Advances in our understanding of pathological mechanisms can inform the identification of various biomarkers for risk stratification, monitoring drug efficacy and toxicity, and enabling careful monitoring of polypharmacy. In the broadest sense, biomarkers refer to "biological markers," and these can be blood based (e.g., fibrin D-dimer, von Willebrand factor, etc) urine based (e.g., thromboxane), or even related to cardiac or cerebral imaging. Most biomarkers offer improvements over clinical risk scores in predicting high-risk patients, at least statistically, but usually at the loss of simplicity and practicality for easy application in everyday clinical practice. Given that the various biomarkers can be informed by different aspects of pathophysiology (e.g., inflammation, clotting, and collagen turnover), they can consequently contribute to a better understanding of underlying disease processes. Indeed, many age-related diseases share common modifiable underpinning mechanisms (e.g., inflammation, oxidative stress, and visceral adiposity).

Some attention has been directed to oxidative stress in cardiovascular pathophysiology. Oxidative stress arises from an imbalance between rates of generation of reactive oxygen species (ROS) and rates of their removal. Several intracellular and extracellular antioxidant enzymes are upregulated as an adaptation to increased ROS mediated through transcription factors such as Nrf2 and Foxo3a. These antioxidant enzymes include glutathione peroxidases, peroxiredoxin, thioredoxin reductases, superoxide dismutase, and catalase, which work with smaller thiol donors such as thioredoxin and glutathione to remove ROS produced in excess by old mitochondria and inflammatory cells or to repair reversibly oxidized cysteine residues. In older adults, and in concert with an increase in mitochondrial uncoupling and chronic inflammation, adaptive responses are considered poor and can cause oxidative stress in many tissues, including muscle. When adaptation is poor, a vicious cycle links oxidative stress and inflammation because a more oxidizing intracellular environment promotes signaling via transcription factors such as nuclear factor kappa B (NFκB); NFκB increases secretion of proinflammatory cytokines that further activate ROS production in the inflammatory burst of innate immune cells.

Not all molecules secreted under oxidative stress conditions are damaging; some have anti-inflammatory properties. Another transcription factor activated by ROS is p53, which is better known for controlling DNA repair pathways and cell cycle and death, but it also regulates expression and secretion of growth differentiation factor-15 (GDF-15), a member of the transforming growth factor (TGF)-β family. TGF-β is associated with wound healing in the short term, although during chronic inflammation, excessive fibrosis contributes to loss of function.

During the past several decades, various biomarkers relating to pathophysiological mechanisms have been investigated in the quest to improve our identification of patients at high risk of cardiovascular events who could be targeted for various therapies or invasive interventions.

Atrial fibrillation (AF) is no exception, given how prevalent this arrhythmia is and how it confers a substantial increase in the risk of stroke and mortality. Oral anticoagulation (OAC) significantly reduces the risk of stroke (by 64%) and all-cause mortality (by 26%) when compared with control, and when we had only the vitamin K antagonists (VKAs; e.g., warfarin), the focus was on identification of high-risk patients to be targeted for VKAs, whether by using clinical risk scores or biomarkers.

Unsurprisingly, it has been postulated that oxidative stress plays an important role in atrial remodeling and AF. It is critical to consider the temporal relationship between duration of oxidative stress and outcome; reversible oxidative modifications elicited under oxidative stress are required for induction of protective enzymes via Nrf2 and to allow remodeling. Conversely, markers of chronic oxidative stress are much more likely to add value to predictive algorithms for poor outcome. In such a manner, early GDF-15 expression and secretion may be beneficial for wound healing; however, prolonged GDF-15 expression likely increases plasma levels and may signify chronic oxidative stress.

A Role for GDF-15 in Atrial Fibrillation?

Many cells present in the heart secrete regulatory proteins (cardiokines) in response to environmental changes, including myocytes, fibroblasts, vascular cells, and progenitor cells. The secretome may be influenced by redox state, and according to its composition, it may promote normal function, dysfunction (e.g., via fibrosis), and death. GDF-15 is not normally expressed in the heart, but under stretch or episodes of oxidative stress during ischemia and reperfusion, its expression is
increased transcriptionally in cardiomyocytes after p53 activation. It is an antihypertrophic, elegantly demonstrated by Wang et al, in knockout mice, which develop early cardiac hypertrophic growth after pressure overload.9 Paradoxically, GDF-15 provides prognostic information of poor outcome after a myocardial infarction or acute coronary syndrome, suggesting that information about GDF-15 may improve patient selection for early invasive strategy.10

Despite this, few studies have described GDF-15 expression and its plasma levels in AF. During the past 2 years, small studies have emerged; in hypertrophic cardiomyopathy, higher levels of GDF-15 were associated with disease severity;11 however, Rienstra et al showed that GDF-15, did not improve current risk prediction models for AF.12 In contrast, GDF-15 was independently associated with paroxysmal AF after multivariable analyses.13 These studies were not large and were therefore underpowered to detect outcomes.

Thus, the article by Wallentin et al14 in the current issue of Circulation is a timely addition to the literature on GDF-15 in AF and describes its systematic analysis in 14,798 patients enrolled in the ARISTOTLE trial. GDF-15 provided prognostic information for stroke, mortality and major bleeding independent of clinical characteristics and clinical risk scores. Because GDF-15 was correlated with other cardiac biomarkers after adjustment, the prognostic value for mortality and major bleeding still remained.

**What Are the Research Gaps?**

Although GDF-15 is expressed highly by myocytes under stress, it is not specific for cardiovascular disorders and has been found to be elevated in a variety of malignancies. However, the data from Wallentin et al14 suggest that used in combination with clinical risk assessment, GDF-15 may prove to be yet another useful biomarker to improve risk stratification for bleeding and mortality in patients with AF who are receiving anticoagulation therapy. Thus, GDF-15 joins the club of a plethora of biomarkers in AF, only few of which have managed practical application.

Other biomarkers, such as D-dimer, have been used as surrogates of thrombogenesis in phase-II clinical trials of antithrombotic therapies and as a prognostic marker. Given the caveat that GDF-15 may be nonspecific, this analysis by Wallentin et al14 was performed in an anticoagulated trial cohort, so the issues of generalizability to the general AF population remain, given that many patients in an unselected population with AF suitable for anticoagulation were ineligible for trial participation.15 Thus, additional studies are needed in non-anticoagulated AF populations as well as in real-world cohorts that have a broad range of stroke risk and comorbidities. The translational gap for GDF-15 as a prognostic indicator still needs to be bridged before use of GDF-15 becomes common practice to aid risk stratification or make treatment decisions for AF patients.

**Do We Need Yet Another Biomarker?**

Biomarkers have come and gone, and new ones keep emerging. Treatment optimization remains challenging in cases of polypharmacy and should be prioritized as an area for investigation, particularly for older adults, to reduce adverse outcomes. Theoretically, a multimarker approach that combines indices of adverse outcomes from particular drugs in combination with clinical indices has the potential to improve patient-centric therapy, but at the cost of losing simplicity and practicality, as well as increasing expense.

Indeed, previous focus in older guidelines to improve our identification of patients with high risk of stroke did not improve rates of anticoagulation use, with the proportion of high-risk patients receiving OAC being broadly similar to that in the low-risk category. Thus, the 2012 focused update of the European guidelines6 and the 2014 National Institute for Health and Care Excellence (NICE) guidelines17 recommends that there should be a clinical practice shift so that the initial step (STEP 1, see Figure) is to identify low-risk patients (essentially a CHA2DS2-VASC score = 0 [males] or 1 [females]) who do not need any antithrombotic therapy. The next step (STEP 2) would be to offer effective stroke prevention (which is OAC, whether as one of the non-VKA oral anticoagulants [NOACs], or well-managed VKA with a time in therapeutic range >70%)18 to patients with ≥1 additional stroke risk factors. Thus, the management decision (to use OAC or not) is already made after that initial first step to pick out the low-risk patients; making subsequent refinement of stroke risk in those with CHA2DS2-VASC score ≥2 (with biomarkers, single or multiple, old or new) matters much less19 (Figure).

In summary, biomarkers in AF offer additional insights into pathophysiology and may be potential surrogates for complications or risk. For treatment decisions beyond identification...
of low-risk patients (that can be successfully done with clinical risk scores such as CHA\textsubscript{DS}_{2}-VASc), additional efforts to identify high-risk patients by multiple biomarkers may not necessarily change management decisions, at least for thromboprophylaxis. New biomarkers such as GDF-15 are academically interesting but need to be proved before adoption in influencing clinical decision making.

Disclosures
Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Boehringer Ingelheim and has been on the speakers’ bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, and Sanofi Aventis. Dr Griffiths reports no conflicts.

References

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New Biomarkers and Risk Stratification in Atrial Fibrillation: Simplicity and Practicality

Matter

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