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From the authors:

We would like to thank S.N.C. Barra and co-workers for their thoughtful response to our article [1]. We agree with the authors that prognostic assessment of patients with acute pulmonary embolism is of pivotal importance and, thus, is an area of active investigation for our group. We would like to comment on just a few of the points raised by the authors. First, the authors comment that the Low-Risk Pulmonary Embolism Decision score is the only model derived completely from haemodynamically stable patients, which they define as those without any evidence of myocardial necrosis or echocardiographic right ventricular dysfunction (RVD). We agree that risk stratification tools should be derived from haemodynamically stable pulmonary embolism patients. However, we disagree that markers of myocardial injury and RVD should be performed prior to clinical scores. In fact, there is increasing evidence that the Pulmonary Embolism Severity Index (PESI) and Simplified PESI (sPESI) identify low-risk patients who might benefit from outpatient therapy of their disease without the need for echocardiography or troponin tests [2, 3].

S.N.C. Barra and co-workers seem to take away from our study that the PESI score 48 h after admission (PESI48) and sPESI48 are more accurate than the PESI and sPESI. This is not really true. As the authors note later in their correspondence, we did not compare PESI with PESI48 but retested PESI in those who were initially PESI class III. We were not interested in finding a score better than PESI but rather a way to increase our ability to identify patients who will have a good outcome regardless of the treatment setting. Thus, our intention in the current study was to further risk-stratify patients who are at intermediate risk on presentation. In essence, calculation of PESI48 can identify a portion of intermediate risk patients who have responded favourably to their initial treatment and can be safely discharged early from the hospital. From a clinical application standpoint, we would suggest that PESI and/or sPESI can be used to identify a very low-risk population that can be treated entirely as outpatients. Calculation of the PESI48/sPESI48 can then be used to identify patients appropriate for early discharge after an initial hospitalisation.

The authors asked us to consider further assessment of PESI48 by calculating discrimination, calibration and accuracy scores. We have gladly done so. For PESI48, the area under the curve is 0.75 (95% CI 0.66–0.84), Hosmer–Lemeshow goodness-of-fit is 5.38 ($p=0.72$) and Brier score is 0.073. Finally, we thank the authors for identifying a typographical error in our manuscript. They note that we reported a negative integrative discrimination index (IDI). In fact, the IDI was positive. In other words, the new score improves classification by 2%. This error has been corrected in this issue of the *European Respiratory Journal*, both in print and online.

Thank you again for the correspondence and the opportunity to further clarify our findings.

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Re-think first-line tuberculosis treatment

To the Editor:

In the June issue of the *European Respiratory Journal* (*ERJ*), A. Skrahina and co-workers reported alarming rates of multidrug-resistant tuberculosis (MDR-TB) in Minsk, Belarus. In their survey, they diagnosed MDR-TB in 35.3% of new patients and 76.5% of previously treated patients [1]. The reflex response to such figures is to strengthen classical infection control activities, to intensify case detection, and to strengthen adherence to and rational use of the first-line antituberculosis regimen. Unfortunately, with the MDR-TB rates now emerging from Eastern Europe and Central Asia, it is questionable how appropriate the current first-line regimen and its rigid use in newly diagnosed cases are in that setting. Is it not time to consider an entirely new first-line treatment for countries or regions where, for example, >25% of tuberculosis in previously untreated patients is MDR-TB? In a different setting, that of community-acquired pneumonia, the use of macrolides as first-line therapy despite 25% macrolide resistance among its causative agents results in therapy-attributable mortality in around one in 100 persons treated [2]. Generally speaking, should we not consider revising the current first-line regimen once a yet-to-be-determined level of MDR-TB is measured, in order to prevent therapy-attributable mortality?

Prolonged continuation of current first-line regimens in high-prevalence MDR-TB settings favours the further emergence of such strains. Strains with resistance to the initial treatment choice are given a selective advantage and opportunity to spread in the community or nosocomially, which they would not otherwise have. Initial treatment with an ineffective regimen also provides conditions which may favour their adaptation towards preservation of transmissibility (*e.g.* by acquiring so-called compensatory mutations) [3].

Recent studies have found that regimens including bedaquiline (TMC207), PA-824, pyrazinamide, moxifloxacin and clofazimine have similar or stronger bactericidal activity than the current regimen of isoniazid, rifampicin and pyrazinamide with ethambutol or streptomycin. These novel compounds lack any cross-resistance with existing drugs [4, 5]. Different strategies for their implementation can be used. First, these regimens could serve as a universal regimen for settings where MDR-TB is so prevalent that it is unsafe and perhaps unethical to continue by just enforcing the old first-line regimen.

As a second strategy would entail the use of a new universal regimen followed by de-escalation to the current first-line regimen for patients infected with strains treatable with current first-line therapy. Unrestricted access to rapid molecular resistance detection or phenotypic susceptibility testing is critical to this strategy. Such screening also provides the opportunity for separate quarantine measures for patients with sensitive tuberculosis, who rapidly become uninfectious after initiation of therapy. Where possible, these patients would not be admitted to hospitals where they are at risk of super-infection with MDR-TB. This may help to slow the truly alarming increases in resistance rates seen in areas where prolonged in-patient treatment of tuberculosis is the norm.

Of course, the switch to a universal regimen can only be successful if it is part of a stable programme that also involves rigid infection control activities, active case detection, close monitoring of individual treatment adherence and rational use of the novel drugs, as set out in the recent review series in the *ERJ*, introduced and summarised by ZUMLA *et al*. [6].

The use of an initial regimen that is ineffective for a sizeable proportion of the patients and encourages the spread and further adaptation of resistant strains is unacceptable. The tuberculosis community must now push forward and start clinical trials of universal regimens that are equally active against pan-susceptible and MDR-TB.

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