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Editorial

ULISSE – Facilitating the odyssey toward individualized DAPT☆

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As treatment for cardiovascular disease increases over time, there has been a concomitant rise in percutaneous coronary intervention (PCI) – particularly among older, comorbid patients who are at high bleeding risk [1]. This study by Godino et al. evaluates the clinical outcomes of patients with biodegradable polymer sirolimus-eluting stents (BP-SES) treated with short dual antiplatelet therapy DAPT (S-DAPT) through retrospective analysis of the Ultimaster Italian multicenter all comers stent registry (ULISSE) [2]. The registry includes data from nine centers in Italy totaling 1660 patients who underwent PCI with Ultimaster BP-SES. This abluminal gradient coated biodegradable polymer stent has shown approximately 85% and 95% strut coverage at one and three months after implantation, similar to other recently tested stents in the US and Europe [3]. Patients with at least one high risk bleeding feature were placed in the S-DAPT group, and the remainder received at least six months of DAPT (R-DAPT). Although not powered for such, the results suggest the S-DAPT group had no difference in target lesion failure (TLF), stent thrombosis, or significant bleeding at one year. However, at three months the non-randomized, convenience S-DAPT sample had significantly higher mortality and bleeding – potentially related to additional systemic anticoagulation.

The authors clearly defined patients stratified to the S-DAPT arm due to bleeding risk or necessity of urgent major non-cardiac operations, and identified clinically relevant endpoints to the study adopted from the LEADERS FREE trial [4]. At baseline, the S-DAPT patients had a considerably higher risk profile, and not surprisingly, significantly higher all-cause and cardiac death; yet achieved similar rates of TLF and bleeding at 12 months. The authors use these results to reinforce the argument that S-DAPT is similar in safety and efficacy when compared to R-DAPT in patients with BP-SES designed abluminal drug coated stents.

Despite the strengths of this prominent registry-based analysis, there are limitations. Operator directed treatment resulted in several possible DAPT regimens coupled with the need for additional anticoagulation in many (64%) high-risk patients. Procedurally, the study included 1660 patients, yet only 82 patients (5%) were discharged with S-DAPT and only 76 were followed to the one-year study completion. Unfortunately, the small sample size without adjudicated follow-up did not allow authors to use propensity matching to account for missing data (14% of patients – all in the R-DAPT group), and there are known limitations with inverse probability weighting in these patient-reported scenarios. These methodological concerns leave open the possibility for future prospective trials.

PCI methods have improved dramatically through a fascinating 40-year Odyssey beginning with balloon angioplasty developed by Dr. Gruentzig. This led to pioneering bare metal stents that help maintain lumen integrity, ultimately yielding to drug eluting stents (DES) in attempts to lower restenosis rates. Recently, newer biodegradable polymers and abluminal drug placement are being investigated to address inflammation and early neoatherosclerosis seen with minor bioincompatibilities. Other tools, such as intravascular imaging, are further reducing rates of acute closure and restenosis as demonstrated in the STOP-DAPT2 trial where exceedingly low stent thrombosis rates were noted when intravascular ultrasound was universally incorporated [5].

Several studies have now evaluated differing DAPT durations in an effort to minimize recurrent ischemic and bleeding risk. An I-LOVE-IT2 trial substudy investigated the efficacy and safety of six versus 12 months of DAPT using similar stents and patients to the ULISSE registry. The noninferiority study concluded that there were no significant difference in composite cardiac death, TLF, target lesion revascularization, stroke, or major bleeding at 18 months [6]. Another study, SMART-CHOICE, evaluated patients with S-DAPT followed by SAPT with a $P2Y_{12}$ inhibitor versus 12 months of DAPT suggesting non-inferiority of S-DAPT [7]. Evaluating one-month DAPT then clopidogrel monotherapy versus 12 months DAPT, the STOPDAPT-2 trial revealed non-inferiority at preventing major adverse ischemic events as well as superiority at preventing major bleeding [5]. This recent flood of data has spurred the notion that in high risk bleeding patients, with properly

Abbreviations: PCI, Percutaneous coronary intervention; DAPT, Dual antiplatelet therapy; BP-SES, Biodegradable polymer sirolimus-eluting stents; ULISSE, Ultimaster Italian multicenter all comers stent registry; S-DAPT, Short DAPT; R-DAPT, Regular DAPT; SAPT, Single antiplatelet therapy; DES, Drug eluting stent.

☆ Editorial Re: One-year clinical outcome of biodegradable polymer sirolimus-eluting stent in patients needing short dual anti-platelet therapy. Insight from the ULISSE registry (ULtimaster Italian multicenter all-comerS Stent rEgistry).

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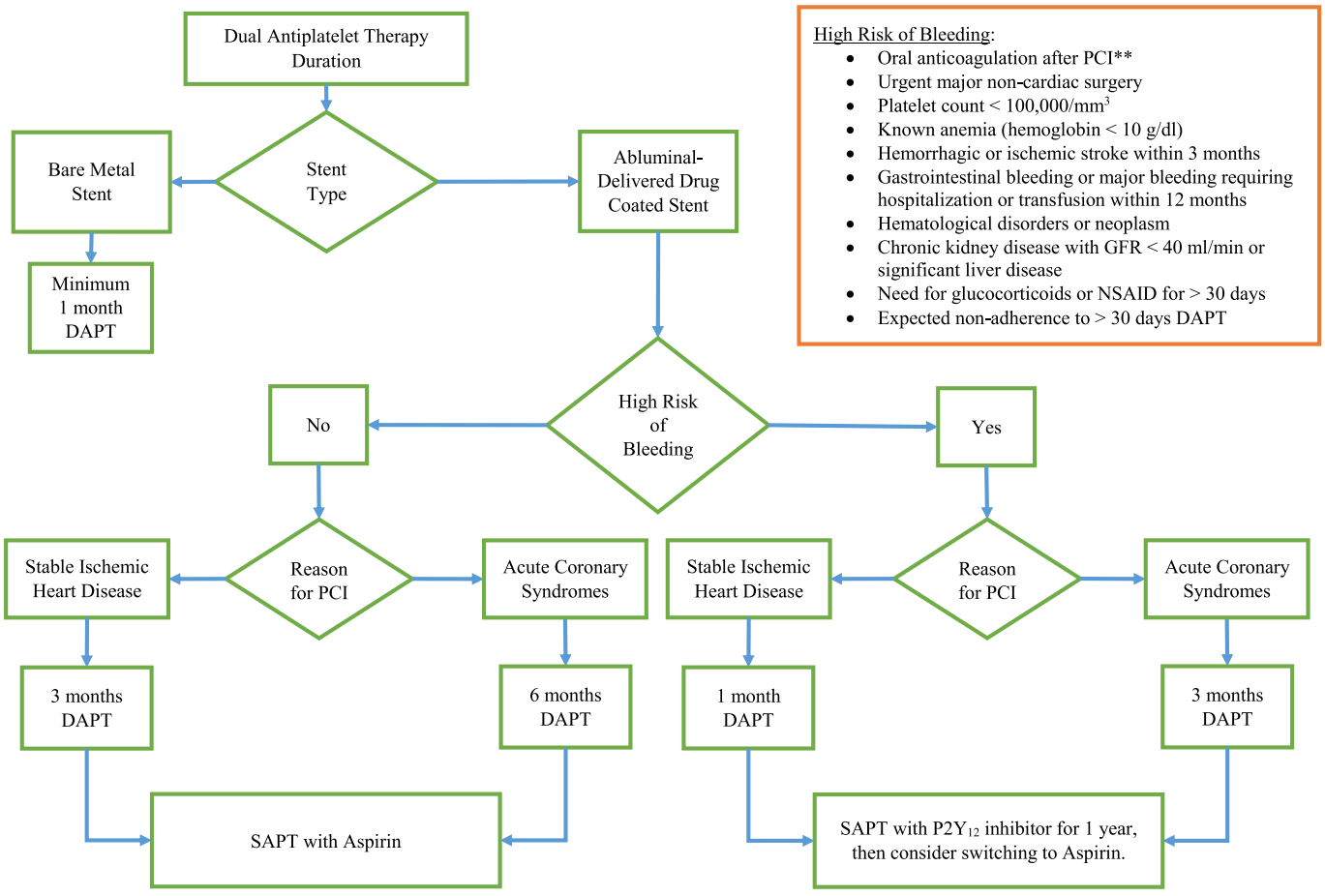

Fig. 1. Proposed algorithm of dual antiplatelet therapy (DAPT) duration followed by single antiplatelet therapy (SAPT) selection. **Patients on oral anticoagulation after PCI should be on $P2Y_{12}$ antagonist with full (>300 mg) Aspirin load at time of PCI; no triple therapy. Algorithm assumes newest generation drug eluting stent. High risk of bleeding criteria adapted from Godino et al. ULISSE subgroup analysis.

designed and deployed stents, up to three months of DAPT might be sufficient to prevent adverse outcomes and reduce bleeding risk.

Some of the highest risk patients in the ULISSE registry were on anticoagulation for atrial fibrillation, which coincides with recent studies evaluating similar patient populations. The PIONEER study suggests that combining traditional DAPT with warfarin results in increased risk of bleeding compared to a $P2Y_{12}$ inhibitor plus low dose rivaroxaban with similar efficacy [8]. The RE-DUAL PCI trial also showed reduced bleeding in those on dabigatran and a $P2Y_{12}$ inhibitor when compared with warfarin plus DAPT with no difference in the risk of thromboembolic events [9]. Finally, the AUGUSTUS trial also demonstrated that $P2Y_{12}$ monotherapy reduces bleeding [10]. These trials might pave the way not only for shorter DAPT, but also for $P2Y_{12}$ monotherapy in high-risk patients. This also begs the question as to what to do with long-term antiplatelet therapy in these anticoagulated patients once $P2Y_{12}$ therapy is no longer indicated – aspirin with anticoagulation or anticoagulation alone?

The authors of this editorial propose an updated treatment algorithm to guide the necessary duration of DAPT (Fig. 1). Subdivision of patients will occur first by stent type, then using the high risk of bleeding criteria adapted from Godino et al. and the LEADERS FREE trial [2,4], followed by separation by indication for PCI – stable versus unstable disease. Finally, we recommend switching patients to aspirin monotherapy – based mostly on convention and historical societal guidelines, yet begging for additional study – at one-year post PCI given that the long-term effects of $P2Y_{12}$ antagonists are unknown and notwithstanding a relative increase in cancer-related deaths in patients treated with extended DAPT.

In conclusion, the subgroup analysis of the ULISSE registry suggests similar rates of bleeding and TLF when comparing S-DAPT to R-DAPT in patients who received BP-SES. Given the small, non-randomized, retrospective nature of the study it should be viewed as hypothesis generating. Additional studies are required before S-DAPT treatment strategies become the standard of care in all patients. While momentarily detoured toward longer DAPT duration by recent data, the journey toward individualized DAPT appears to be headed back toward Ithaca.

References

[1] H.M. Krumholz, S.T. Normand, Y. Wang, Twenty-Year Trends in Outcomes for Older Adults With Acute Myocardial Infarction in the United States, JAMA Netw. Open 2 (3) (2019) e191938.
[2] C. Godino, A. Beneduce, G. Ferrante, et al., One-year clinical outcome of biodegradable polymer sirolimus-eluting stent in patients needing short dual antiplatelet therapy. Insight from the ULISSE registry (ULtimaster Italian multicenter all comerS Stent rEgistry), Int. J. Cardiol. 290 (2019) 52–58.
[3] B. Chevalier, P.C. Smits, D. Carrié, et al., Serial assessment of strut coverage of biodegradable polymer drug-eluting stent at 1, 2, and 3 months after stent implantation by optical frequency domain imaging, Circulation: Cardiovascular Interventions. 10 (12) (2017)https://doi.org/10.1161/circinterventions.116.004801.
[4] NEJM, Polymer-free drug-coated coronary stents in patients at high bleeding risk. N. Engl. J. Med. https://www.nejm.org/doi/full/10.1056/NEJMoa1503943. Accessed April 18, 2019.
[5] Bavry AA. One-Month Dual Antiplatelet Therapy Followed by Clopidogrel Monotherapy vs. Standard 12-Month Dual Antiplatelet Therapy with Clopidogrel After Drug-Eluting Stent Implantation. American College of Cardiology. https://www.acc.org/latest-in-cardiology/clinical-trials/2019/03/17/00/01/stopdapt-2. Published March 18, 2019. Accessed April 14, 2019.
[6] Y. Han, B. Xu, K. Xu, et al., Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent, Circulation:

Cardiovascular Interventions. 9 (2) (2016)https://doi.org/10.1161/circinterventions.115.003145.
[7] Kumbhani DJ. P2Y12 Inhibitor Monotherapy vs. Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention. American College of Cardiology. https://www.acc.org/latest-in-cardiology/clinical-trials/2019/03/17/00/03/smart-choice. Published March 21, 2019. Accessed April 14, 2019.
[8] C.M. Gibson, R. Mehran, C. Bode, et al., Prevention of bleeding in patients with atrial fibrillation undergoing PCI, N. Engl. J. Med. 375 (25) (2016) 2423–2434.
[9] C.P. Cannon, D.L. Bhatt, J. Oldgren, et al., Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation, N. Engl. J. Med. 377 (16) (2017) 1513–1524.
[10] NEJM. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N. Engl. J. Med. 380 (2019) 1509-1524.