84</sup> In addition, cystatin C significantly improves risk stratification compared with creatinine-based estimation of GFR in both elderly and in coronary artery disease populations.<sup>85–89</sup> The significance of cystatin C in an AF population was recently reported from the ARISTOTLE and RE-LY biomarker substudies.<sup>75,90</sup> Rising cystatin C levels were independently associated with increased rates of stroke or systemic embolism, mortality, and major bleedings, and yielded an improved risk stratification and risk prediction.

Despite that renal impairment, measured with either creatinine-based equations or cystatin C, constitutes a major risk factor for thrombo-embolic and cardiovascular events in AF, renal impairment is not represented in current risk stratification models. This is a major problem as patients with renal dysfunction currently tend to be undertreated with oral anticoagulation therapy due to the associated higher bleeding risk especially when treated with vitamin-K antagonist therapy.<sup>91,92</sup> Although cystatin C achieved improved stroke risk stratification, creatinine-based estimates of renal function were better indicators of the risk of bleeding during oral anticoagulant treatment in the ARISTOTLE study. Moreover, each of the novel oral anticoagulants is cleared to some extent by the kidneys, and more so with dabigatran than the oral factor Xa inhibitors. Thus, creatinine-based estimates of GFR have the potential to be of value in estimating risk of events, as well as to select the best dose, of the new as well as old oral anticoagulants.<sup>75,90</sup>

## Markers of coagulation

### D-dimer

The prothrombotic state in AF was first described two decades ago.<sup>93–96</sup> Among markers of coagulation in AF, plasma D-dimer, a marker of fibrin turnover, is essentially used as an index of thrombogenesis and has been studied frequently. Levels of D-dimer are elevated compared with matched controls in sinus rhythm and even seem to remain elevated despite successful cardioversion.<sup>93–97</sup> Levels of D-dimer further seem to rise along with the accumulation of clinical risk factors for thromboembolism or by the presence of left atrial appendage thrombi.<sup>98–100</sup> Until recently, there were only relatively small studies to describe the prognostic value of D-dimer levels for stroke in univariable analysis or combined cardiovascular events with limited Cox adjustments.<sup>101,102</sup> However, the recent preliminary reports from the RE-LY biomarker study in 6216 patients with AF describe a

significant association between baseline D-dimer levels and the risk of stroke, cardiovascular death, and major bleeding outcomes independent of established risk factors including the CHADS<sub>2</sub> variables.<sup>103</sup> The risk increased with higher D-dimer levels as evidenced by a three-fold increase of stroke or systemic embolism and 3.5-fold increase for cardiovascular mortality when the top vs. bottom quartiles were compared. These results were recently confirmed in the larger ARISTOTLE biomarker substudy demonstrating that D-dimer levels at baseline, regardless of ongoing vitamin-K antagonist treatment, are related to stroke, mortality, and major bleeding.<sup>104,105</sup> These results suggest that D-dimer may also be a clinically useful risk marker in AF.

## Markers of inflammation

### Interleukin 6 and C-reactive protein

There is growing evidence that inflammation may be associated with AF as well as the pathogenesis of the arrhythmia.<sup>6,106–109</sup> C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to stimuli by among others interleukins such as interleukin 6 (IL-6) triggered by inflammation.<sup>110–112</sup> Interleukin 6 and CRP are robust and established markers of inflammation and have been most frequently studied in cardiovascular diseases and AF.<sup>113,114</sup> Although some inconsistencies exist, the majority of studies have reported elevated CRP levels or other inflammatory markers to be independent risk factors for incidence of AF in subjects with no history of AF.<sup>106,115–118</sup> The majority of trials also indicate elevated levels of inflammatory markers in AF compared with control despite some differences in significance when applying multivariable modelling.<sup>106,108,119–121</sup> Further, there are data indicating a correlation between markers of inflammation and AF burden,<sup>106</sup> increasing levels of inflammatory markers with accumulation of risk factors<sup>121–123</sup>, and the effect on cardioversion such that higher levels attenuate success rate and independently confers poorer sinus rhythm maintenance.<sup>124–131</sup> Together, the results indicate that the inflammatory process has an importance both for the development and perpetuation of AF.<sup>114</sup> Inflammation also seems to have prognostic importance in AF populations. In 2004, Conway *et al.*<sup>132</sup> based on a small study, reported the association between IL-6 and a composite outcome of stroke and death. Later, the prognostic value of CRP to all-cause mortality and a composite of ischaemic stroke, myocardial infarction, or vascular death was displayed in a larger cohort based on the Stroke Prevention in Atrial Fibrillation (SPAF) III trial.<sup>133</sup> Recent studies confirm these results in which CRP has been independently related to mortality and IL-6 to all-cause death and a composite consisting of stroke/TIA, systemic embolism, acute coronary syndrome, acute heart failure, and cardiac death.<sup>25,134</sup> Preliminary results from the RE-LY biomarker substudy showed an independent association between IL-6 and stroke or systemic embolic events in ~ 6200 AF patients.<sup>135</sup> In patients with top quartile levels compared with the bottom quartile, there was a doubling of stroke risk in adjusted analysis. IL-6 was also independently and incrementally associated with cardiovascular mortality. C-reactive protein quartile levels, however, only remained independently associated with cardiovascular

mortality after multivariable adjustments. The association between inflammatory markers and thrombo-embolic events may be due to the link between inflammation and the prothrombotic state in AF seen in several settings.<sup>121,136–138</sup> The indications of an inflammatory state as a component of the AF disease and its relation to several outcomes makes inflammatory activity an interesting target for further investigation in this condition. Still it seems too early to include an unspecific indicator of inflammatory activity as a routine marker in the risk stratification of patients with AF.

## Future prospects

### Therapeutic decisions based on biomarkers

Identification of patients needing oral anticoagulant treatment might be improved by addition of biomarkers to clinical risk factors. However, such a strategy needs further evaluation before implementation in clinical practice. Tailoring of other therapeutic options based on biomarkers has not been studied in AF cohorts. There is some evidence of improved outcomes in chronic heart failure patients in which participants randomized to NT-proBNP level guided treatment had improved outcomes compared with standard care.<sup>139–141</sup> Whether biomarkers can play a similar role in AF needs to be elucidated.

## Discussion

A multitude of biomarkers are available and new ones are constantly being identified and assessed. Biomarkers may increase the understanding of the pathogenesis of AF as well as refine future risk prediction. Some markers appear to reflect the pathophysiologic process for development of AF, while others may simply be suited as markers of risk for future cardiovascular events. It is typically difficult to draw firm conclusions concerning the involvement of a biomarker in the aetiology of a disease. Often a biomarker may simply be a marker of disease severity or comorbidity that relates to risk. However, biomarkers have increasing clinical importance and will anticipate that biomarkers will play a key role in refining clinical risk assessment in patients with AF as presented in this review. Further, the biomarkers discussed in this review have mostly been assessed individually. The implementation of a multimarker strategy will likely further improve risk stratification as have been described for coronary artery disease populations.<sup>16,17</sup> In fact, in the AF population, the importance of a multimarker approach was highlighted by the incremental prognostic information by the simultaneous use of cardiac troponin and natriuretic peptides compared with information obtained by each biomarker separately.<sup>23</sup> Therefore, the forthcoming testing and verification of multimarker-based risk stratification in the large clinical trial cohorts and other materials are eagerly awaited. Biomarkers may further have a role in predicting treatment response and treatment selection as indicated by results concerning pulmonary vein isolation outcomes, the use of renal markers regarding assessment of bleeding risk with new oral anticoagulation drugs, or data supporting genetic markers for tailoring of warfarin dosage.<sup>70,71,75,142–145</sup> It is also likely that as proteomics

evolves and the field of studying biological systems improves, an even greater number of useful biomarkers will be identified that may enhance the understanding of the pathophysiology in AF, treatment monitoring, potential drug targets, and possibly even early disease detection.

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