Editorial

To add incremental information: the main problem in cardiovascular risk evaluation

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Introduction

Adrenomedullin (ADM) consists of 52 amino acids with a C-terminal amination and one intra-molecular disulfide bond between residues 16 and 21 (1,2) (*Figure 1*). This peptide hormone has been first isolated from human pheochromocytoma cells in 1993, hence its name (1). ADM is expressed and secreted by many tissues and organ systems, including cardiovascular, renal, pulmonary, cerebrovascular, gastrointestinal and endocrine tissues (2,3).

After acute administration, ADM shows several important physiological autocrine and paracrine actions, also including natriuretic, vasodilatory, and hypotensive effects, and it also inhibits aldosterone production (2,3). These effects are mediated by the cyclic adenosine monophosphate (cAMP), nitric oxide and renal prostaglandin systems (3). After chronic administration, ADM shows antihypertrophic, anti-apoptotic, antifibrotic, antioxidant and angiogenesis effects (3).

Considering these important physiological effects, ADM was proposed as a potential cardiovascular biomarker (3,4). Indeed, increased ADM circulating levels have been reported in patients with hypertension, chronic renal disease and heart failure (HF) (3,4). However, the accurate measurement of circulating levels of ADM is challenging using immunoassays, due to short half-life *in vivo* (about 22 min) and rapid degradation *in vitro* of this peptide. Moreover, the presence in plasma/serum samples of some binding proteins may interfere in the assay (5,6). Finally, other specific analytical aspects (such as preliminary extractions, low circulating levels, absorption on blood tube walls) would make the measurement of ADM by means of immunoassays rather unsuitable for clinical laboratory routine (5,6).

In human tissues, ADM is produced throughout of a post-translational processing from a larger precursor peptide, the preproADM, consisting of 185 amino acids (2,3) (*Figure 1*). During processing of preproADM, other peptides are generated, including another biologically active peptide (defined pro-ADM N-terminal 20 peptide, PAMP), the midregional part of proADM (MR-proADM 45–92) and the COOH terminus of the molecule (proADM 153–185) (1,2,6) (*Figure 1*). From an analytical perspective, it is theoretically conceivable that other peptides characterized by higher molecular mass and plasma/serum concentrations than the ADM hormone should be more accurately measured. An immunoradiometric method specific for the MR-proADM peptide has been first set up in 2005 (6) and, more recently, a homogeneous time-resolved fluoro-immunoassay system has been implemented on a fully automated platform (7). The measurement of MR-proADM with these immunoassay systems was shown to accurately reflect those of the active peptide ADM (6,7).

Clinical relevance of MR-proADM measurement

Using fully automated immunoassays (7), several studies have recently evaluated the prognostic relevance of MR-proADM in different clinical settings such as patients

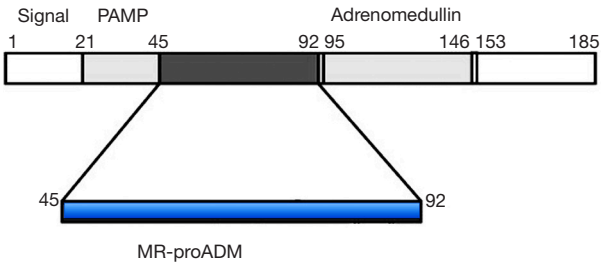

Figure 1 Schematic representation of the pre-proadrenomedullin gene and biosynthesis of the peptides from the adrenomedullin prepropeptide (preproADM): signal peptide, aminoterminal peptide of proadrenomedullin (PAMP), mid-regional pro-adrenomedullin (MR-proADM), adrenomedullin (ADM), and COOH terminus peptide (also named adrenotensin).

with chronic obstructive pulmonary disease (8) and cardiovascular diseases (3), or admitted to emergence department and intensive care units (9). In particular, three recent meta-analyses demonstrated that increased levels of MR-proADM were significantly associated with complications and both short-term and long-term mortality in patients with community-acquired pneumonia (10-12).

As regards cardiovascular diseases, the prognostic accuracy of a large number of biomarkers (over 100) has been evaluated in different populations of patients with HF (13-15). The criteria to evaluate and compare the prognostic efficacy and efficiency of new cardiovascular risk biomarkers have been recently reported and discussed in details (16,17). Innovative risk biomarkers should be evaluated in several phases, including the initial proof of concept, the prospective validation in independent populations, the documentation of incremental diagnostic or prognostic information when added to standard risk markers, the assessment of effects on patient management and outcomes and, ultimately, cost-effectiveness (16,17). Notably, biomarkers not changing disease management are probably unable to significantly affect patient outcome and are thus very seldom cost-effective (as assessed in terms of quality-adjusted life-years gained) (13-17). According to the 2016 guidelines of the European Society of Cardiology (ESC) for management of HF (18), multivariable risk scores may help predicting the risk of death in patients with HF, but they are seemingly less useful for predicting subsequent hospitalizations.

The 2013 guidelines of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) (19), updated in 2017 (20), recommend the use of natriuretic peptides (in particular the measurement of BNP and NT-proBNP) and cardiac troponin I (cTnI) and T (cTnT) as first line biomarkers for prognostic stratification of HF patients. Accordingly, a new biomarker should demonstrate to provide incremental prognostic information compared to brain natriuretic peptide (BNP)/NT-proBNP and cTn assays, especially in terms of increased risk discrimination (using C-statistics analysis) and reclassification (16,17).

Morbach *et al.* (21) recently reported that MR-proADM was correlated with global disease burden in 917 patients (68±12 years, 28% females) hospitalized for acute systolic HF and then followed up for 18 months. The results of this study also suggest that MR-proADM is a strong prognostic indicator, capturing incremental risk for both cardiac and non-cardiac death (21). Unlike NT-proBNP, which only predicted cardiac death, MR-proADM was capable of predicting both cardiac and non-cardiac death (21). In addition, the combination of MR-proADM with a clinical prediction model including NT-proBNP showed improved efficiency for risk stratification throughout the entire 18-month observation period. In particular, among 173 patients who subsequently died, 12 (6.9%) were reclassified in a higher risk category, whereas 7 (4.0%) were reclassified to a lower risk category, whilst 89 (12.6%) patients were reclassified to lower risk category and 68 (9.6%) to a higher risk category amongst 705 survivors (21). Morbach *et al.* (21) reported that MR-proADM outperformed NT-proBNP for predicting all-cause and cardiac mortality and, to a lesser extent, all-cause rehospitalization.

The authors explain the better predictive value of MR-proADM compared to NT-proBNP with the fact that MR-proADM may more efficiently identify patients at high risk of both cardiac and non-cardiac death. Indeed, patients with low NT-proBNP but high MR-proADM experienced non-cardiac death more frequently (21). It is well known that increased MR-proADM levels are associated with a higher risk across various non-cardiac disorders (3,4,8-12). It is hence theoretically conceivable that increased MR-proADM levels in HF patients may not only be associated with worse HF symptoms and cardiac function, but also with non-cardiac comorbidities, which can negatively impact on outcomes by promoting adverse cardiac remodeling and HF progression (18,19). Therefore, data published by Morbach *et al.* (21) may reflect the risk associated to high MR-proADM levels due to systemic manifestations of HF syndrome, which are not (or poorly) detected by variations of NT-proBNP levels.

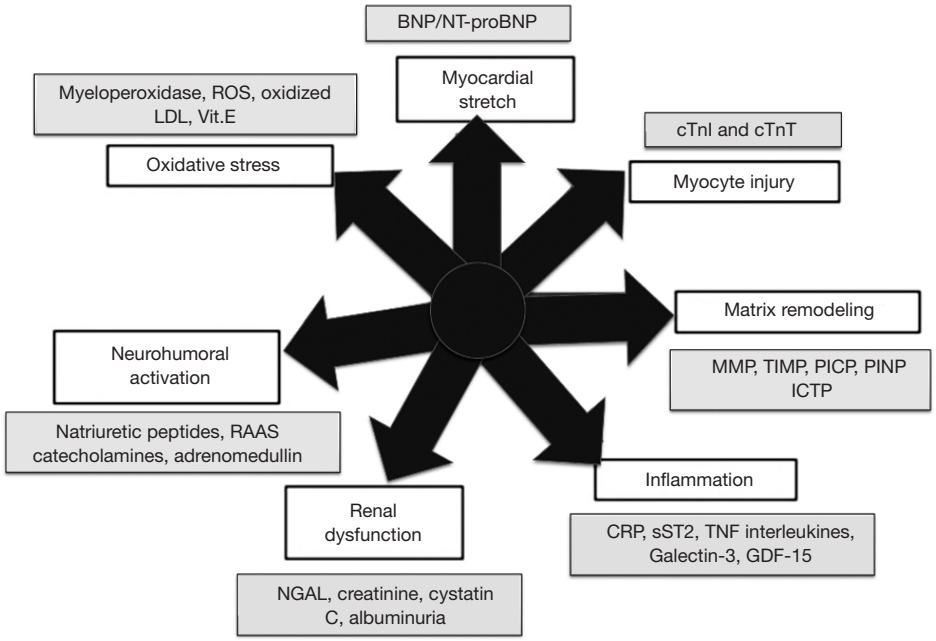

Figure 2 Putative biomarkers classified according to their pathophysiological mechanisms.

Future perspectives

Previous studies which examined the combined use of up to ten biomarkers suggest modest improvements in risk prediction, at best (17). As observed by Wang (17), it is not realistic to expect that any set of biomarkers can substantially improve risk prediction above and beyond traditional risk scores, whilst it is theoretically possible to improve the performance of risk models with a relatively small number of biomarkers, provided that these are weakly or not intercorrelated.

According to Braunwald (22), seven major classes of biomarkers can contribute to set a biomarker profile in HF due to their different pathophysiological mechanisms (*Figure 2*). We would assume that including biomarkers sharing the same pathophysiological mechanism may not be useful, because they are probably highly intercorrelated and do not add additional information to risk prediction. Conversely, it is conceivable that biomarkers with different pathophysiological mechanisms can significantly improve the statistical analysis, because they can add differential, and so incremental information, to risk prediction, by targeting a number of different biological pathways converging to HF (17).

The results of the study published by Morbach *et al.* (21) confirm the assumption that biomarkers sharing different pathophysiological mechanisms may significantly improve risk prediction accuracy. Another recent study (23) reported similar results. Jackson *et al.* (23) measured several biomarkers in 628 patients recently hospitalized with decompensated HF, including MR-proADM, MR-proANP, copeptin, hs-cTnT, suppressor of tumorigenicity 2 (ST2), galectin-3, cystatin C, combined free light chains (cFLC) and high-sensitivity C reactive protein (hsCRP). Using dichotomized cut-points derived from receiver operating characteristics (ROC) curve analysis, MR-proADM, hs-cTnT, cFLC, hsCRP and ST2 remained independent predictors of mortality, and improved model performance (as assessed by C-statistic and net reclassification index). The results of these two studies also confirm that MR-proADM should be considered a valuable predictive biomarker in HF patients. However, large clinical trials are needed to conclusively define that novel biomarkers, such as MR-proADM, may improve management of HF patients and so they may also express a favorable cost/benefit ratio as assessed by accurate methodologies (such as QALY evaluation) (24).

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