Application of Biomarkers for Risk Stratification in Patients with Atrial Fibrillation

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BACKGROUND: Atrial fibrillation is the most common sustained arrhythmia and an important contributor to cardiovascular morbidity and mortality. Several strategies have been proposed for prediction of outcomes and individualization of treatments to better balance the benefits of stroke prevention and risks of bleeding during anticoagulation.

CONTENT: The availability of analytically more specific and sensitive methods to measure circulating biomarkers of cellular and organ stress and dysfunction has led to testing of their utility in several cardiovascular conditions. In patients with atrial fibrillation, biomarkers of myocardial injury (troponin) and cardiovascular stress and dysfunction (natriuretic peptides, growth differentiation factor 15), myocardial fibrosis (galectin-3), renal dysfunction (creatinine, cystatin C), inflammation (C-reactive protein, cytokines) and coagulation activity (D-dimer) have all been found associated with underlying pathophysiology, clinical outcomes and effects of treatment. Measurements of these markers might therefore expand the understanding of the pathophysiology, improve risk assessment and optimize treatment in individual patients with atrial fibrillation.

SUMMARY: Biomarkers for risk stratification have potential roles as tools for evaluation of patients with atrial fibrillation and for selection of the best treatment strategies to prevent stroke, major bleeding, and mortality.

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Atrial fibrillation (AF)4 is the most common sustained arrhythmia in clinical practice and an important contributor to cardiac morbidity and mortality. Patients with AF have a mean 3 to 5-fold increased risk of stroke and a doubling in mortality (1, 2). However, patients with AF are very heterogeneous, and the risk for these events and the need for stroke prevention treatment are therefore variable. In patients with AF and an indicator or a raised risk of stroke, treatment with oral anticoagulation, vitamin-K antagonists, or the new non–vitamin K antagonist oral anticoagulants (NOACs) reduces the risk of stroke by 65%–80% compared with placebo, but raises the risk of bleeding (3–5). Various risk stratification models have been developed to identify patients with different risks of stroke and bleeding, enabling an assessment of the risk-benefit balance before deciding on oral anticoagulant treatment (3). At present, the risk for stroke in AF is commonly estimated by clinical risk factors, e.g., the CHADS2 or the later refined CHA2DS2-VASc score [which assigns 1 point each for a history of congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65–74 years, and female sex, 2 points for age ≥75 years, and prior stroke/transient ischemic attack (TIA)] (6). The risk of bleeding may be estimated with the HAS-BLED score [which assigns 1 point for hypertension, abnormal renal or liver function, stroke, bleeding history/predisposition, labile INR, elderly (≥65 years), and drug or alcohol use] (7). During the last years, a new line of research has emerged evaluating circulating biomarkers to further improve the prediction of stroke, mortality, and the risk of bleeding as well as the response to treatment (8).

The availability of analytically specific and sensitive methods to measure circulating biomarkers of cellular and organ stress and dysfunction has led to testing of their utility in several cardiovascular conditions. In patients with AF, biomarkers of myocardial injury (troponin) and cardiovascular stress and dysfunction (natriuretic peptides, growth differentiation factor 15), myocardial fibrosis (galectin-3), renal dysfunction (creatinine, cystatin C), inflammation (C-reactive protein, cytokines) and coagulation activity (D-dimer) have all been...
associated with underlying pathophysiology, clinical outcomes, and effects of treatment. Information on the concentrations of these markers might therefore contribute to the understanding of the pathophysiology, improve risk assessment, and optimize treatment in individual patients with AF (Fig. 1). In this review, we provide an overview of the current knowledge on biomarkers as tools for evaluation of patients with AF and discuss their potential utility for selection of the best treatment strategies to prevent stroke, mortality, and major bleeding during anticoagulation.

**Cardiac Biomarkers**

**CARDIAC TROPONIN**

Cardiac troponin (cTn) is an independent indicator of increased cardiovascular risk and mortality in a wide range of cardiac diseases, such as acute coronary syndromes (9, 10), stable coronary artery disease, heart failure, and also in apparently healthy elderly individuals (11–13). The high-sensitivity cTn assays have made it possible to detect and measure cTn in almost all individuals (14, 15) and have improved the prognostic properties even further in these settings (12, 16–18). The association of cTn concentrations with stroke and other cardiovascular events in stable patients with paroxysmal or persistent AF was initially reported from the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) biomarker substudy (19–21). In a substudy of 6189 out of a total 18113 patients, with biomarkers available and treated with either warfarin or dabigatran, the results showed that cTnI, measured with a conventional assay (Access AccuTnI, Beckman Coulter), was detectable (≥0.01 μg/L) in approximately 55% of the patients (21). Adjusted for other risk factors, patients with increased cTnI concentrations had almost a 1.7-fold increased risk of stroke or systemic embolism, 3-fold increased risk of cardiovascular mortality, and 1.9-fold increased risk of major bleeding when comparing the group with increased concentrations against the group with nondetectable cTnI, respectively. The addition of cTnI to the CHADS2 and CHA2DS2-VASc scores provided incremental prognostic information for the risk of stroke, even more so for the risk of cardiovascular death. These results were later confirmed and further expanded in the Apixaban for the Prevention of Stroke in Subjects with
Atrial Fibrillation (ARISTOTLE) study randomizing patients with paroxysmal or persistent AF and a raised risk of stroke to either apixaban or warfarin (22, 23). The ARISTOTLE biomarker study (24, 25) included around 14,897 patients and included troponins measured with high-sensitivity assays [limit of detection 1.3 ng/L for cTnI-hs (ARCHITECT, Abbott Diagnostics) and 5 ng/L for cTnT-hs (Cobas Analytics, Roche Diagnostics)]. Thereby an even larger proportion of patients had detectable concentrations: 98.5% cTnI-hs and 93.5% cTnT-hs. The ARISTOTLE biomarker study confirmed that the concentrations of cTnI-hs and cTnT-hs, even within the normal range, were related to the risk of each of the individual events of stroke, cardiac and total death, and major bleeding events up to a maximal event rate at a concentration ≥30 ng/L (Fig. 2,A and B). There was an independent prognostic value of both the cTnI-hs and cTnT-hs concentrations concerning all these events regardless of other prognostic clinical risk factors and biomarkers. Accordingly, both high-sensitivity troponin assays permitted a greater discriminatory power than the conventional troponin assays concerning all outcome events. Similar associations between cTn and adverse cardiovascular events have been reported from a registry cohort of stable chronically anticoagulated AF patients (26). These studies clearly demonstrated the incremental prognostic value of the cTn-hs concentration in addition to clinical factors and other biomarkers in patients with AF. Thus, regardless of the risk of stroke, as estimated by the CHADS₂ or CHA₂DS₂-VASc scores or bleeding as estimated by the HAS-BLED scores, a higher concentration of cTn-hs was independently associated with a

Fig. 2. Estimated 12-month rates of stroke/systemic embolic events (SE) (blue line), major bleeding (red line), and mortality (black line) in relation to continuous plasma levels of cardiac cTn (A), cTnT (B), NT-proBNP (C), GDF-15 (D), creatinine clearance CKD-EPI (E), cystatin C (F), IL-6 (G), CRP (H), and D-dimer (I), respectively, using restricted cubic regression splines.

Data based on 14,897 (cTn), 14,892 (NT-proBNP), and 14,798 (GDF-15) patients with AF and a raised risk included in the ARISTOTLE trial [Hijazi et al. (22), Hijazi et al. (23), Hijazi et al. (39), Wallentin et al. (98)].
2-fold increased risk of stroke, 4-fold increased risk of cardiac mortality, and 2-fold increased risk of major bleeding. The prognostic properties also seem to be similar by using either cTnI or cTnT (27).

The underlying mechanisms for the increased concentration of cTn in patients with AF and its independent relation to cardiovascular events are probably multifactorial. Increased concentrations of cTn are observed with aging, tissue vulnerability, myocardial necrosis and apoptosis, myocardial stress due to elements of increased or variable heart rates, myocardial dysfunction with variations in atrial and ventricular volume and pressure load, and potential episodes of myocardial ischemia (3, 17, 28–31). When using high-sensitivity assays, circulating cTn is also detectable in patients with stable coronary artery disease as well as in apparently healthy individuals, indicating a relationship to increased myocyte turnover, increased cellular troponin release, and reversible increase in cell wall permeability of cTns or troponin fragments, which also might have relevance in patients with AF (32, 33). AF might also be associated with underlying inflammatory and fibrotic processes, contributing to the perpetuation of the arrhythmia, to the hypercoagulable state, and to the risk of thromboembolism and adverse events (30, 34–37). However, even without a thorough understanding of the mechanisms, information on the cTn concentration still seems useful for improved risk assessment in patients with AF.

**Natriuretic Peptides**

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. BNP has a central part in volume regulation and cardiovascular remodelling, although the inactive N-terminal fragment [N-terminal pro B-type natriuretic peptide (NT-proBNP)] has a longer half-life (38). The concentrations of NT-proBNP increase during states of hemodynamic stress such as in heart failure, acute coronary syndrome, and arrhythmias including AF as well as renal dysfunction, female sex, and aging (21, 38).

The concentrations of natriuretic peptides provide significant prognostic information on the risk of several cardiovascular outcomes and mortality in all these settings. During the last years the prognostic properties of NT-proBNP have also been extended to patients with AF (21). In the RE-LY biomarkers substudy, in 6189 anticoagulated patients with AF, >75% of the patients had increased NT-proBNP concentrations (>387 ng/L). The concentration of NT-proBNP was significantly associated with risk of thromboembolic events and cardiovascular mortality (21). After adjustment for known clinical risk factors, the risk of stroke or systemic embolism was 2-fold, and the risk of cardiovascular mortality was 5-fold higher in patients with the highest compared to the lowest quartile of NT-proBNP concentration, which mainly included patients with normal NT-proBNP concentrations. In relation to the commonly used CHADS2 and CHA2DS2-VASc risk stratification models, the addition of NT-proBNP resulted in substantial improvements of the discriminatory performance for both outcomes. These results have been validated in the larger ARISTOTLE biomarker study (n = 14892) and recently also in registry cohorts (39–41). In the ARISTOTLE biomarker study, it was verified that NT-proBNP was increased in 3 out of 4 patients with AF. Additionally, in the ARISTOTLE trial the NT-proBNP concentration had a strong positive association with the risk of stroke and cardiovascular mortality (Fig. 2C). The prognostic value of NT-proBNP was independent of clinical risk factors and other biomarkers, indicating that a NT-proBNP in the top quartile (>1250 ng/L) independently conferred more than a doubled risk of stroke as well as cardiovascular mortality as compared with the lowest quartile (≤363 ng/L) (39). Importantly, NT-proBNP seemed to be a specific indicator of cardiovascular events without being related to the risk of major bleeding in patients with AF on oral anticoagulation. This finding may be important in the clinical setting when trying to identify factors differentiating between a patient’s risk of ischemic stroke and risk of major bleeding during anticoagulation.

NT-proBNP is well established as a diagnostically sensitive indicator of both systolic and diastolic cardiac dysfunction (38, 42, 43). The reason for the common occurrence of increased NT-proBNP in AF even without clinical heart failure might be related to the tachyarrhythmia leading to variable hemodynamics, intracardiac filling pressures and myocardial distension, and also by concealed cardiac dysfunction with preserved systolic function (44, 45). In several studies of patients with AF, NT-proBNP concentrations have also been associated with presence of atrial dysfunction and atrial thrombus, which may represent another pathophysiological link between an increased NT-proBNP concentration and the risk of thromboembolic events (43, 46, 47). The prospect of using measurements of natriuretic peptides for improvement of risk stratification in patients with AF therefore seems very attractive for routine clinical practice.

**Markers of Renal Function**

During recent years the increased risk of thromboembolic, cardiovascular, and major bleeding events in patients with renal dysfunction and AF has drawn much attention (48–51). The most accurate measurement of glomerular filtration rate (GFR), as an index of renal function, requires urinary or plasma clearance of exogenous markers, and is thus complex and demanding to
perform in daily clinical practice (52). GFR is therefore more often estimated from serum concentrations of endogenous filtration markers such as creatinine (52, 53). There are several equations available that incorporate demographic variables such as age, sex, body size, and ethnicity together with serum creatinine to estimate GFR. At present, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation seems to estimate renal function most accurately (53). Beyond increased AF prevalence as GFR decreases, impaired renal function is also associated with poorer preservation of sinus rhythm in patients selected to rhythm control strategies (54, 55). For risk stratification, reduced GFR is associated with an increased risk of death, adverse cardiovascular outcomes and bleeding events in patients with coronary artery disease, as well as in the general population (56, 57). In 2009, an independent association between renal impairment and increased stroke risk in patients with AF was reported (58). In patients with an estimated GFR <45 mL/min, the relative risk for ischemic stroke was 1.39 as compared with patient with GFR ≥60 mL/min. Similar findings have thereafter been reported from several clinical trials and registry cohorts indicating associations between increased risk of stroke, mortality, and major bleeding and impaired renal function in AF, albeit some inconsistencies exist in regards to the independent association with risk of stroke in patients receiving anticoagulants (48–51, 59–63). The relation between outcomes and estimated renal function by CKD-EPI in AF is illustrated in Fig. 2D. Estimation of renal function provides important information not only concerning the risk of bleeding and stroke but also concerning the optimal dose and associated efficacy and safety of pharmacological treatment such as oral anticoagulant. It is noteworthy that impaired renal function is associated with a raised risk of major bleeding both during anticoagulation with vitamin-K antagonists as with the renally eliminated non-vitamin K anticoagulant such as dabigatran (49, 64). In contrast, new oral anticoagulants with less dependence on renal elimination, e.g., apixaban, have a weaker association between renal function and bleeding outcomes (50). Thus, biomarkers for estimation of renal function are important for selection and dosage of oral anticoagulation in AF (65).

**Cystatin C**

Cystatin C, a cysteine protease inhibitor, consists of 1 polypeptide chain with a molecular mass of 13 kDa (66). It is synthesized at a constant rate in all nucleated cells and is eliminated through glomerular filtration (66, 67). It is believed to be a better endogenous marker of GFR than creatinine and has therefore been proposed as a more reliable indicator of renal function than serum creatinine, in particular for the detection of small reductions in GFR (67, 68). Importantly, concerning risk stratification, cystatin C significantly improves the prognostication as compared with creatinine-based estimation of GFR in both general populations and in the setting of coronary artery disease (69–71). Recently the relation between cystatin C and risk for adverse outcomes was displayed in AF populations as well (49, 50). On the basis of evaluations in the ARISTOTLE and RE-LY biomarker substudies, increased cystatin C concentrations were associated with higher rates of stroke and systemic embolism, mortality, and major bleeding (Fig. 2E). Chronic kidney disease is associated with a prothrombotic state and progressive vascular atherosclerosis in general. However, it has been suggested that cystatin C is more strongly associated to these vascular states beyond solely being a marker of renal function that offers a more accurate detection and staging of chronic kidney disease (68, 72–74). Cystatin C is therefore an interesting alternative marker both for estimation of renal function and risk of complications in AF, especially when treated with oral anticoagulation. The recent development of an international reference standard for cystatin C may facilitate and increase its utility further (75).

**Inflammation, Oxidative Stress, Fibrosis**

**C-Reactive Protein and Interleukin-6**

Inflammatory activity was linked to AF in the 1990s when Fruscì et al. were able to identify inflammatory activity by analyzing myocardial biopsies from patients with AF (37, 76). Most studies on inflammatory activity in AF have focused on the clinically established biomarkers C-reactive protein (CRP) and interleukin-6 (IL-6) (77). CRP, an acute-phase protein, is produced by the liver in response to a variety of stimuli, among other interleukins such as IL-6, prompted by inflammation (78). The concentrations of these inflammatory markers are associated with AF burden (35) and poorer sinus rhythm maintenance (79–81). In addition, increased concentrations of CRP and IL-6 have been associated with increased risks of mortality and composites of cardiovascular events in AF, both in registry cohorts and in clinical trial populations (26, 82–84). Recently, these results were validated in 2 large cohorts from the RE-LY and ARISTOTLE biomarker substudies of 6187 and 14954 AF patients, respectively (34, 85). CRP and IL-6 displayed an association with several outcomes (Fig. 2, F and G), although the association only remained independent with all-cause mortality in fully adjusted models including other prognostic biomarkers such as troponin and NT-proBNP. The indications of inflammatory activity as a component of the AF disease, its associations to a prothrombotic state, and its relation to worse outcomes make inflammatory activity an interesting area for further investigation and eventual treatment target (86–89). However, unspecific indicators of inflammatory ac-
tivity such as CRP or IL-6 might not be useful to include as routine biomarkers to improve risk stratification in patients with AF.

GROWTH DIFFERENTIATION FACTOR 15

Growth differentiation factor 15 (GDF-15) is a distant member of the transforming growth factor-β cytokine family. It is expressed in a broad range of cells, such as adipocytes and myocytes in response to inflammation and stress (e.g., cellular ischemia, mechanical and oxidative stress) (90, 91). GDF-15 is an emerging prognostic biomarker that provides independent information of cardiovascular events in patients with coronary artery disease or heart failure and in apparently healthy community-dwelling adults (90, 92–97). The potential prognostic usefulness of GDF-15 in patients with AF was recently presented in 14798 patients with AF in the ARISTOTLE biomarker substudy (98). GDF-15 concentrations displayed a significant association to stroke, cardiovascular and total mortality, and major bleeding independent of clinical risk factors (Fig. 2H). When also adjusted for other biomarkers the independent association to major bleeding and cardiovascular and total death but not stroke was maintained (98). In adjusted analyses the highest vs the lowest quartile of GDF-15 had a 2-fold higher risk of major bleeding and mortality. Including GDF-15 in risk scores of major bleeding led to significant and substantial improvements of the risk prediction in comparison with the clinically used HAS-BLED bleeding risk stratification model in AF, with an improvement of the C-index from 0.63–0.68. Also, when including GDF-15 in multivariable risk scores for all-cause mortality, and major bleeding independent of clinical risk factors and other biomarkers, a hazard ratio of 1.31 was displayed for every 50% increase in galectin-3 concentrations. However, there was no independent association with the risk of stroke or major bleeding. Although galectin-3 reflects a different pathophysiological pathway than the other reviewed biomarkers, its eventual usefulness for risk stratification in patients with AF is uncertain and needs further exploration.

Markers of Endothelial Function

Von Willebrand factor (vWF) is a glycoprotein produced by endothelial cells (107). vWF plays a crucial role in platelet adhesion and thrombus formation, is used as a marker of endothelial dysfunction and platelet activation, and has been studied most extensively among the endothelial markers in patients with AF (107, 108). In some but not all studies of patients with AF there was an association between vWF concentrations and the risk of stroke (107, 109–111). The relation between the vWF concentration and an increased mortality and major bleeding were although more consistent (107, 109–111). On the basis of 1209 patients with AF in the Atherosclerosis Risk in Communities (ARIC) cohort, 1 SD increase in baseline vWF concentration conferred a hazard ratio of approximately 1.2 for mortality (109). Other substances such as asymmetric dimethylarginine, an endogenous inhibitor of endothelial nitric oxide synthase, are related to poorer outcomes in several settings (112–114). In AF, the concentrations of asymmetric dimethylarginine are increased and may provide prognostic information beyond clinical risk factors, although further confirmatory data is required (115–117). The eventual usefulness of markers of endothelial dysfunction for understanding of the pathophysiology, and their contribution to risk stratification in patients with AF, requires further clarification.

Markers of Coagulation

The initial biomarker research in AF was focused on markers of coagulation and the prothrombotic state that accompanies the arrhythmia, which might be associated with the thromboembolic complications (118–121). The plasma concentration of D-dimer is a marker of fibrin turnover. In patients with AF, concentrations of D-dimer are increased as compared to matched controls in sinus rhythm (118–122). The concentration of
D-dimer is associated with an accumulation of clinical risk factors for thromboembolism, and increased concentrations have been associated with the presence of left atrial appendage thrombi (122–125). On the basis of a few relatively small studies with limited opportunities for adjustments for confounders, the concentration of D-dimer has been found associated with stroke risk in AF (126, 127). The concentration is decreased by oral anticoagulation treatment in the majority of treated patients, and a reduction is also associated with better outcome (121, 128–131). Recently, the relation between D-dimer and risk of thromboembolic and bleeding events in a total of 14,878 patients with AF on oral anticoagulation from the ARISTOTLE biomarker study was presented (Fig. 2I) (132). As expected, the D-dimer concentration was lowered in patients starting treatment with oral anticoagulation. Adjusted for the CHADS2 score, the concentration of D-dimer at baseline was significantly associated with stroke or systemic embolism in patients without, but not in those already treated with, oral anticoagulation before blood sampling for D-dimer measurement. However, the relation with mortality and major bleeding risks was more consistent with up to a doubled risk for major bleeding and approximately a 4-fold increased risk for death comparing the top vs bottom quartiles adjusted for the CHADS2 score. Similar results have been presented recently from 6202 patients in the RE-LY biomarker substudy (133). On the basis of these data the concentration of D-dimer might be a clinically useful risk marker in AF. However the D-dimer concentration shows large variability within and between subjects and is also an unspecific acute phase reactant, which diminishes its usefulness in many settings. In addition, there are several different methods for measuring D-dimer concentration, which creates difficulties for its implementation in routine care.

Clinical Implications

Biomarker research in AF has contributed to the progress of current understanding of the pathophysiological mechanisms involved both in the development of arrhythmia, its underlying substrate, and its long-term complications. The value of measurements of circulating biomarkers for improved risk stratification in patients with AF seems substantial. Many biomarkers provide independent information on increased risk of different outcomes (Table 1).

Utilization of biomarkers might improve the identification of individuals with larger absolute benefit of new oral anticoagulants as compared with warfarin in patients with AF (21–23, 39, 98, 132). It is also conceivable that some biomarkers may provide further guidance regarding selection of specific treatments, such as mechanical interventions, or dosages as previously demonstrated for the markers of renal function and for genetic markers for warfarin dosage (49, 50, 134–136).

Biomarker-Based Risk Scores

Recently, biomarker-based risk scores have been developed for improved risk prediction in AF. A biomarker-based risk score for stroke risk, the ABC-stroke score (Fig. 3A), including age, biomarkers (troponin and NT-proBNP), and clinical disease history of prior stroke, has been developed and outperformed the present recommended CHA2DS2-VASc risk score for stroke risk prognostication (137, 138). Moreover, a biomarker-based risk score for prediction of major bleeding in AF, the ABC-bleeding score (Fig. 3B), including age, biomarkers (troponin, hemoglobin, GDF-15 or renal functions markers), and clinical history of prior bleeding, was also recently developed and validated in 2 large cohorts and found to outperform risk scores for bleeding based on traditional variables such as the HAS-BLED and also the newer ORBIT score (139). In both ABC risk scores, the included biomarkers were more strongly predictive of each outcome as compared to most clinical risk factors. Apart from better risk stratification, calibration, and higher discriminatory abilities, both ABC risk scores are constituted by more specific markers with less overlap.

<table>
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<tr>
<th>Biomarker</th>
<th>Stroke/systemic embolism</th>
<th>Mortality</th>
<th>Major bleeding</th>
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<td>Cardiac biomarkers</td>
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<td>Troponin</td>
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<td>NT-proBNP</td>
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<td>Renal dysfunction</td>
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<td>Inflammation, fibrosis</td>
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<td>D-Dimer</td>
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* Association of biomarkers discussed in this review with outcomes unadjusted (+), adjusted for clinical risk factors (+), or adjusted for clinical risk factors and other biomarkers (+++).

* Only biomarkers that have been evaluated in models containing clinical risk factors and other biomarkers and displayed independent association with the specific outcome can achieve a rating of +++, if a biomarker has been evaluated only in models adjusting for clinical risk factors without including other biomarkers they may at best achieve a rating of ++.
between thromboembolic and bleeding risk, which makes them even more interesting and potentially useful in the efforts of improving outcomes in AF as decision support tools for personalization of anticoagulation strategy.

**Biomarker-Guided Therapy**

Information from biomarkers provides incremental information beyond clinical data concerning both clinically silent and apparent disease processes and the degree of organ dysfunction in patients with atrial fibrillation. Thereby, the concentrations of biomarkers may provide further guidance regarding selection of specific treatments.

Increases in the concentrations of cardiac markers, i.e., NT-proBNP and cTn, are indicators of myocardial stress and dysfunction and increased thrombogenicity, and may therefore strengthen the indications for rhythm and rate regulation, strict blood pressure control, ACE-inhibition and effective anticoagulation. Increased concentrations of renal and inflammatory markers, i.e., creatinine clearance, cystatin C and GDF-15, provide incremental information on vascular stress and general frailty, and are related to the risk of severe complications both of the disease processes and pharmacological treatments with consequences for selection and dosing of specific pharmacologic agents. The biomarker based ABC risk scores for stroke and for bleeding seem to offer a practical tool.
for implementation of biomarkers in clinical practice for patients with AF, where it may be useful for optimizing stroke prevention treatment for the individual patient.

Several of the cardiovascular, inflammatory, renal, and coagulation biomarkers are already available in clinical practice for other purposes and therefore have the potential for rapid implementation for improvement of risk stratification in patients with AF. Newer biomarkers, such as GDF-15, have recently been made available as routine assays for automatic analyzers.

Although this review focuses on biomarkers for risk stratification in AF concerning the major outcomes of stroke, major bleeding, and death, there are also several other important outcomes in AF such as risk of dementia, congestive heart failure, or myocardial infarction where biomarkers may provide important incremental information.

**Future Perspective**

Currently there is a rapid development of new promising biomarkers for prognostication and risk stratification in AF as in other areas of medicine. When moving on from the pioneering to the confirmation and implementation phase, it becomes very important to have a systematic approach in the evaluation of the usefulness of these potential new tools. The assays used to quantify biomarkers need to be validated concerning the preanalytical and analytic properties. The evaluation of novel risk markers and risk scores should be performed in several phases; after the initial proof of concept there needs to be prospective validation in independent populations, including documentation of incremental information when added to standard risk markers, assessment of effects on patient management and outcomes, and ultimately, cost-effectiveness. Adherence to proposed quality standards would assure robust and unbiased results and strengthen the development of the biomarker research (140–143).

So far, most studies of the prognostic value of biomarkers in AF have been based on a single measurement at study entry. However, repeated measurements may provide additional information concerning determinants for increase of these biomarkers and subsequent risk in AF. Indeed, it has been shown that sustained or incremental increases of troponin and NT-proBNP concentrations over time are associated with cardiovascular co-morbidities and confer an even higher risk of stroke and mortality (144). In a clinical setting, some of the risk factors in such patients might possibly be modified by pharmacological and/or interventional treatments. Identification of individuals at risk based on transient or persistent increases might therefore also be useful for instituting specific treatment to lower the risk of future cardiovascular events, similar to proposed NT-proBNP concentration guided treatment strategies in heart failure (145–148). The proposed biomarker strategies need to be validated in several AF cohorts, and the additional costs for a biomarker approach with baseline and sequential measurements considered acceptable before broad implementation of these new innovative ways to improve the individual treatment in patients with AF.

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