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EDITORIAL COMMENT

MaXIMAl Benefits in the Elderly?*

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The overall performance of percutaneous coronary intervention (PCI) in the United States has been slightly decreasing over the past 5 years (1). Meanwhile, patients older than 75 years of age account for an increasing proportion of cases of PCI among the general population, and annual rates of PCI have quadrupled in this subset of patients (2). Multicenter registries of all-comer PCIs in the United States and Europe have reported similar proportions of ~12% of patients ≥80 years of age (2–4).

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Octogenarians undergoing PCI are typically burdened by multiple comorbidities and a doubled risk of mortality (4,5). In comparison with younger patients, they are more likely to have diabetes mellitus, chronic renal insufficiency, left ventricular dysfunction, multivessel disease (MVD), previous myocardial infarction (MI) or coronary artery bypass grafting, and increased tortuosity and calcification of their aorta and coronary and peripheral arteries; all are reasons for advanced procedural complexity (3,6). Interventions on calcified plaques are associated with increased frequency of periprocedural complications and inadequate stent expansion resulting in higher rates of in-stent restenosis (7), whereas tortuous vessels increase vascular access site complications and the difficulty of coronary device deployment (8). Increased bleeding events in elderly patients are due to age-related reduced weight and muscle mass, altered drug metabolism, and changes in hemostasis (9). Moreover, the indication for surgical revascularization has become better defined in patients with MVD (10,11), which is related to the 16.5% decrease in the prevalence of MVD among younger and operable patients undergoing PCI. Conversely, the prevalence of MVD in elderly patients undergoing PCI remains constant (2).

In this context of changing demographics (toward a higher-risk patient subset and increasing complexity) in the PCI population, de Belder et al. (12) should be congratulated on conducting a dedicated clinical study of elderly patients. The results of the XIMA (Xience or Vision stents for the Management of Angina in the Elderly) trial, published in this issue of the *Journal*, showed that patients ≥80 years of age undergoing PCI with drug-eluting stents (DES) had similar rates of all-cause death, stroke, and major hemorrhage, but reduced incidence of MI and target vessel revascularization when compared with bare-metal stent (BMS) implantation (12). The XIMA trial adds valuable knowledge to clinical decision making for several reasons. Most importantly, elderly patients are often excluded or under-represented in randomized trials. Because no other randomized trials have specifically addressed stent strategies in elderly patients, the results of DES in those patients have been based on large retrospective registry analyses thus far (13,14). Of particular interest is 1 previous randomized trial in elderly patients showing that PCI by radial access has higher technical success and lower complication rates in terms of bleeding than the femoral approach (15). This was confirmed in the pre-specified subgroup analysis of the XIMA trial.

However, the findings of the XIMA trial have to be considered in the light of several methodological limitations. The study was powered for the primary endpoint of 1-year composite of death, MI, stroke, revascularization, or major hemorrhage, with an estimated event rate of 12% for the DES arm and 20% for the BMS arm. Noncardiac death was more than doubled in the DES group (5.3% vs. 2.5%; $p = 0.04$), thereby causing an imbalance within the groups because we would not expect noncardiac mortality to be affected by the choice of DES versus BMS. It is unclear whether bleeding was regarded as a reason for noncardiac death. The endpoint of major hemorrhage was defined by major Thrombolysis In Myocardial Infarction bleeding (1.7% in the BMS group and 2.3% in the DES group; $p = 0.62$). The occurrence of major hemorrhage was greater in the DES group from 6 to 12 months (1.0% vs. 0.2%; $p = 0.22$), but did not reach statistical significance because the trial was underpowered to answer the isolated question of harm by bleeding. It would be interesting to review the long-term follow-up in regard to bleeding issues. Reporting bleeding endpoints also by Bleeding Academic Research Consortium or including Thrombolysis In Myocardial Infarction minor bleeding might have changed the outcome measure with respect to 1-year mortality. Bleeding events also relate to dual antiplatelet therapy (DAPT) therapy and its duration. At 1 year, the rates of DAPT were 32% and 94% in the BMS and DES groups, respectively. In most of these patients, discontinuation of DAPT was due to treatment disruption by noncompliance or treatment withdrawal for clinical concerns. Recently, disruption of DAPT in DES-treated patients was found to have a 12-fold hazard for major adverse cardiac events within the first 7 days after disruption (16). Other reports have

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questioned the utility of the continuation of DAPT beyond 6 months with respect to risk reduction of stent thrombosis (17); this may be particularly applicable to everolimus-eluting DES because they are associated with a low incidence of stent thrombosis and restenosis (18). The XIMA trial would have provided very valuable lessons on duration, interruption, and disruption of DAPT if detailed data on these variables were available. Bleeding (and perhaps noncardiac death) rates might have been lower if the duration of DAPT were shorter.

Furthermore, the primary endpoint treatment benefit was driven by MI and target vessel revascularization. It is unclear whether the higher MI rate in the BMS group (3.5% at 1 month, 8.7% at 1 year) was associated with periprocedural MI, stent thrombosis, restenosis, plaque rupture in non-target vessels, or severe demand ischemia due to noncardiac comorbidities.

Finally, 800 patients were recruited from 20 centers over 36 months, equaling an average of 1.1 patients per center per month. This certainly indicates a highly-selected population, limiting the generalizability of the results.

In conclusion, a clinical strategy of everolimus-eluting stenting via radial access in elderly patients appears to be attractive because it reduces vascular complications while improving rates of MI and target vessel revascularization. In addition, the duration of DAPT in potentially frail patients remains an important question, and outcomes may improve if the duration of DAPT can be shortened safely. A crucial aspect of this trial and any other clinical investigation in elderly patients is AN understanding of the noncardiac mortality trends and their relationship with treatment arms and primary outcome measures. The only way to decipher these questions is to conduct more trials including elderly patients.

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