Biomarker-guided clinical decisions: for patients, health economists or neither?

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In this issue of the *European Respiratory Journal*, ALBRICH *et al.* [1] report on a randomised trial. Their hypothesis is that triage decisions in patients with respiratory infections, guided by adding measurements of the calcitonin-superfamily gene derived peptide, mid-regional proadrenomedullin, are more effective than if guided according to clinical assessment alone. Length of hospital stay is, amongst other end-points, compared between the groups.

The authors should be commended for their effort in conducting a randomised trial with a biomarker-strategy; this implies a much increased workload when compared to epidemiological studies.

Adrenomedullin is a 52 amino acid polypeptide. It is formed by amino acids 95–146 of "pre-proadrenomedullin" and is involved in multiple effects, which include vasodilation [2, 3], osteoblast activity [4], renoprotection [5] and angiogenesis [6]. Mid-regional proadrenomedullin (amino acids 45–92 of "pre-proadrenomedullin") is produced in 1:1 ratio with adrenomedullin and is not a pro-hormone of adrenomedullin. The physiological role, if any, of mid-regional proadrenomedullin is largely unknown.

Mid-regional proadrenomedullin levels in blood have been shown to be related to the prognosis of the patient. In a study of 228 patients with community acquired pneumonia, a high ability to predict a Pneumonia Severity Index score of 4–5 (*versus* 1–3), was reported (area under the curve of the receiver operating characteristic curve: mid-regional proadrenomedullin 0.81, procalcitonin 0.62, C-reactive protein 0.59) [7]. However, knowledge of prognosis indicated by a biomarker is not always translated into better patient care. In a study of 472 intensive care patients, increasing levels of procalcitonin were observed to be a strong independent predictor of mortality [8]. A subsequent randomised trial, involving 1200 patients, was designed to use this prognostic knowledge of procalcitonin levels proactively, together with the knowledge that procalcitonin is closely linked to bacterial infection [9]. The aim of the trial was to improve survival by using procalcitonin guided interventions (*e.g.* change of antibiotic treatment), but the results proved different from the prognostic study; the findings were disappointingly negative, procalcitonin guided treatment did not improve survival in intensive care patients [9].

The results of the current randomised trial are negative and, as the authors state, this finding was also robust to subgroup analysis and, thus, no benefit was observed from the explored strategy of using mid-regional proadrenomedullin guided clinical decisions compared with clinical assessment alone. Basically, two explanations can account for this: either a genuine lack of effect of the strategy, or methodological issues causing a false negative result by skewing or diluting the results. The authors argue for the latter, stating that

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the trial was under-powered. This is, indeed, a possibility since the power of the trial was based on an assumption of a reduction in length of hospital stay of 1.5 days, a rather high expectation. Although it is stated in the trial registration (at www.controlledtrials.com) that the trial has been completed with a target number of participants of 400, the final recruitment was substantially less than this, and so, a higher degree of uncertainty on the final result should be anticipated than if the trial had been completed with the target number of participants. Additionally, the effect limit of detection in the pre-specified power-calculation is of less value.

Another methodological issue deserves special attention: non-adherence to the algorithm was close to 40%; a common feature of several biomarker-guided trials, non-adherence even approached 50% in some trials [10]. This raises two major concerns. First, was a potential benefit of the strategy lost by the non-consistent intervention and, thus, was the effective sample size of the trial considerably lower than planned? Secondly, a more general challenge, which should be met with humbleness amongst investigators running biomarker trials: if non-adherence is as high as in the current trial, how can clinicians use the strategy safely? If the treating clinicians in the current trial overruled the algorithm whenever they felt it was not safe (a quite realistic scenario), how can clinicians implement the strategy and be sure it is safe? In other words, how should clinicians act in these situations, covering nearly half of the clinical decisions, where the biomarker strategy was planned to work, but was, according to the treating clinicians, not safe enough?

The possible lack of effectiveness of the strategy should be mentioned: in the intervention group, treating physicians were reminded to consider discharge on days three and six. In this context, it is important to focus on the current knowledge of the (patho)physiological role of mid-regional proadrenomedullin, which remains rather obscure. In the, to date, tenuous body of evidence on this substance, there has been no systematic approach to uncover the possible physiological role. This may carry two important limitations for biomarker-guided trials: loss of the opportunity to design relevant interventions and low adherence caused by a low degree of understanding of the hypothesis by the treating physicians. Even in high evidence-based treatments, limited physician understanding has been observed to be the main cause for non-adherence to a strategy [11].

Biomarker trials can, however, be pivotal for changes in clinical practice; this has been demonstrated regarding use of procalcitonin for reduction of antibiotic overuse in different settings [12, 13]. In primary care, BURKHARDT *et al.* [14] explored a single procalcitonin measurement strategy and antibiotic stop algorithm. They observed a >40% drop in antibiotic prescription rates while maintaining the same clinical effect [14]. In this trial, adherence to the intervention protocol was 87%, the sample size was 550 patients based on a non-inferiority assumption of a maximum 1 day increase in ''significant health impairment'' and a standard deviation of 4 days. Thus, the close to complete adherence has two beneficial consequences: 1) high external validity, physicians who would like to use the strategy can to a large extent trust it; and 2) the planned limit of detection in the power calculation is not compromised. Several explanations for this trial's success can be considered, among these, it may have been crucial that the pathophysiological role of procalcitonin has been studied more intensely. Most physicians are aware of the close relationship between procalcitonin increases and severe bacterial infection in the patient [15, 16]. By contrast, the pathophysiological role of mid-regional proadrenomedullin in severe hospital treatment demanding disease is not clear.

The conclusion of the current trial is a non-conclusion. It remains an open question whether patients will benefit from the use of mid-regional proadrenomedullin in assisting discharge decisions or whether hospital economists should welcome it. Future studies should initially focus on understanding the physiological role of this substance and other candidate biomarker molecules, to increase the ability to design meaningful and effective interventions guided by the biomarker. When biomarker-trials are designed, more attention should be put into assuring a clinically relevant sample size to allow for robust conclusions and, importantly, a vigorous effort to increase adherence to the biomarker intervention should be attempted wholeheartedly, since a low adherence may, isolated from the main results of the trial, compromise the entire concept of implementing biomarker-guided strategies.

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