Bioresorbable Scaffolds versus Metallic Stents in Routine PCI

TO THE EDITOR: Wykrzykowska et al. (June 15 issue)[1] report the results of AIDA (Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial), in which investigators compared an everolimus-eluting bioresorbable vascular scaffold (Absorb) with an everolimus-eluting metallic stent (Xience) in patients who were undergoing percutaneous coronary intervention (PCI). The results of this trial are consistent with previous observations that have shown an increased risk of device thrombosis among patients receiving the bioresorbable scaffold.[2]

The causes of the higher rate of thrombosis with bioresorbable scaffolds than with metallic stents are only partly understood. Despite the use of better implantation techniques, different trials have consistently shown that acute lumen gain is lower among patients with bioresorbable scaffolds than among those with metallic stents.[2,3] In the AIDA trial, the investigators found a higher incidence of residual diameter stenosis of at least 30% among patients who had device thrombosis than among those without device thrombosis. It seems that the lower radial strength and the higher acute recoil of the bioresorbable scaffold (which is responsible for a smaller residual lumen diameter) could act as a substrate for device thrombosis.[4] New scaffolds that incorporate different materials might allow for better radial strength.

Gian-Battista Danzi, M.D.
Ospedale Santa Corona
Pietra Ligure, Italy
gbdanzi@tin.it

Raffaele Piccolo, M.D.
Bern University Hospital
Bern, Switzerland

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TO THE EDITOR: Wykrzykowska and colleagues report that patients undergoing coronary implantation of bioresorbable scaffolds had more than three times the rate of definite or probable device thrombosis at 2 years than did those who received metallic stents. No association between implantation technique and scaffold thrombosis was reported.

Several reasons for this finding could be hypothesized. First, it is uncertain whether the adopted implantation protocol represents the most effective technique.[1] Second, unfavorable angiographic results (e.g., residual stenosis and small minimum lumen diameter) or angiographically unrecognizable technical issues (e.g., dissection, malapposition, underexpansion, and fracture) could have triggered scaffold thrombosis. Third, the discontinuation of dual antiplatelet therapy could play a key role in late or very late scaffold thrombosis, regardless of implantation technique. Indeed, in an analysis of the cases of definite or probable scaffold thrombosis (as described in Table S12 in the Supplementary Appendix of the article, available at NEJM.org), it appears that at least 11 of 14 patients (79%) who had thrombosis events that occurred after 6 months were not receiving dual antiplatelet therapy. Finally, even among the patients who were receiving dual antiplatelet therapy, the implantation technique could have influenced the rate of early but not late or very late scaffold thrombosis. Thus, we need additional analyses to assess the causes of scaffold thrombosis in order to define the best implantation techniques, lesion selection, and antithrombotic regimens.

Corrado Tamburino, M.D., Ph.D.
Piera Capranzano, M.D.
University of Catania
Catania, Italy
pcapranzano@gmail.com

No potential conflict of interest relevant to this letter was reported.

1. Serruys PW, Onuma Y. Dmax for sizing, PSP-1, PSP-2, PSP-3 or OCT guidance: interventionalist's jargon or indispensable implantation techniques for short- and long-term outcomes of Absorb BRS? EuroIntervention 2017;12:2047-56.
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TO THE EDITOR: Although some observers have interpreted the results of the AIDA trial as the

death knell for bioresorbable scaffolds because of their association with scaffold thrombosis, several attributes of the trial should be considered. First, nearly half the patients who were enrolled in the trial presented with acute myocardial infarction, which is a deviation from the instructions for use of the device and is considered to be unlabeled use. Second, patients were enrolled between 2013 and 2015, when the most effective deployment techniques had not been established. Third, the number of devices per patient was higher in the group that received bioresorbable scaffolds than in the group that received metallic stents, which usually translates into an increased rate of major cardiac events, including a higher rate of thrombosis. Given these factors, caution should be exercised to adhere to instructions for the use for bioresorbable scaffolds, and the boundaries of the safety and efficacy of the devices should be prospectively studied.

Ron Waksman, M.D.

MedStar Washington Hospital Center
Washington, DC

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THE AUTHORS REPLY: In reply to Danzi and Piccolo and to Tamburino and Capranzano: it is true that we currently have only a partial understanding of the causes of scaffold thrombosis — particularly, the late and very late events. Currently, the most frequently observed findings in these later events include scaffold-strut malapposition and late discontinuity of scaffold struts.[1] Strut malapposition can result from problems with implantation techniques or be acquired during the resorption process. The presence of evaginations is relatively common after scaffold implantation and is most likely due to positive remodeling of the vessel wall.[2] Furthermore, late structural discontinuity and device dismantling can lead to isolated intraluminal, stacked, or malapposed scaffold struts.

An important phase in the resorption process of all scaffolds composed of polymer is the gradual replacement of the polymeric strut by a malleable structure made of proteoglycan. It is hypothesized that contact of the highly thrombogenic proteoglycans with blood is related to the late and very late events of scaffold thrombosis that have been observed in multiple trials of the bioresorbable scaffold.[3] Therefore, we believe that patients who are treated with bioresorbable scaffolds should be protected with dual antiplatelet therapy for a period of at least 3 years, until the polymer struts are completely replaced by connective tissue. The 4-year follow-up analyses of the ABSORB II trial should shed light on whether the risk of thrombosis significantly decreases after 3 years.

In addition to the proteoglycan hypothesis, the concept of continuing or prolonging dual antiplatelet therapy in patients who are enrolled in the AIDA trial is partly driven by the observation pointed out by Tamburino and Capranzano. Since all the polymer bioresorbable scaffolds are replaced by proteoglycan, we support the suggestion made by Danzi and Piccolo to incorporate different materials into new scaffold designs. Scaffolds that are made of bioresorbable metals, such as magnesium, could potentially provide improved radial strength with less strut thickness and be less thrombogenic, since magnesium struts are replaced by calcium and metabolized into magnesium hydroxide and hydrogen gas.[4]

In reply to Waksman: we did not observe a difference in the rate of scaffold thrombosis between patients who presented with myocardial infarction and those who did not (as shown in Fig. S3 in the Supplementary Appendix of our article). Furthermore, we did not find a correlation between the implantation techniques used in the trial and scaffold thrombosis. A detailed analysis is ongoing regarding implantation techniques and outcomes in the AIDA trial.

Robin P. Kraak, M.D.
Joanna J. Wykrzykowska, M.D., Ph.D.

Academic Medical Center
Amsterdam, the Netherlands
j.j.wykrzykowska@amc.uva.nl

Since publication of their article, the authors report no further potential conflict of interest.

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Olaparib for Metastatic Germline *BRCA*-Mutated Breast Cancer

TO THE EDITOR: In this trial involving women with metastatic breast cancer and a *BRCA* mutation, Robson et al. (Aug. 10 issue)[1] randomly assigned patients to receive olaparib or standard therapy. A total of 46% of patients in the olaparib group and 47% in the standard-therapy group died (hazard ratio, 0.90; 95% confidence interval, 0.63 to 1.29). This trial is presented as a major advance in the *Journal* and in the popular press.[2] As is common practice in trials of treatment for metastatic breast cancer, the primary end point was progression-free survival, for which the results were favorable; however, time to disease progression can be extended without extending life. The authors report that "the risk of disease progression or death was 42% lower" with olaparib than with standard therapy. This suggests to the casual reader that death rates were lowered, when there was no effect on death. The response rate was 60% in the olaparib group and 29% in the standard-therapy group, but response rates are poor surrogates for survival. The use of surrogate end points as indicators of success when the natural outcome is the extension of life is likely to lead to false hope for patients with metastatic breast cancer and to an unsustainable drug budget.

Steven Narod, M.D.
Women's College Hospital
Toronto, ON, Canada
steven.narod@wchospital.ca

Christopher M. Booth, M.D.
Queen's University
Kingston, ON, Canada

William D. Foulkes, M.D.
Research Institute of the McGill University Health Centre
Montreal, QC, Canada

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Narod and colleagues raise the question of whether progression-free survival is a meaningful end point in trials of new therapies for patients with incurable metastatic breast cancer. Although improvements in overall survival are the most desirable goal of treatment (other than cure), it can be difficult to demonstrate such benefits with feasible sample sizes, especially without control of crossover to other effective treatments.[1] Regardless, patients and clinicians recognize that survival without progression is generally more desirable than survival with progression, since prolonged progression-free survival may be associated with improved health-related quality of life, as shown in the OlympiAD study,[2] provided the treatment-related toxic effects are acceptable. The value of progression-free survival as an end point is also affirmed in the value frameworks of the American Society of Clinical Oncology and European Society for Medical Oncology and is recognized by regulators as a legitimate indicator of treatment benefit.[3] Although we agree with Narod and colleagues that we should continue to strive for improvements in overall survival, we also suggest that a prolonged period without progression represents a meaningful advance in the treatment of *BRCA*-associated breast cancer.

Mark Robson, M.D.
Memorial Sloan Kettering Cancer Center
New York, NY
robsonm@mskcc.org

Carsten Goessl, M.D.
AstraZeneca
Gaithersburg, MD

Susan Domchek, M.D.
University of Pennsylvania
Philadelphia, PA