



## EDITORIAL COMMENT

# D-dimers in the identification of vascular risk: A good tool or just another one?



## D-dímeros na identificação do risco vascular: uma boa ferramenta ou apenas mais uma?

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The need for an increasingly thorough risk assessment after percutaneous coronary treatment for acute coronary syndrome (ACS) has led investigators to search for biological and clinical markers that act as specific predictors of severity, better identifying patients at greater risk and who should, therefore, be candidates for more aggressive pharmacological therapy.

Despite the high efficacy of preventive treatments defined in clinical guidelines at managing vascular risk, many patients present a clinical condition with a very high probability of major ischemic events. This “residual risk” is particularly relevant in patients with severe symptomatic atherothrombosis.<sup>1</sup> Previously this status was not included in decisions on establishing long-term treatment guidelines, whereas now it is recognized and identified as a differentiating factor when establishing prognosis.

There is, therefore, a clear need for markers that can identify the probability of recurrent manifestations of cardiovascular disease in its most varied forms of clinical presentation, identifying patients at greater atherothrombotic risk, redefining prognosis and orienting with differentiated therapies.

Alongside classic myocardial lesion markers, D-dimers have recently been presented as candidates for profiling ACS,<sup>2</sup> and for stratifying short and long-term risk.<sup>3–5</sup>

D-dimers are produced by the breakdown of fibrin and are markers of hypercoagulability and thrombotic events.<sup>6</sup>

Many studies have confirmed the association between high D-dimer value and increased long-term mortality in patients with stable coronary disease,<sup>7</sup> acute coronary syndromes<sup>8</sup> and ST-elevated myocardial infarction (STEMI).<sup>9</sup>

The observation that elevated D-dimers are of clinical interest in the identification of conditions as different as complementary, such as the differential diagnosis in ACS between infarction and unstable angina,<sup>2</sup> to risk stratification associated with STEMI<sup>10</sup> patients or other ACSs,<sup>4</sup> has drawn attention to the potentially major role these markers may play in the definition of therapeutic strategies. Elevated baseline levels are associated with cardiovascular mortality and increased non-cardiovascular mortality in clinical follow-up windows, from the hospital phase up until at least 16 years after ACS.<sup>6</sup> A high rate of infarction and stroke has also been recorded within six months of an index percutaneous coronary intervention (PCI) event.<sup>10</sup>

The use of this marker together with the remaining vascular risk factors to define populations at risk requiring close monitoring and suitable therapeutic measures seems clear, as D-dimers have been identified as a long-term marker of mortality and major complications in hospital and within six months following a PCI. The goal of these measures is to control ischemic and residual risk. Based on the results and study conditions of the ATLAS ACS 2 – TIMI 51 Trial (ClinicalTrials.gov number, NCT00809965), the use of the so-called “vascular dose” of rivaroxaban 2.5 mg bid (anti-

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factor Xa action) in this elevated risk group would make sense.<sup>11</sup> This study assessed a population of more than 15 000 patients with stable coronary artery disease (CAD) seven days after PCI in ACS. The indicated dose of rivaroxaban reduced the composite endpoint comprised of cardiovascular death, infarction or stroke, mainly at the expense of a reduction in mortality in patients with a high vascular risk score. It is therefore more pertinent to propose coagulation in the pathophysiological mechanism, which associated with platelet aggregation, defines events that lead to cardiovascular death.

Studies have performed to obtain optimized information on the association of other risk markers with D-dimers to identify patients at greater risk of clinical recurrence of CAD manifestations. They then associated them with clinical risk scores (Grace)<sup>3</sup> and morphological risk, based on the severity of the coronary disease (Syntax score).<sup>4</sup>

Elevated baseline D-dimers upon arrival at hospital in patients with ACSs, who had undergone PCI, was identified as an independent predictor of hospital mortality. Use in combination with the Grace Score has to led improved prognosis performance, compared to the isolated use of this score.<sup>3</sup>

With respect to the complexity of coronary anatomy, increased D-dimer values were associated with the severity of coronary disease, represented by high Syntax Score values in patients with STEMI, successfully revascularized in a primary angioplasty. Elevated D-dimers were also linked to more serious intracoronary thrombotic content (thrombotic burden) and a more frequent occurrence of acute occlusion with complete interruption of the coronary flow during primary angioplasty (bailout),<sup>4</sup> which is associated with worse prognosis.

It appears to be clear that the baseline D-dimer levels, in the context of several types of CAD presentation, are associated independently with clinical and morphological markers of severity, which have themselves already been identified as negative prognostic factors. The association between elevated D-dimers and other prognosis markers reinforces the identification of patients who are at a higher risk of mortality and have a worse prognosis.

However, the identification of D-dimers as markers of long term risk is not limited to vascular risk, as demonstrated by the LIPID Study.<sup>6</sup> It involved almost 8000 patients with follow-up over 16 years and demonstrated the association between elevated levels of D-dimers and a significant and independent rise in mortality with an identified cause (cardiovascular and neoplastic), in addition to non-cardiovascular and non-neoplastic mortality.

It is therefore evident that a variable of increased cardiovascular risk is also associated with other causes of mortality, supporting the notion that this marker's lack of specificity identifies a population that presents comparatively higher mortality, justifying more highly differentiated clinical follow-up guidelines that favor a tighter control of overall risk stratification.

Only the future will tell us to what extent current evidence can condition new approaches effectively in this complex group of patients with elevated vascular risk before and after the first clinical manifestation of the disease.

## Conflicts of interest

The author has no conflicts of interest to declare.

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