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EDITORIAL COMMENT

To EncourAGE Individualized Dual Antiplatelet Therapy Duration After Drug-Eluting Stent Implantation

A New pAGE of an Intriguing Book*

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Dual antiplatelet therapy (DAPT) is an evidence-based, guideline-recommended, standard-of-care treatment after percutaneous coronary intervention (PCI) (1). Nevertheless, the optimal treatment duration of DAPT remains controversial (1,2). Although DAPT has showed to be highly effective in preventing stent thrombosis (ST) during follow-up, as well as non-stent-related myocardial infarction (MI) and stroke, the increased risk of bleeding is not negligible and has relevant impact on prognosis (1-3). It is now clear that a "one-size-fits-all" approach to balance ischemic and bleeding risks is not applicable; therefore, individualization of DAPT therapy is a key measure and includes the identification of risk factors for ischemic and bleeding events helping to weigh risks against the potential benefits of DAPT prolongation (1,2). Tailored therapy should be based on clinical and procedural considerations, as well as dedicated, clinical risk scores that might better advise the decision making in the context of a comprehensive clinical evaluation. Although some subgroups of patients undergoing drug-eluting stent (DES) implantation have shown to benefit from longer DAPT (i.e., prior MI, acute coronary syndrome [ACS] at presentation, complex PCI, or peripheral arterial disease), others may not (i.e., female, diabetic, chronic kidney disease, elderly, and high-bleeding risk patients) (1,2,4-6).

Elderly individuals represent a growing proportion of patients with coronary artery disease undergoing PCI because of aging of the population with increased life expectancy. Nonetheless, extrapolating findings from randomized trials to elderly patients is challenging because such patients have been underrepresented in these studies and are characterized by peculiar bleeding or ischemic risks.

In PRODIGY (PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY) trial, elderly patients experienced a greater risk of both ischemic and bleeding events, with risk trajectories proceeding similarly with aging (6). In both elderly and nonelderly individuals, DAPT prolongation (24 months) did not reduce the risk of the primary efficacy endpoint of death, MI, or cerebrovascular accidents, and rather increased the risk of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 (the relative magnitude of treatment effect on bleeding was similar between age subgroups, but the absolute risk difference with prolonged DAPT was greater in elderly compared with nonelderly patients) compared with 6-month DAPT. This suggested that elderly individuals were probably more prone to benefit from a shorter DAPT compared with their younger counterparts. Notably, a treatment by age heterogeneity for the primary endpoint according to age has been observed in ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) (interaction $p = 0.03$), IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions) (interaction $p = 0.051$), and ITALIC (Is There A LIfe for

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TABLE 1 Age Subgroups in Randomized Clinical Trials Comparing Short (3–6 Months) vs. Long (≥12 Months) DAPT After PCI

Trial	Design	Primary Endpoint	Mean Age (yrs)	Elderly*	Age Subgroups	Interaction p Value
RESET	3 vs. 12	Cardiovascular death, MI, ST, ID-TVR, bleeding	62	46%	<65 yrs of age: 4.4% vs. 4.5% ≥65 yrs of age: 5.1% vs. 4.8%	0.599
OPTIMIZE	3 vs. 12	All-cause death, MI, stroke, major bleeding	62	NA	NA	NA
EXCELLENT	6 vs. 12	Cardiac death, MI, ID-TVR	63	47%	<65 yrs of age: HR 1.61 (95% CI: 0.78–3.31) ≥65 yrs of age: HR 0.83 (95% CI: 0.42–1.65)	0.19
SECURITY	6 vs. 12	Cardiac death, MI, stroke, ST, BARC 2, 3, or 5 bleeding	65	NA	NA ≥75 yrs of age was predictor of the primary endpoint at the multivariable analysis	NA
ISAR-SAFE	6 vs. 12	All-cause death, MI, ST, stroke, major bleeding	67	50%	<67.2 yrs of age: HR 2.02 (95% CI: 0.81–4.99) ≥67.2 yrs of age: HR 0.60 (95% CI: 0.31–1.13)	0.03
I-LOVE-IT 2	6 vs. 12	All-cause death, MI, stroke, major bleeding	60	32%	<65 yrs of age: RR 1.02 (95% CI: 0.66–1.60) ≥65 yrs of age: RR 1.12 (95% CI: 0.71–1.76)	0.79
IVUS-XPL	6 vs. 12	Cardiac death, MI, stroke, major bleeding	64	46%	≤65 yrs of age: HR 6.50 (95% CI: 0.80–52.81) >65 yrs of age: HR 0.67 (95% CI: 0.28–1.62)	0.051
PRODIGY	24 vs. 6	All-cause death, MI, CVA	68	63%/30%	<65 yrs of age: HR 0.57 (95% CI: 0.28–1.16) ≥65 yrs of age: HR 1.12 (95% CI: 0.82–1.51) <75 yrs of age: HR 1.48 (95% CI: 0.95–2.30) ≥75 yrs of age: HR 0.80 (95% CI: 0.55–1.16)	0.09/0.036
ITALIC	6 vs. 24	All-cause death, MI, stroke, urgent TVR, major bleeding	62	14%	<75 yrs of age: NA ≥75 yrs of age: HR 0.35 (95% CI: 0.11–1.09)	0.048
NIPPON	6 vs. 18	All-cause death, MI, stroke, major bleeding	67	21%	≤75 yrs of age: 1.5% vs. 1.5% >75 yrs of age: 3.8% vs. 1.4%	0.15
DAPT-STEMI†	6 vs. 12	All-cause death, MI, stroke, any revascularization, major bleeding	60	NA	Not available	NA
REDUCE†	3 vs. 12	All-cause death, MI, ST, stroke, TVR, major bleeding	61	13%	<75 yrs of age: OR 0.85 (95% CI: 0.56–1.28) ≥75 yrs of age: OR 1.66 (95% CI: 0.71–3.86)	0.16

*Percentage of elderly patients reported is based on the age cutoff used in the study. †Data from TCT 2017 presentations.

BARC = Bleeding Academic Research Consortium; CI = confidence interval; CVA = cerebrovascular accident; DAPT = dual antiplatelet therapy; DAPT-STEMI = Six versus twelve month dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction; EXCELLENT = Efficacy of Xience/Promus Versus Cypher in rEducing Late Loss After stENTing; HR = hazard ratio; I-LOVE-IT 2 = Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization; ID-TVR = ischemia-driven target vessel revascularization; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; ITALIC = Is There A LIfe for DES after discontinuation of Clopidogrel; IVUS-XPL = Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; MI = myocardial infarction; NIPPON = Nobori Dual Antiplatelet Therapy as Appropriate Duration; NA = not available; OPTIMIZE = Optimised Duration of Clopidogrel Therapy Following Treatment with the Endeavor Zotarolimus-Eluting Stent in Real-World Clinical Practice; OR = odds ratio; PCI = percutaneous coronary intervention; PRODIGY = PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY; REDUCE = Randomized Evaluation of Short-term DUal Anti Platelet Therapy in Patients With Acute Coronary Syndrome Treated With the COMBO Dual-therapy stEnt; RESET = REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; RR = relative risk; SECURITY = Second-generation Drug-eluting Stent Implantation Followed by 6- versus 12-month dual antiplatelet therapy; ST = stent thrombosis.

DES after discontinuation of Clopidogrel) trials (interaction p = 0.048 at 2 years) favoring the use of short-term DAPT in elderly rather than younger patients (Table 1). It should be noted, however, that the primary endpoint in these latter trials included a composite of ischemic and bleeding events, which makes difficult to completely assess the risk-benefit ratio associated with DAPT in elderly patients. In line with this evidence, age is a predominant risk factor for bleeding in both the PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) score and the DAPT score, supporting that, in the absence of high ischemic risk, a shorter DAPT may be desirable (1).

In this issue of *JACC: Cardiovascular Interventions*, Lee et al. (7) explored the impact of age in an individual participant data meta-analysis of randomized clinical trials where they compared 3-6 month DAPT versus 12-month DAPT after PCI with DES implantation. The authors pooled 6 trials encompassing 11,473 patients of whom 42% presented with ACS and 90% received newer-generation DES. Overall they observed that a 3- to 6-month DAPT regimen was as effective as but safer than 12-month DAPT duration. When exploring age-based subgroups (using 65 years of age as cutoff) they observed that shorter DAPT, as compared with longer DAPT, was noninferior in terms of the ischemic composite of MI, ST, or stroke in elderly patients (n = 5,319, 46.4%), but inferior in younger patients with a significant p value for interaction. A shorter DAPT reduced the risk of bleeding compared with longer DAPT irrespective of age (negative interaction); however, this benefit was statistically significant in elderly but not in younger patients. Thus, the authors concluded that elderly patients might be those with the highest advantage of shortening DAPT within 1 year of PCI.