Editorial

Dual Antiplatelet Therapy in Percutaneous Coronary Intervention
A Tale of 2 Decades With New Perspectives in the Era of New-Generation Drug-Eluting Stents

Raffaele Piccolo, MD; Stephan Windecker, MD

In 2016, dual antiplatelet therapy (DAPT) assumes its 20th anniversary since the publication of the first randomized clinical trial establishing the superiority of DAPT over anti-coagulant therapy among patients undergoing percutaneous coronary intervention (PCI) (Figure).1 Because then, both antiplatelet therapy and PCI have undergone continued refinement. Clopidogrel substituted ticlopidine, and subsequently, more potent oral and intravenous P2Y12 receptor inhibitors (prasugrel, ticagrelor, and cangrelor) entered the field of DAPT, whereas the advent of metallic drug-eluting stents (DES) and, more recently, completely bioresorbable scaffolds marked important milestones in the field of PCI. For several years, the duration of DAPT did not play a critical role in the pharmacological therapy after PCI. Indeed, DAPT was prescribed for 2 to 6 months after PCI in pivotal trials leading to the approval of the early-generation DES by the US Food and Drug Administration.2–4 It was only in the aftermath of increasing safety concerns related to the phenomenon of very late stent thrombosis after implantation of early-generation DES that prolongation of DAPT to 12 months was recommended by the American College of Cardiology Foundation/American Heart Association/Society for Cardiac Angiography and Interventions guidelines.5 In the meantime, coronary stent technology rapidly evolved with the transition from early- to newer generation DES, featuring lower drug loads, thinner stent struts, more bio compatible or bio degradable polymers, and eventually improved patient outcomes.6 Although new-generation DES are currently recognized as default therapy in almost all lesion and patient subsets, the optimal duration of DAPT still remains the subject of debate.6,7

Available evidence suggests that prolonging DAPT in patients undergoing PCI is associated with a lower risk of long-term atherothrombotic events, including stent thrombosis and myocardial infarction, benefits that are partially offset by an increased risk of clinically relevant bleeding.6,8 Although these data are derived from >10 randomized trials involving >30 000 patients, they are driven to a large extent by the DAPT study that included 9961 patients randomly assigned to 12-month versus 30-month DAPT after DES implantation.9 Several converging lines of evidence, however, indicate that the effects of prolonged DAPT on stent-related outcomes may be attenuated by new-generation DES and that previous concerns of DES safety are replaced by focus on long-term patient-related outcomes.6,9

In this issue of Circulation: Cardiovascular Interventions, Han et al10 report the results of a randomized trial comparing 6-month versus 12-month DAPT among 1829 patients who received a thin-strut, cobalt-chromium, polylactide-co-glycolide, biodegradable polymer-based, sirolimus-eluting stent (Tivoli; Essen Tech, Beijing, China). The study population represents the experimental arm of the Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for the Treatment of Coronary Revascularization (I-LOVE-IT 2) trial that compared the biodegradable polymer sirolimus-eluting stents against durable polymer sirolimus-eluting stents among 2737 patients.11

At 1-year, 6-month DAPT was found noninferior to the 12-month DAPT regimen for the primary end point target-lesion failure, a composite of cardiac death, target-vessel myocardial infarction, or clinically indicated target-lesion revascularization (6.8% versus 5.9%; P for noninferiority=0.0065). The rate of target-lesion failure (7.5% versus 6.3%; P=0.32) and net adverse clinical events, a composite of all-cause mortality, myocardial infarction, stroke, or major bleeding (7.8% versus 7.3%; P=0.60), was similar at 18 months of follow-up. Of note, there were no differences in rates of the individual components of the primary end point, as well as definite or probable stent thrombosis (0.6% versus 0.2%; P=0.25). Consistent findings were observed in the subgroup of patients presenting with ST-segment–elevation myocardial infarction (n=248) and non–ST-segment–elevation acute coronary syndrome (n=1248). Bleeding events (type ≥3 according to Bleeding Academic Research Consortium Criteria) occurred at comparable rates (5.5% versus 5.7%; P=0.90) although rates of bleeding were somewhat higher than in previously reported trials despite the prevalent use (>90%) of radial access with the corollary effect to reduce access-site related bleeding.

What are the clinical implications of the study? First, the study provides the largest source of data comparing different durations of DAPT among patients treated with metallic,
biodegradable polymer–based DES. Before the I-LOVE-2 trial, only 763 (54%) and 336 (8%) patients enrolled in the Second Generation Drug-Eluting Stent Implantation Followed by Six-Versus Twelve-Month Dual Antiplatelet Therapy (SECURITY) and Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) trials, respectively, had been treated with biodegradable polymer–based DES.12,13
However, there was no randomization according to stent type in SECURITY and ISAR-SAFE, and no data were specifically provided for patients who had been implanted solely with biodegradable polymer–based DES.\

Second, the findings are in line with 6 other randomized trials comparing ≤6-month DAPT versus 12-month DAPT. In a network meta-analysis, Palmerini et al5 found that ≤6-month versus 12-month DAPT was associated with a similar risk of all-cause mortality (hazard ratio, 0.95; 95% credible intervals, 0.76–1.20), myocardial infarction (hazard ratio, 1.00; 95% credible interval, 0.75–1.30), and definite or probable stent thrombosis (hazard ratio, 1.10; 95% credible interval, 0.66–1.70) but a lower risk of major bleeding (hazard ratio, 0.59; 95% credible interval, 0.36–0.95). Individually, none of these studies reported a significant difference in the risk of major bleeding. Although these data indicate that previous concerns of stent-related outcomes are less dependent on DAPT duration, they do not resolve the competing risks of long-term atherothrombotic versus bleeding adverse events associated with prolonged DAPT.

Third, ≈80% of participants had an acute coronary syndrome at the time of inclusion although acute myocardial infarction was present only in a quarter of patients. The analysis of this patient subset did not reveal a greater risk of adverse events with 6-month DAPT. This supports the notion that new-generation, biodegradable polymer–based DES have addressed the unmet needs of early-generation DES in this setting.14–16 However, it should be noted that both the European Society of Cardiology and American College of Cardiology Foundation/American Heart Association/Society for Cardiac Angiography and Interventions guidelines recommend DAPT for at least 12 months in the absence of contraindications in patients with acute coronary syndrome.5,7 Moreover, continuation of thienopyridines on a background of aspirin beyond 1 year in the DAPT trial prevented major adverse cardiovascular and cerebrovascular events to a greater extent in patients with acute myocardial infarction (4.4% versus 5.3%; P=0.08) than among patients without an index presentation of acute myocardial infarction (3.9% versus 6.8%; P=0.001; P for interaction=0.03).7 In this context, the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI-54) trial showed that long-term ticagrelor treatment in addition to aspirin reduced the risk of major adverse cardiovascular and cerebrovascular events, as well as myocardial infarction and stroke while increasing the risk of major bleeding among 21,162 patients with a history (>1 year) of myocardial infarction.18 An earlier initiation of ticagrelor monotherapy after new-generation DES is currently tested in the Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-Day Intensive Dual Antiplatelet Therapy in All-Comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-Eluting Stent Use (GLOBAL-LEADERS) trial, which will compare a short course of ticagrelor plus aspirin followed by 23-month ticagrelor monotherapy versus 12-month standard DAPT among 16,000 patients.19 Thus, the focus is shifting toward antiplatelet strategies that afford long-term prevention against atherothrombotic adverse events while minimizing the risk of bleeding.

Some limitations of the present study are noteworthy. The 1-year rate of target-lesion failure was lower than expected (6.3% versus 8.3%), resulting in a relatively wide margin of noninferiority. Moreover, approximately half of primary end point events occurred during the periprocedural period and therefore well before the timepoint when the 2 randomized treatment regimens actually differed in terms of DAPT duration. In view of the high proportion of patients included with acute coronary syndrome, the use of clopidogrel instead of more potent and effective P2Y12 receptor inhibitors represents another important limitation.20 Finally, the extrapolation of trial findings to other biodegradable polymer–based DES is not feasible because of the wide-ranging differences in degradation products and kinetics, which may importantly affect DAPT duration. Furthermore, there remains limited evidence supporting the Firebird DES when compared with other thin-strut, biodegradable polymer DES that have been tested against US Food and Drug Administration–approved, new-generation DES.21–23

In summary, the I-LOVE-IT 2 trial reports noninferiority of 6-month versus 12-month DAPT with respect to the primary end point target-lesion failure in a cohort of patients undergoing PCI with a new-generation, biodegradable polymer–based DES. How can we reconcile the differences between trials investigating DAPT ≤12 months versus beyond 1 year? Unfortunately, a definitive answer cannot be provided at the present time. However, it is plausible that trials investigating DAPT beyond 1 year are more likely to capture atherothrombotic manifestations, particularly outside the stented coronary segments. In contrast, trials investigating different DAPT durations within 1 year are more sensitive to stent-related adverse events linked to the arterial healing processes. The advent of DAPT ≥2 decades ago importantly contributed to improve safety and efficacy of PCI and, as a result, its widespread diffusion in clinical practice. In the meantime, various iterations in coronary stent technology have largely resolved stent-related adverse events with rates of definite stent thrombosis amounting to <0.50% per 100 person-years with new-generation DES.24 Accordingly, the optimal DAPT duration will largely be determined by the prevention of new atherothrombotic events rather than the nuisance of stent-related thrombotic complications, and novel, more personalized concepts toward the optimal DAPT duration are under clinical investigation.

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糖尿病对复杂性冠状动脉疾病患者药物洗脱支架植入血管重建术预后的影响
——6081 例患者水平的荟萃分析

糖尿病是动脉粥样硬化与经皮冠状动脉介入（Percutaneous coronary interventions, PCI）术后再阻塞的明确危险因素。虽然糖尿病与复杂性冠状动脉疾病（coronary artery disease, CAD）严重影响 PCI 术后患者的预后，但两者对接受 PCI 药物洗脱支架植入术的患者长期预后的影响仍存在争议。本研究旨在通过 SYNTAX 评分（Synergy Between PCI With Taxus and Cardiac Surgery）——可定量评估 CAD 复杂性的血管造影术综合评分系统，并可对行 PCI 的患者进行有效的风险分层。

对 4 项全体受试者研究中的 6081 例患者行荟萃分析，根据 SYNTAX 评分≤11 或>11 以及是否患有糖尿病对患者进行分层，1,310 例（22%）患者确诊为糖尿病，4,554 例（75%）患者植入了新一代药物洗脱支架。主要研究终点为主要心脏不良事件，如心肌梗死。其中 173 例（14.5%）糖尿病患者和 436 例（9.9%；P<0.001）非糖尿病患者到达主要研究终点。校正的 Cox 回归分析结果表明，SYNTAX 评分与糖尿病均与主要终点事件相关（P<0.001 及 P=0.028）及交互检验 P=0.07）。多变量分析结果表明，与非糖尿病患者相比，糖尿病患者发生主要心脏不良事件的风险更高（HR=1.25；95% CI 1.03−1.53；P=0.026），血运重建风险更高（HR=1.54；95% CI 1.18−2.01；P=0.002），而两者发生心源性死亡（HR=1.41；95% CI 0.96−2.07；P=0.08）及心肌梗死（HR=0.89；95% CI 0.64−1.22；P=0.45）风险相似。SYNTAX 评分≤11 或>11 对于任何一种终点事件均没有显著交互作用。

基于接受新一代药物洗脱支架植入术后患者的研究结果表明，糖尿病患者发生血运重建的风险更高。为期 2 年的随访结果表明，SYNTAX 评分可作为临床预后的独立预测因素，但不能改变糖尿病患者结局。


经皮冠状动脉介入术后再双联抗血小板治疗
对新一代药物洗脱支架时代的展望

2016 年是经皮冠状动脉介入（percutaneous coronary intervention, PCI）术后双联抗血小板治疗（dual antiplatelet therapy, DAPT）的 20 周年纪念日。1996 年，第一项证明 PCI 术后 DAPT 效果更佳的随机试验结果发表了。得益于该项研究结果，20 年来，PCI 术得到了广泛的应用和巨大的提升，P2Y12 受体抑制剂（氯吡格雷、普拉格雷等）也不断地推陈出新。

早期，美国 FDA 批准的 PCI 药物洗脱支架（drug eluting stent, DES）植入术后 DAPT 时限为 2~6 个月，伴随着极晚期支架内血栓形成的严重不良后果，美国心脏学院基金会等推荐 DAPT 时限延长至 12 个月。与此同时，更少载药量、更不易排斥且预后更好的新一代 DES 面市了。虽然新一代 DES 已经被认为是心血管病变的常规治疗选择，但对于术后 DAPT
最佳治疗时限的问题仍存在争议。

为评估生物可降解聚合物西罗莫司 DES (Tivoli) 和永久聚合物西罗莫司 DES (Firebird) 在冠状动脉血运重建术后的安全性及有效性 研究招募2,737例患者进行试验 (I-LOVE-IT 2) 并进行随访。1年随访期结果表明，在主要终点靶血管失败率、心源性死亡、靶血管支配区心肌梗死以及临床证据支持的血管重建等方面，DAPT-6个月不劣于DAPT-12个月（6.8% vs. 5.9%；非劣性 P = 0.0065）。后续的18个月随访期结果表明，两种治疗在靶病变失败率（7.5% vs. 6.3%；P = 0.32），全因死亡率、心肌梗死、卒中或出血等净临床不良事件发生率（7.8% vs. 7.3%；P = 0.60）没有明显差异。同时，在单一主要终点事件发生率以及明确或可疑的支架内血栓形成方面，DAPT-6个月与DAPT-12个月也没有显著差异（0.6% vs. 0.2%；P = 0.25）。

I-LOVE-IT 2试验结果表明，DAPT-6个月主要终点靶病变失败率不劣于DAPT-12个月，结果与另一项Meta分析一致；PCI术后DAPT治疗时限超过1年者在支架外冠脉节段更易发生动脉粥样硬化，而DAPT治疗时限小于1年者对动脉愈合相关的支架内不良事件更敏感。最后，DAPT最佳治疗时限应该取决于防止新动脉粥样硬化血栓形成，而非支架相关的血栓形成并发症。


鹿特丹桡动脉获取研究
——基于超声的桡动脉评价冠状动脉介入术的诊断与治疗

与股动脉入路的冠脉介入术相比，桡动脉入路的介入术血管并发症和患者死亡率更低，而患者满意度更高，因此桡动脉入路的心导管插管术已经被广泛使用。但是桡动脉入路的心导管插管术后可能发生桡动脉损伤。

本研究旨在通过评估桡动脉插管后桡动脉结构的改变情况以探究其作为预测桡动脉搏动消失或闭塞、局部疼痛以及上肢功能减弱的效力。

研究招募90例接受经桡动脉入路的冠状动脉血管造影或介入治疗的患者，分别于插管术前、术后3小时、术后30天应用高分辨率40-MHz超声技术扫描检查患者桡动脉结构。所有患者均表现为桡动脉急性损伤：夹层和壁内血肿最为常见。但这些表现并不能作为术后30天发生桡动脉搏动消失或闭塞、局部疼痛和上肢功能减弱的有利预测因素。总的来说，穿刺点远端的桡动脉管腔内径显著减少。桡动脉内膜以及动脉壁总厚度在穿刺后3小时即显著增加并维持至术后30天。桡动脉插管术后30天，3.9%的患者发生桡动脉闭塞，9.2%的患者发生搏动消失。基线水平桡动脉管腔内径较小的患者术后30天发生桡动脉搏动消失的风险增加（OR = 1.23；P = 0.049）。桡动脉穿刺次数可以预测术后30天发生桡动脉搏动消失（OR = 2.64；P = 0.027），桡动脉闭塞（OR = 3.49；P = 0.022）以及症状（OR = 2.24；P = 0.05）。