Dear Sir,

We read with interest the recent article of Gibson et al. on the diagnostic utility of a simplified decision rule based on the Wells score for ruling out pulmonary embolism (PE) (1), concluding that ~30% of patients with suspected PE can be safely withheld from further diagnostics by combining an unlikely clinical probability and a normal D-dimer test. The newly developed rule, instead of attributing one, one and a half, or three points for each of the features included, assigns unit weights for the presence of all individual variables in the model. This is an important progress, in that the simplified rule eases the clinical reasoning, with no apparent decrease of diagnostic efficiency over the original score.

Several lines of evidence confirm that the introduction of D-dimer testing together with clinical prediction rules, has greatly improved the diagnostic workup of patients with suspected venous thromboembolism (VTE) (2–4). A strategy based on clinical pre-test probability of deep vein thrombosis (DVT) using the Wells score together with D-dimer testing to determine which “low probability” patients need to proceed to ultrasound, has also been recommended by the Institute for Clinical Systems Improvement (ICSI) (5) and, more recently, has been included in the Clinical Practice Guideline of the American Academy of Family Physicians and the American College of Physicians (6).

In the report by Gibson et al., emphasis was placed on the view that “an alternative diagnosis is less likely than PE”, in that the predictivity of this variable was extremely high, second only to “Clinical signs & symptoms of DVT”, both in the original Wells score and in the simplified approach. The variable “Other diagnosis at least as plausible” has also been included in the four-item score developed for calculating the clinical probability of upper extremity deep venous thrombosis by Constans et al. (7). This is consistent with universal agreement that the most cost-effective diagnostic approach to VTE and PE should be developed...
around a “rule-out” strategy, including tests with high negative predictive value, which should allow both differential diagnosis between PE and other diseases with symptoms of shortness of breath or thoracic pain (Table 1) and rapid discharge of patients with non-urgent conditions (8, 9). The Wells score approach has been widely accepted whilst previous attempts, sometimes with similar variables, have failed. This could partly be explained because the variables in these alternative rules were complicated by the need for additional expensive and invasive tests, such as blood gas analysis, electrocardiography or chest radiographs. However, we believe that serious consideration should be given to the introduction of additional selected laboratory tests (i.e. cardiac biomarkers), as these might further assist the clinical decision making process, particularly risk assessment and identification of high-risk patients (9). Serum troponins, either T or I, are highly specific markers of myocardial injury, widely used for diagnosing acute coronary syndrome (ACS). The measurement of these might be justified for several reasons in patients with suspected VTE and PE. Depending on the diagnostic threshold, several PE patients, up to 50%, have a positive troponin test at the time of diagnosis in the absence of angiographic coronary artery disease; moreover, a diagnostic value is present in nearly all patients with severe cardiac involvement such as right ventricular dysfunction, haemodynamic instability or cardiogenic shock (10). In fact, submassive and massive PE can lead to right ventricular dysfunction, secondary to increased right ventricular wall stress and right ventricular micro-injury. A dilated right ventricle under increased wall stress further augments right ventricular oxygen demand, resulting in right ventricular hypoperfusion and ischemia (11). Accordingly, troponin elevation occurs after onset of myocardial ischemia and microinfarction, due to alterations in oxygen supply and demands of the failing right ventricle. When detectable, troponin correlates with the extent of right ventricular dysfunction (12, 13), predicts the risk of short-term death and adverse outcome events and may justify a more aggressive treatment approach (14). Although similar prognostic information may be obtained from echocardiography, the ease and general availability of troponin measurement may be a significant advantage in this setting. The troponin increase in patients with PE is usually transient and remains elevated for >7 days in most cases of PE, whereas even in patients with small non-ST-segment-elevation acute myocardial infarction (NSTEMI), cardiac troponins remain elevated for >7 days (10). Therefore, if a negative troponin testing might be helpful to exclude cardiac damage from either myocardial infarction or PE, a positive value deserves further scrutiny in both circumstances. It has also been suggested that while troponin measurements add most of the prognostic information for identifying high-risk patients, a normal echocardiogram combined with a negative troponin level might be most useful to identify patients at lowest risk for early death from acute PE (16), and patients with elevated troponin and right ventricular enlargement are at significantly greater risk for death after PE than patients with only one or with neither adverse prognostic marker (17).

The natriuretic peptides are useful diagnostic and prognostic markers for patients with congestive heart failure. Although there are no prospectively validated cut-off values, elevated levels of natriuretic peptides, especially the pro-Brain natriuretic peptide (proBNP), are also observed in the setting of acute PE (from 58–84% of patients), reflecting right heart strain (18). Their measurement is therefore helpful and highly accurate in identifying low-risk PE patients, displaying a negative predictive value for in-hospital death close to 99%. In patients with levels of natriuretic peptides below the assay-specific cut-off, echocardiography will not usually add incremental prognostic information (13). Because of the short half-life of the natriuretic peptides, particularly proBNP, these biomarkers may also be helpful in serial monitoring and gauging the success of different PE treatment regimens (19). Combined use of natriuretic peptides and cardiac troponins further enhances the accuracy in risk stratification of normotensive patients with acute PE (20). Serum myoglobin is also elevated in nearly half of patients with acute PE on admission; its value significantly predicts fatal outcome and in-hospital deaths (21). Recently, Turedi et al. showed that ischemia-modified albumin (IMA), a sensitive marker of localized and generalized hypoxia, may be useful to exclude PE, since up to 98% of PE patients have values exceeding the specific diagnostic cut-off (22). Preliminary evidence also suggests that cytoplasmic heart-type fatty acid binding protein (H-FABP), a sensitive and specific biomarker of myocardial damage, might be useful to optimize risk stratification algorithms and treatment strategies in acute PE, since its measurement might be superior to that of troponins, NT-proBNP and myoglobin in the prediction of 30-day acute PE-related mortality (23, 24).

Expert opinion on the best algorithm combining clinical prediction rules and laboratory testing for identification of PE continues to evolve, as does our understanding of disease pathophysiology and the utility and availability of biomarkers. However, some clinical evidence heralds a paradigm shift in the spectrum of clinical decision making for PE, attributing a new and/or increasing role for cardiac biomarkers, so that a “dyspnea
References


