Biomarkers in patients with acute dyspnoea: what for?

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This editorial refers to ‘Mid-regional pro-atrial natriuretic peptide and pro-adrenomedullin testing for the diagnostic and prognostic evaluation of patients with acute dyspnoea’†, by R.V. Shah et al., on page 2197

When patients present with acute dyspnoea, clinicians are faced with relevant issues. Particularly, making the right diagnosis and choosing the best therapies in a timely manner are crucial. To assess the latter, it may help to know the patient’s risk, both short and long term, but the direct clinical benefit is less certain. History, physical examination, lab testing, and imaging techniques are cornerstones in order to come to the right conclusions, but they leave important open questions. Biomarkers circulating in the blood are attractive tools to improve care since they represent underlying pathophysiological processes and are relatively easy to measure. However, the question remains of what is their actual role in the clinical setting of acute dyspnoea (Figure 1).

Ten years ago, the first large study was published that investigated the value of biomarker measurement for diagnostic purposes in patients presenting with acute dyspnoea.1 Brain natriuretic peptide (BNP) measurement significantly improved accuracy in diagnosing acute heart failure (HF) beyond clinical judgement, electrocardiogram (ECG), and X-ray. Two years later, BNP measurement in the emergency room was found to speed up correct diagnosis and to reduce time to discharge and costs in such patients.2 One year later, the PRIDE study revealed that the N-terminal part of the precursor hormone (NT-proBNP) is equally helpful to diagnose acute HF in the emergency setting.3 Many studies confirmed these findings, and guidelines consider BNP or NT-proBNP as useful to improve diagnosis and management of HF in the acute setting.4 Moreover, BNP and NT-proBNP are helpful in the prognostic assessment of chronic HF5 and may even help to guide therapy in outpatient HF care.6 As a consequence, BNP and NT-proBNP measurements have been widely adopted in clinical practice.

However, measuring BNP or NT-proBNP has limitations, not only in the chronic, but also in the acute setting. Thus, diagnostic value is particularly high if levels of these peptides are at their extremes, leaving the physician with a grey zone of uncertainty.4 Low levels help to exclude acute HF, particularly in untreated patients or if levels remain unchanged or decrease during episodes of dyspnoea, although there are exceptions that need to be considered.7 If levels are very high, the likelihood of acute HF is also high, but again there are circumstances that may result in high levels not related to HF.8 In contrast to the initial assumption, BNP and NT-proBNP levels may be influenced by various factors unrelated to cardiac wall stress which renders interpretation more complex. Levels are higher in women, elderly patients, and those with concomitant renal failure, and lower in obese patients, but they are also influenced by other (neuro-)hormones, inflammation, ischaemia, and drugs.9 The prognostic value of BNP and NT-proBNP in hospitalized patients has important limitations unless they are measured not only at admission, but also at discharge,9 whereas they are a relatively poor indicator at initial presentation.10

Various other biomarkers have been tested in different settings of cardiovascular disease including patients presenting with acute dyspnoea.11 However, only a minority of them are considered to be sufficiently supported by trial results to be clinically useful in cardiovascular diseases at present (Figure 1).12 Nevertheless, this large variety shows the clinical need for new, better biomarkers or a stratified combination of biomarkers to improve clinical judgement in different settings. In patients presenting with acute dyspnoea, this is of particular importance because of the poor prognosis and difficulties in properly assessing patients at risk.

An analysis of some of these new biomarkers in the PRIDE (Pro-BNP Investigation of Acute Dyspnoea in the Emergency Department) study cohort has now been reported.13 The authors focused in particular on mid-regional peptides of neurohormones that play an important role in the pathophysiology of HF and that are known to be elevated in patients with acute dyspnoea.10 To a large extent, Shah et al.13 are able to confirm previous findings of...
the BACH study, where mid-regional pro-atrial natriuretic peptide (MR-proANP) was found to be of similar diagnostic value to BNP and NT-proBNP, and mid-regional pro-adrenomedullin (MR-proADM) to be of superior prognostic value.10 Confirmatory studies are important since the diagnostic value of biomarkers may differ significantly between different patient groups. For example, the BACH study10 found somewhat less diagnostic accuracy of BNP testing at the same cut-off value as in the Breathing-Not-Properly trial,1 and the diagnostic value of NT-proBNP differed considerably between BACH and the present analysis of PRIDE.10,13 Still, Shah et al.13 showed that the diagnostic value of MR-proANP may add to that of NT-proBNP,11 and both studies found significantly higher prognostic value of MR-proADR compared with BNP and NT-proBNP, respectively.10,13 The study by Shah et al. expanded on previous findings in that the authors showed not only short-term prognostic value, but also long-term value over a follow-up of up to 4 years. Interestingly, short- and long-term prognostic value differed between MR-proADM and natriuretic peptides. This might be useful depending on the setting studied and the information required, but additional studies are required to confirm this and to define its potential clinical impact. In addition, it is important to note that, in contrast to the diagnostic value of natriuretic peptides, which are relatively specific for acute HF, the prognostic value of both MR-proADM and natriuretic peptides is not restricted to HF patients as they are rather unspecific markers of poor outcome.14,15 The PRIDE analysis additionally investigated the prognostic value of galactin-3 as a biomarker in this setting, but found nothing of relevance.13

The question, however, remains as to what extent both BACH and the additional analysis of PRIDE may improve care in patients presenting with acute dyspnoea. At present, the potential implications are unfortunately limited. First, the diagnostic value of mid-regional peptides does not seem to be superior to that of well-established biomarkers such as KIM-1, or NGAL which are less well established;†, well documented, but of unknown clinical benefit; ††, less well established, unknown clinical benefit; 0, potential clinical benefit, but little or no data available; †Study by Shah et al.; renal markers = serum creatinine, urea, uric acid, and to some extent cystatin C, newer renal markers such as KIM-1, or NGAL which are less well established; a large number of other biomarkers have been shown to be related to poor outcome,11 of which (hs-)cTnT, haemoglobin, and creatinine are among the most widely studied so far.
purely to the diagnosis of acute HF. The prognostic information provided by different studies including that by Shah et al., but also the recent BACH trial, poses more questions than it answers. The solution would be to know what therapeutic interventions are best for an individual patient with acute dyspnoea or HF. Biomarkers may play a central role in this regard (Figure 1), but their clinical value remains limited until such studies are done.

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**References**


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**Corrigendum**


On p. 1636, the name of one of the Document Reviewers was published as ‘Enno van der Velde’. Please note that for citation purposes this should have read ‘Enno T. van der Velde’.

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