

EDITORIAL COMMENT

The Importance of Subgroup Analysis in Drug-Eluting Stent Trials*



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Cardiovascular drugs and devices may have different safety and efficacy profiles in certain populations. Performance of separate trials or subgroup analysis is important if there is a biological reason, either intrinsic and/or extrinsic, for a varied response to a therapy. For example, compared with men, women have different body size, hormonal milieu, sex-specific physiology, and sociocultural influences. Randomized controlled trials are generally powered for the primary outcome in all enrolled individuals, and the results are generalized to subgroups. Pre-specified or post-hoc analyses of subgroups within a study are often exploratory due to lack of randomization and small numbers. Caution must be exercised in the number of subsets examined due to the potential for chance findings. In addition, interaction terms in statistical models should only be pursued if there is an a priori hypothesis being examined. In trials of percutaneous coronary intervention (PCI), the low enrollment of women has led to less robust data and the inability to study the interaction between sex and other important clinical characteristics, for example, diabetes mellitus and chronic kidney disease (CKD), which are associated with high rates of major adverse cardiovascular events in PCI trials. In an effort to examine the performance of drug-eluting stents (DES) in women, the Society for Cardiovascular Angiography and Interventions' Women in Innovation Initiative held a Gender Data Forum. Through collaborative efforts of cardiology societies, study investigators, and industry, an individual patient-level

pooled dataset from women in 26 randomized DES trials was created.

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In this issue of *JACC: Cardiovascular Interventions*, harnessing the power of numbers, the relationship between renal function, DES platform, and adverse outcomes in women is reported (1). The analysis included 4,217 women receiving DES in a randomized trial comparing DES and bare-metal stents (BMS), or 2 or more DES types, between 2002 and 2013. Earlier trials were predominantly with first-generation durable polymer sirolimus- and paclitaxel-eluting stents, with 3 to 6 months duration of dual antiplatelet therapy (DAPT), in patients with stable coronary artery disease. Newer DES trials included durable polymer everolimus- and zotarolimus-eluting stents and biodegradable polymer stents. Higher-risk patients including those with acute coronary syndrome were included, and DAPT duration in general was longer at 6 to 12 months. Endpoints were adjudicated per protocol in each clinical trial, and the Academic Research Consortium definition was used for stent thrombosis.

RENAL FUNCTION AND PCI OUTCOMES IN WOMEN

The dataset included patients with moderate CKD; however, patients with severe and end-stage renal disease were excluded from the clinical trials. Outcomes were compared in women with creatinine clearance (CrCl) >60 ml/min, between 60 and 45 ml/min, and <45 ml/min. Among the women, only 14% had a CrCl of <45 ml/min. Two important trends in women undergoing PCI with DES were observed. First, as CKD worsened, major adverse cardiac events increased. Specifically, moderate renal dysfunction (CrCl <45 ml/min) was independently associated with higher risks of death and myocardial infarction and a trend toward stent thrombosis at 3 years. Second,

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target lesion revascularization was low, around 6% at 3 years, and was not related to severity of CKD. The efficacy of DES in women, therefore, is not affected by CKD, and outcomes are overwhelmingly driven by nonculprit-related events with a small contribution from stent thrombosis. The higher risk of stent thrombosis in CKD is not only observed in women. In a large, observational study of patients undergoing elective DES, CKD was an independent predictor of 1-year definite or probable stent thrombosis (2).

STENT PLATFORM AND PCI OUTCOMES IN WOMEN

The second focus of the analysis was a comparison between first- and newer-generation DES. In women, independent of renal function, use of newer-generation DES was associated with a lower risk of both safety (cardiac death, myocardial infarction, and stent thrombosis) and efficacy (target lesion revascularization) endpoints. This is in keeping with the results of large randomized controlled trials and meta-network analyses of DES types. The effect of this data is small, because the first-generation DES are no longer in use (sirolimus-eluting stents) or are known to be inferior to current DES (paclitaxel-eluting stents), and the study could not evaluate individual stent types. There may, for example, be different healing characteristics of the newer-generation stents in women, particularly in CKD patients. Currently, there is no data to suggest a difference between newer-generation durable polymer DES in women (3). Whether bioabsorbable polymer DES offers an advantage in women or CKD patients is unknown. In a virtual histology intravascular ultrasound study comparing DES neointimal characteristics in patients with and without CKD, neoatherosclerosis was related to neointimal volume, which was greater in patients with CKD (4). Although differences in neointimal volume may not translate into higher rates of clinical restenosis, neoatherosclerosis is 1 potential mechanism of late ischemic events in stents, including very late stent thrombosis. Assessment of surrogates of healing with intracoronary imaging may be an avenue to form hypothesis-generating questions about novel DES types.

IMPROVING OUTCOMES IN INDIVIDUAL SUBGROUPS

Standard-dose clopidogrel remains the most common P2Y₁₂ inhibitor in PCI for stable coronary artery disease and was used in the trials included in the current analysis. Female sex and CKD, however, are both

associated with high on-treatment platelet reactivity (5,6). The association between residual platelet reactivity and adverse outcomes is irrespective of sex or renal function. Women and patients with CKD, therefore, may benefit from a more aggressive or tailored approach to DAPT. In a randomized controlled trial of 370 patients with CKD and clopidogrel resistance, double-dose compared with standard-dose clopidogrel resulted in greater inhibition of platelet aggregation and improved 1-month outcomes in PCI patients, including stent thrombosis and major adverse cardiac events, without increasing bleeding (7). Generalizing data from large randomized controlled trials, more potent P2Y₁₂ antiplatelet agents should be used in women and CKD patients undergoing PCI in the setting of acute coronary syndromes unless contraindicated. The optimal duration of DAPT in PCI subgroups has not been fully examined. Prolonged DAPT reduces both stent thrombosis and nonculprit myocardial infarction events but may not translate into a mortality benefit due to risk of bleeding. In an Embase and Cochrane database review, the benefit of antiplatelet therapy in CKD patients was deemed uncertain (8).

Not addressed in the current study is the comparison of DES to BMS in CKD patients including those with end-stage renal disease on dialysis. Although there have been conflicting reports on whether the efficacy of DES is lower in CKD, it is clear that DES are the preferred stent platform. In the RENAL-DES (Randomized Comparison of Xience V and Multi-Link Vision Coronary Stents in the Same Multi-vessel Patient with Chronic Kidney Disease) trial, clinically driven target vessel revascularization at 1 year was markedly lower in DES: 2.7% versus 11.4% ($p < 0.001$) (9). In a meta-analysis of DES compared with BMS in end-stage renal disease, target lesion revascularization, target vessel revascularization, and major adverse cardiovascular events were significantly lower with DES (10). In the listed trials, outcomes according to sex were not reported. The atherosclerotic milieu in CKD patients, with more diffuse and complex disease, inflammation, and endothelial dysfunction, may not attenuate the benefit of DES, but the disease in advanced stages may be more optimally treated with surgical revascularization, similar to patients with diabetes mellitus. In a recent propensity-matched analysis of unselected patients from Ontario, Canada, PCI with DES was compared with coronary artery bypass grafting in patients with CKD (CrCl < 60 ml/min). During 3 years of follow-up, coronary artery bypass graft patients had greater survival and freedom from major adverse cardiac and cerebrovascular events. Female sex was a

negative predictor of late mortality but had no effect on the composite of late major adverse cardiac and cerebrovascular events (11). In an analysis of the Society of Thoracic Surgeons National Adult Cardiac Database, women undergoing coronary bypass more often had CKD, and CKD was associated with higher operative mortality and post-operative complications. Female sex, however, was not independently associated with adverse outcomes (12).

CONCLUSIONS

Despite the enormity of data on current DES platforms, there remains a need to examine subgroups

and interactions between subgroups to understand the best device for the individual patient. Differences in physiology and pharmacodynamics in women and men necessitate equal representation in clinical trials. Certain high-risk clinical subgroups, such as patients with CKD or diabetes mellitus, also deserve increased attention as both qualitative and quantitative differences may be observed compared with patients without these comorbidities.

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