Letters

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Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule

Haasenritter *et al*[1] performed an external validation of the Marburg Heart Score (MHS), a clinical prediction rule to rule out coronary heart disease (CHD) in patients presenting with chest pain in primary care. We read this potentially important article with great interest because ruling out CHD in primary care is of special concern. The authors concluded that, according to its generalisability, ease of application, and accuracy, its use in clinical practice is recommended.

However, we have some doubts about their outcome measure and conclusion. The outcome measure, the reference diagnosis, was established using a delayed-type reference standard and an expert panel. Our main concern was that this expert panel was not blinded to the results of the index test. The authors acknowledged this problem, but stated that blinding of this panel would have led to fewer available data for this study. In addition, another study showed a 'substantial and satisfying' agreement (kappa = 0.62) between a blinded and unblinded panel. We think that having used two independent experts without knowledge of the MHS, blinding without loss of data would have been possible without risk of bias. Furthermore, the reported agreement was derived from another study, and is therefore not generalisable to this study. We would be inclined to rate a kappa of 0.62 at best as moderate rather than 'substantial and satisfying'.

The authors report an impressive negative predictive value of 97.9%. Nevertheless, still one in 50 patients with CHD would have been missed using the MHS. Moreover, four of 21 patients with acute coronary syndrome (ACS) were falsely classified as 'CHD-negative'. In our opinion, missing almost one in five patients with ACS does not justify recommending the MHS for use in clinical practice. Besides, the low positive predictive value may lead to more unnecessary investigations and costs.

Lastly, the authors did not demonstrate that there is a strong need for the MHS, nor published data that the MHS performs better than a GP's own judgment based on common practice. Apart from statistical evidence, do GPs feel that the MHS will positively contribute to their diagnostic practice?

Therefore, it is hard for us to see the diagnostic accuracy of the MHS in the right perspective and estimate its clinical relevance. In our opinion, it is premature to recommend the MHS. Nevertheless, we would like to encourage the authors to continue validating the MHS, for example, in a prospective cohort study, and demonstrate its surplus value.

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DOI: 10.3399/bjgp12X654470

Authors' response

We would like to thank Djasmo, Echteld, and Spee for their well-founded and insightful comments on our report on the external validation of the MHS.[1]

Regarding the reference standard, Djasmo *et al* point out that the results of our study may be biased since the expert panel establishing the reference diagnosis was not blinded to the results of the MHS, that they assume that blinding without loss of data would have been possible, and that a kappa of 0.62 does not indicate a substantial agreement. Regarding the latter, several authors suggested that a kappa between 0.6 and 0.8 indicates a substantial agreement.[2,3] However, we do not have the primary intention to discuss the appropriateness of such threshold recommendations. We think that the main message is that the agreement was not perfect and that this indicated a difference between the blinded and the unblinded reference panel. But it is important to state that the lack of total agreement did not necessarily mean that the blinded reference panel made the more accurate decision. A reference panel blinded to the items of the MHS would have had to make a decision without knowledge of the sex, age, history of CHD, if pain had depended on effort, or if it had been reproducible by palpation. We found it reasonable to assume that, especially in cases in which only data of the telephone follow-up were available, lack of these data may result in a less accurate decision and a misclassification bias. In the end we had to weigh the risk of a bias introduced by a lack of blinding against a risk of misclassification bias. Based on our practical experience with this kind of reference standard we estimated the latter as higher, but we acknowledge this limitation.

Regarding the accuracy of the MHS, Djasmo *et al* state implicitly that missing one in 50 patients with CHD may be too high and they state explicitly that missing four out of 21 with acute coronary syndrome (ACS) is too high. Regarding the first point we suppose that the predictive values present the most informative measures from a clinical point of view since they account for the prevalence of the target disease in the respective setting. Increasing the sensitivity would substantially decrease the positive predictive value, especially in a low prevalence setting. However, we must state that the accuracy of the MHS regarding the diagnostic outcome, ACS is lower than in regards to the outcome myocardial ischaemia. We also agree that this fact deserves more attention. Diagnosis of ACS remains a major challenge in primary care since patients often present in an early stage and specific tests (for example, biomarkers) lack sensitivity.[4–6] Different,

parallel approaches may be necessary and may already be used by GPs in clinical practice. In one approach the GP could ask in a first step if chest pain is caused by myocardial ischaemia and, if the answer is yes, decide on a second step if the situation should be classified as 'acute' or 'stable'. In another approach GPs may ask in every patient with chest pain if there are any red flags indicative for ACS or other conditions requiring urgent admission to hospital. While the MHS aims to support the first approach it does not substitute the second.

Lastly, Djasmo *et al* state that our study does not prove that the MHS performs better than GPs' own judgment based on common practice. We agree that such a comparison would be an important step in the evaluation of the MHS. Even more interesting would be an impact study investigating the effect of using the MHS on outcomes relevant to patients, like mortality. However, the primary aim of our study was to test the robustness of the MHS. We are currently working on an analysis comparing different diagnostic strategies based on the MHS, GPs' assessments, and combinations of both. Since this will be a secondary analysis and since the study was not powered to answer these questions, results will be explanatory. A major concern in future studies will be the sample size. Let us assume that the sensitivity of GPs' assessments would be 85% and that an increase in sensitivity of 5% would be judged as clinically relevant. Based on these assumptions, and the prevalence of CHD in primary care, a sample size of about 6000 patients would be necessary to compare these two diagnostic tests in an adequately powered study using a paired design.[7] Necessary sample sizes for impact studies using outcomes relevant to patients may even be higher. We are not sure if these studies will ever be conducted and assume that recommendations must be based on the limited evidence we have so far.

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DOI: 10.3399/bjgp12X654489

Scent of a patient: an underestimated role in clinical practice?

Martina Kelly describes well the ways in which doctors use their sense of smell, including in recognising infection.[1] As well as the infections she describes, I would suggest that from my experience there can be a distinct smell in a patient with some upper and lower respiratory tract infections. When my son was 2-years-old he developed rapid onset of fever, earache, and he smelt distinctly 'bacterially infected'. It was the latter that made me seek medical attention the same evening. He was prescribed amoxicillin and within 12 hours was afebrile, in less pain, and no longer smelt as if he was rotting; he went to nursery and I went to work. I had a clear conscience believing that he did not have a viral infection that he may spread to his peers at nursery.

Perhaps related, I know that taste comes into my decision making to use antibiotics. If a patient describes their sputum or nasal discharge as tasting foul I am more likely to resort to prescribing antibiotics. There will sometimes be an associated odour in such cases.

In this age of guidelines rightly helping us to limit our use of antibiotics, I wonder if smell would be a helpful sign to contribute to decision making. However, I suspect it will never end up in the guidelines due to a lack of randomised controlled trials to provide the evidence required.

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DOI: 10.3399/bjgp12X654498

Primary care of children: the unique role of GPs

The editorial on child health in the July issue brings up several points that probably need expanding[1] as it is hugely important to the whole essence of family medicine and its future.

- How many general practice vocational training schemes do not offer paediatrics as a core element of training and how many doctors in training now do a paediatric exam to show competency?
- The out-of-hours services are staffed by GPs but many ill children never get past the triage system and, anecdotally, parents want more than telephone advice and so vote with their feet and turn up in A&E. The most deprived households are likely to be car-free and as such unable to get to remote out-of-hours bases, but do not fit visiting criteria set by the out-of-hours companies. How can these conundrums be solved?
- Pregnant women in our area are directed away from seeing their GP; again anecdotally many women seem not to be aware of folic acid or vitamin D advice prior to their pregnancy. We need to address this in contraceptive reviews.
- There are now waiting lists for paediatric outpatients that were rare in the past