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Commentary: Platelet microvesicles—the dawn of precision medicine in coronary revascularization?

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CENTRAL MESSAGE

Precision medicine in cardiovascular surgery may help guide revascularization strategy in patients with coronary artery disease.

The study of medicine has typically been predicated on observation and generalization. However, with increases in technology, the medical community has been able to look deeper into specific underlying differences between patients that result in diverging outcomes. Camera and colleagues¹ continue this approach by examining the role of circulating microvesicles in the development of long-term graft thrombosis following coronary artery bypass grafting (CABG). Through methodic experiments, the authors show that patients with 18-month graft thrombosis had a larger proportion of microvesicles derived from platelets and tissue factors before surgery. Moreover, they demonstrated increased levels of proteins associated with thrombotic pathways before surgery as well as increased thrombin formation from the microvesicles in patients with graft thrombosis. Lastly, the authors developed a scoring system with the types of microvesicles as well as the presence of D-dimers, which resulted in an impressive area under the curve of the receiver operating characteristic of 0.9. While this work took considerable effort and is a significant step toward precision medicine in the cardiac surgery field, Moore and Harken² address key points in the *Journal* that should

be raised to properly interpret the results as well as direct further research in this area.

Perhaps the most lacking piece of information in this study is the proportion of patients who underwent an off-pump CABG procedure. It is well established that the presence of blood-contacting surfaces, as with cardiopulmonary bypass (CPB), elicits a significant inflammatory response.^{3,4} It is critical to account for this factor for 2 main reasons. The first is that the presence of CPB as well as its duration could have a substantial interaction with the prothrombotic environment seen in this patient cohort, altering the overall significance of these markers. Second, it would help to elucidate if the presence of these markers is sufficient irrespective of CPB, meaning that the presence in conjunction with the other insults of surgery would potentiate graft thrombosis. This would be of considerable interest in clinical decision-making, as the presence of these prothrombotic microvesicles could change operative planning with regards to CPB, if it was shown to worsen the long-term prognosis of this subset of patients. Moreover, the thrombin assay, while measuring thrombin generation potential, is isolated from the complex thrombin systems, which CPB can affect in a myriad of ways.⁵⁻⁷ However, despite not accounting for these factors, the evidence presented by the authors is compelling and warrants continued investigation.

Whether the effect of these microvesicles is as significant as described, the larger question to consider is the end clinical goal. While the authors report a significant difference in major adverse cardiac and cerebrovascular events (MACCE) in the graft thrombosis group at 52 months, there is no single component that is driving this significance.

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However, the largest (by percent) component of MACCE is percutaneous coronary intervention, occurring in 30% in the graft thrombosis cohort. Despite this, there was no significant difference in cardiovascular death over the study period, suggesting either the increased MACCE or graft thrombosis was not deleterious enough in these populations or, and more likely, this needs to be studied in a larger and more robust patient population. The greater reintervention rate raises an intriguing idea if the microvesicle and plasma environment not only potentiates thrombosis following surgery but is a marker for the severity of vasculopathy at baseline in these patients, as the microvesicles and plasma proteins found in this cohort are implicated in thrombotic pathways. This could change the clinical lens to apply more aggressive medical management in these patients as opposed to solely aggressive antiplatelet therapy following surgery. It is hard to draw any substantial conclusions, as the number of patients in each arm is small, reducing significance and questioning the external validity of the findings, as CABG remains the most performed procedure.⁸ The last question to pose is, if the findings are corroborated, how easily implementable is this workflow into current clinical practice, especially from a cost–benefit viewpoint? Undoubtedly, there is a substantial cost and skill set required to not only have this in practice but also for others to try

to replicate these methods with different and larger patient cohorts. Nevertheless, the findings here are compelling and should be further examined on a larger patient cohort; this could represent the first step toward personalized medicine for patients undergoing CABG.

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