Editorial

What are diagnostic implications and limitations of assessing D-dimer and fibrin degradation products levels in the management of patients with acute aortic dissection?

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Acute aortic dissection (AAD) is an uncommon but potentially catastrophic condition, with an early mortality rate as high as 1% per hour. Acute myocardial infarction (AMI) is also a serious cardiovascular disease with high mortality, albeit much lower than in AAD. One of the reasons for the lower mortality in AMI than AAD is that the former can be diagnosed with high specificity using biomarkers such as Troponin T or Troponin I. In contrast, AAD can only be diagnosed by MRI or CT imaging, as there are no unequivocal diagnostic biomarkers available. Certain biomarkers have been proposed for this purpose, such as myosin-heavy chain (1), creatinine phosphokinase-BB (2), calponin (3), TGF-beta (4) or serum elastin (5), but they have too low a specificity to be clinically useful in practice.

D-dimer (DD) levels were also proposed as a biomarker of AAD by Weber for the first time in 2003 (6), and thereafter many reports (7-10), systematic reviews and meta-analyses (11-13) have been published. With a specificity of 40–70% the usefulness of DD for diagnosing AAD is minimal, but its high sensitivity of 95–97% is useful for excluding this condition (7-10). Nonetheless, in the clinical setting, even if DD is within the normal range in a patient with suspected AAD, CT should still be performed in order not to overlook AAD because sensitivity is not 100% (11-13). The challenge of using DD for diagnosis of AAD by elevating the cut-off value is to achieve a 100% sensitivity, but this has not proven possible. If we could decrease the cut-off value, the sensitivity might rise to close to 100%, but the negative predictive value would also decrease. In addition, the cut-off value determined is affected by the type of kit used to measure DD. Thus, there are severe limitations on the use of DD as a diagnostic marker for AAD.

In addition to DD itself, fibrin degradation products (FDPs) have also been proposed as biomarkers of AAD. FDPs are protein fragments cleaved by the action of plasmin on fibrin and fibrinogen, whereby the DD is the final degradation product of cross-linked fibrin. Currently, differences in the clinical significance of FDP relative to DD for diagnosis of AAD are not clear. Hagiwara reported that the sensitivity of FDP for AAD diagnosis was actually 100% using a cut-off value of 5.6 μg/mL (14). However, Nagaoka reported that the best achievable sensitivity for diagnosis of AAD was 98% with a cut-off value of 2.05 μg/mL (15). These two reports showed that FDP might be useful for excluding AAD when the FDP value is lower than the determined cut-off. However, there are still very few studies showing an association between FDP values and AAD, so further work is needed to determine its true usefulness for AAD diagnosis.

Recently, Dong *et al.* published a paper entitled "Diagnostic implication of fibrin degradation products and D-dimer in aortic dissection" (16) in which they reported on

the usefulness and limitations of DD and FDP for diagnosis of AAD. They concluded that "Diagnostic value of FDP and DD were not high to distinguish aortic dissection patients from the non-dissection patients. However FDP and DD could be available diagnostic marker to differentiate aortic dissection and healthy controls." In this paper, the sensitivity of DD for diagnosis of AAD (68.8%) is reported to be much lower than in several previous publications by others (>90%), although a similarly low sensitivity (<70%) has occasionally been reported in the literature (17,18). This is intriguing because the sensitivity of DD for diagnosis of AAD could become low under "certain conditions" that might explain these disparities. The low sensitivity in the Dong *et al.* study might be due to the finding that the DD and FDP values in many patients with AAD did not increase sufficiently over the cut-off value, or that the determined cut-off value was too high relative to the DD levels in AAD patients, or both. The reasons for the low sensitivity cannot be ascertained because the following important data were not shown: First, this paper did not indicate the DD cut-off value applied for the diagnosis of AAD. The upper limit of the normal value of the DD assay kit employed for this study was also not stated. Second, this paper did not report on the false lumen condition, i.e., whether patent or thrombosed, or on the expansion of aortic dissection, or the timing of the DD measurements. The only shown data associated with low DD values was the age of the AAD patients, which, at 55.3±13.6 years, is much younger than the usual average age of such patients. Previous data have shown that a thrombosed false lumen (8), limited expansion of aortic dissection (8), late DD measurement after AAD onset (19), and young age (8) are all associated with lower DD values. In addition, again in distinction to previous reports, the sensitivity (53.1%) of FDP for AAD diagnosis was also very low. Thus, when we see such low values of DD in patients with AAD, we always need to consider whether some DD-lowering factors are in play.

What is the most effective timing for using DD to manage AAD? Based on the many available data supporting the use of DD for AAD management, here I present some recommendations. First, for patients who are unlikely to be suffering from AAD, even without CT there is a very low risk of overlooking AAD if DD is within the normal range. This avoids unnecessary radiation exposure and reduces medical costs, although the risk of overlooking AAD can never be exactly zero. Second, for patients with AAD during the acute phase of hospitalization, sudden DD elevation may indicate some change of the condition of the false lumen and CT should therefore be performed (20). Third, in patients with cerebral infarction, whether DD values are elevated because of the disease should always be determined because this condition might be caused by AAD. If the value of DD is higher than some predetermined value (21,22), CT should be performed to screen for AAD complicated by cerebral infarction.

It is concluded that DD is a convenient biomarker that may be useful for the management of AAD, but using it appropriately is challenging. The availability of diagnostic biomarkers with high specificity and sensitivity for AAD remains an unmet medical need.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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