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Dual Antiplatelet Therapy duration after percutaneous coronary intervention in High Bleeding Risk: a meta-analysis of randomized trials

Francesco Costa, MD, PhD,[1] Claudio Montalto, MD,[2] Mattia Branca, PhD,[3] Sung-Jin Hong, MD,[4] Hirotoshi Watanabe, MD,[5] Anna Franzone, MD,[6] Pascal Vranckx, MD, PhD,[7] Joo-Yong Hahn,[8] MD, Hyeon-Cheol Gwon, MD,[8] Fausto Feres, MD,[9] Yangsoo Jang, MD,[10] Giuseppe De Luca, MD, PhD,[11] Elvin Kedhi, MD, PhD[12] Davide Cao, MD,[13] Philippe Gabriel Steg, MD,[14] Deepak L. Bhatt, MD,[15] MPH, Gregg W. Stone, MD,[16] Antonio Micari, MD, PhD,[1] Stephan Windecker, MD,[17] Takeshi Kimura, MD,[5] Myeong-Ki Hong, MD,[4] Roxana Mehran, MD, PhD,[13] Marco Valgimigli, MD, PhD[18]

[1]Department of Biomedical and Dental Sciences and Morphological and Functional Imaging, University of Messina, A.O.U. Policlinic "G. Martino" Messina 98165, Italy

[2] De Gasperis Cardio Center, Interventional Cardiology Unit, Niguarda Hospital, Milan, Italy

[3] CTU Bern, University of Bern, Bern, Switzerland

[4] Severance Cardiovascular Hospital, Yonsei University Health System, Seoul, Korea

[5] Department of Cardiology, Hirakata Kohsai Hospital, Hirakata, Japan

[6] Department of Advanced Biomedical Sciences, Federico II University Hospital, 80131 Naples, Italy

[7] Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium; Faculty of Medicine and Life Sciences, University of Hasselt, Hasselt, Belgium

[8] Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[9] Istituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil

[10] Department of Cardiology, CHA Bundang Medical Center, Seongnam, Korea

[11] Clinical and Experimental Cardiology Unit, AOU Sassari, Italy

[12] Clinique Hopitaliere Erasme, Université Libre de Bruxelles, Brussels, Belgium

[13] Cardio Center, Humanitas Research Hospital IRCCS, Milan, Italy

[14] Université Paris-Cité, FACT, INSERM_U1148 and AP-HP, Hôpital Bichat, all in Paris, France

[15] Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA, USA

[16] The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai Hospital, New York, NY, USA

[17] Department of Cardiology, Inselspital, Bern University Hospital, Bern, Switzerland

[18] Cardiocentro Ticino Institute and Università della Svizzera Italiana (USI), Lugano, Switzerland

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Address for correspondence:

Francesco Costa MD, PhD
Interventional Cardiology Unit
Policlinico G. Martino, via C. Valeria 1, Messina, Italy
Phone: +39 (0)90 2212341
Fax: +39 (0)90 2212337
Email: fcosta@unime.it
Twitter handle: @Costa_F_8

Abstract:

Aims: The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in patients at high bleeding risk (HBR) is still debated. The current study, using the totality of existing evidence, evaluated the impact of an abbreviated DAPT regimen in HBR patients.

Methods and results: A systematic review and meta-analysis was performed to search randomized clinical trials comparing abbreviated (i.e., very-short [1 month] or short [3 months]) with standard (≥6 months) DAPT in HBR patients without indication for oral anticoagulation. A total of 11 trials, including 9,006 HBR patients, were included. Abbreviated DAPT reduced major or clinically relevant nonmajor bleeding (MCRB) (risk ratio [RR] 0.76, 95% CI 0.61–0.94; I2= 28%), major bleeding (RR 0.80, 95% CI 0.64–0.99, I2= 0%), and cardiovascular mortality (RR 0.79, 95% CI 0.65–0.95, I2= 0%) compared with standard DAPT. No difference in terms of all-cause mortality, MACE, myocardial infarction or stent thrombosis was observed. Results were consistent irrespective of HBR definition and clinical presentation.

Conclusion: In HBR patients undergoing PCI, a one- or three-month abbreviated DAPT regimen was associated with lower bleeding and cardiovascular mortality, without increasing ischemic events, compared with a ≥6 month DAPT regimen.

Keywords: Dual antiplatelet therapy, High Bleeding Risk, Percutaneous Coronary Intervention, Aspirin, P2Y12 inhibitor, Monotherapy

Study registration: PROSPERO registration number CRD42021284004

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor blocker is the standard antithrombotic treatment after percutaneous coronary intervention (PCI).[1,2] Yet, the optimal duration of treatment is still a matter of debate. DAPT has a narrow therapeutic window , as it is associated with a substantial increase of major bleeding as a function of its duration and composition.[1,2] It has been known for a decade that bleeding is not merely an inconvenience of antithrombotic therapy but carries important subsequent risks of adverse cardiac outcomes[3]: a bleeding complication has been associated with a 3 to 5-fold increase of subsequent mortality, and could easily offset the benefit of ischemic protection from prolonged DAPT. Preserving the balance between ischemic and bleeding risk during DAPT is even more challenging among patients at high bleeding risk (HBR). Roughly 1 in 3 patients undergoing PCI is at HBR, and these can be identified based on clinical features such as older age, lower haemoglobin, thrombocytopenia, renal insufficiency, cancer, prior stroke and bleeding history.[4] Importantly, HBR features are also associated with an increased ischemic risk, posing further challenges to the selection of optimal treatment duration.[5] International guidelines recommend standardized bleeding and ischemic risk evaluation to inform treatment decisions, favoring a more conservative approach in terms of therapy type or duration in HBR patients.[1,6,7] Previous studies have suggested that shortening DAPT to mainly 6 months in HBR patients may reduce bleeding without significant ischemic liability.[8] More recent studies have further assessed whether DAPT durations of 1 or 3 month(s) after PCI could improve the ischemic/bleeding trade-off compared with more prolonged regimens.[9,10]

The aim of the current study was to estimate the impact of an abbreviated DAPT (≤3 months) compared standard DAPT (for at least 6-months) after PCI in HBR patients, using the totality of available evidence from randomized clinical trials.

Methods:

Study selection, eligibility criteria and risk of bias:

Two authors (FC, CM) independently searched PubMed, Embase, BioMedCentral, Google Scholar, and the Cochrane Central Register of Controlled Trials for articles published between Jan 1, 2000, and Oct 31, 2021, using the following combinations of search keywords: 'percutaneous coronary intervention', 'PCI', 'coronary stenting', 'acute coronary syndrome', 'ACS', 'dual antiplatelet therapy', 'aspirin', 'clopidogrel', 'prasugrel', 'ticagrelor', 'P2Y12 inhibitor', 'monotherapy', 'dual antiplatelet therapy duration', 'high bleeding risk', 'HBR-ARC', 'PRECISE-DAPT', 'randomized trial'. The full search strategy is reported in **Supplementary Table 1**. Articles were initially screened by title and abstract content. In addition, the reference lists from all eligible studies were screened to identify any additional citations. Randomized clinical trials of patients treated with PCI who were randomized to abbreviated (≤3 months) or standard (≥6 months) DAPT durations, and reporting outcome data for bleeding and ischemic endpoints at a minimum follow-up of 12 months after enrollment were included. Patients' baseline characteristics and treatment outcomes of the subgroup of patients at HBR were obtained as aggregated data through the published literature or, if not available, upon direct request to the study principal investigators. [9–20] Studies including patients treated with OAC were excluded, whereas those that recruited patients with and without OAC (i.e. MASTER-DAPT trial), outcome data were selectively extracted for the latter population only. Events occurring during study phases investigating other treatment strategies than a DAPT duration comparison were censored (i.e. after 12 months from inclusion in the GLOBAL-LEADERS/GLASSY study).

In order to provide a homogenized definition for HBR patients, this was set in all studies according to a PRECISE-DAPT score ≥25, in keeping with current guidelines recommendations.[1,6,8] The present work was reported in accordance with the PRISMA and MOOSE guidelines.[21,22] PRISMA checklist is reported in **Supplementary Table 2**. Two authors (FC, CM) independently assessed the quality of studies and risk of bias according to the RoB-2

tool.[23] All clinical trials were approved by the ethics committees at each study centre, and all patients provided written informed consent. The study protocol is submitted to PROSPERO (CRD42021284004).

Study outcomes:

The co-primary safety and efficacy endpoints of this analysis were the occurrence of major or clinically relevant non-major bleedings (MCRB) and major adverse cardiovascular events (MACE) up to 12 months after PCI. MCRB were analyzed as reported by each individual study (**Supplementary Table 3)**. Two different composite endpoints of MACE of all-cause death, MI or stroke (i.e. MACE 1) and cardiovascular death, MI or stroke (i.e. MACE 2) have been reported. Other safety endpoints of major bleeding as per study definition as well as individual endpoints according to bleeding academic research consortium (BARC) and thrombosis in myocardial infarction (TIMI) bleeding definitions were also collected and analyzed.[24] Other efficacy endpoints including net adverse clinical events (NACE), all-cause death, cardiovascular death, MI, stroke and stent thrombosis were also separately appraised.

Statistical analysis:

For descriptive purposes, incidence rate from individual studies was log transformed and then pooled using a random-effects model with corresponding 95% confidence intervals (CI) adjusted according to the truncated Hartung-Knapp method with adhoc variance correction. Risk Ratios (RR) were used as summary statistics for outcomes of interest and were calculated using a random-effect model with 95% CI adjusted according to the truncated Hartung-Knapp method with adhoc variance correction.[25] Statistical heterogeneity of exposure was assessed by calculating the I2 index which summarizes the amount of variance between studies beyond chance. Heterogeneity was considered to be low if I2 <25%, moderate if I2 <75% and high if I2 >75%.[26] Publication bias was assessed for primary endpoints by visual inspection of funnel plots

and by Egger's and Begg's test.[27]

Several additional analyses were also planned and performed. First, considering the different design of the studies included, that performed randomization and started follow-up immediately after index PCI (i.e. treatment was similar in the two study arms in the first study period) or at the time of treatment divergence (**Supplementary Table 3**), a landmark analysis including only events occurring after treatment divergence in the two study arms was performed. Second, we explored treatment outcomes in studies with centrally adjudicated events only. For this analysis, we excluded the GLOBAL-LEADERS and included the GLASSY trial, which is a pre-specified sub study of the larger GLOBAL LEADERS trial, implementing independent central events adjudication, instead of investigator reported outcomes.[16] Third, we performed ad-hoc subgroup analysis for the type of drug-eluting stent (durable vs. biodegradable/no-polymer) used in the short DAPT arm, and post-hoc analyses according to clinical presentation, separately reporting treatment outcomes for patients presenting with acute coronary syndrome (ACS) or chronic coronary syndrome (CCS), and for the type of continuation therapy with either aspirin or a P2Y12i after short DAPT interruption. Subgroup analysis were performed using a fixed-effect plural model estimating subgroup difference with a Q-test. Ad-hoc sensitivity analysis using an alternative definition of HBR according to the originally proposed or adapted ARC-HBR consensus criteria was also performed.[4,10]

Statistical significance was set at p-value <0.05 (two-sided). Data analysis was performed in the R environment (R Foundation for Statistical Computing, Vienna, Austria; packages meta, metafor).

Results

Searching strategy and study flow diagram are presented in the **Supplementary Table 1-2 and Supplementary Figure 1** respectively. A total of 11 RCTs including 9,006 HBR patients (abbreviated DAPT, n=4,476 vs. standard DAPT, n=4,530) undergoing PCI with coronary

stenting were identified and included. An alternative definition for HBR according to the ARC-HBR definition was available in 7 of the 11 RCTs, with a total of 6,545 HBR patients (abbreviated DAPT, n=3,212 vs. standard DAPT, n=3,333). The main characteristics of the included studies are shown in **Table 1**. Further details on study inclusion/exclusion criteria and clinical endpoints are reported in **Supplementary Table 3 and 4.** Baseline characteristics are presented in **Table 2**: 40% of patients were women, and 58% presented with ACS; drug-eluting stents were used in all patients; complex PCI characteristics such as multivessel PCI and left main PCI were present in 26% and 3.9% of patients respectively. Study quality was high across all included studies (**Supplementary Table 5**).

Bleeding endpoints

The rate of MCRB and major bleeding at 12 months in the control group was 6.07% (95%CI 4.58% to 8.03%) and 3.63% (95%CI 2.40% to 5.49%), respectively in the PRECISE-DAPT identified HBR population. Abbreviated DAPT significantly reduced both MCRB (RR 0.76, 95% CI 0.61–0.94; I2 = 28%)(**Figure 1 and Figure 2A**), and major bleeding (RR 0.80, 95% CI 0.64–0.99; I2 = 0%)(**Figure 1 and Figure 2B**) compared with standard DAPT regimen.

These results were consistent using TIMI or BARC bleeding definitions (**Supplementary Figure 2 and 3)**. The risk of fatal bleeding did not differ (RR 0.63, 95% CI 0.24–1.70; I2 = 0%) (**Figure 1**). Funnel plots for bleeding endpoints are presented in **Supplementary Figure 4 A-B**.

At landmark analysis accounting only for events occurring after treatment divergence in the two study arms, MCRB (RR 0.69, 95% CI 0.57–0.85; I2 = 0%) and major bleeding (RR 0.73, 95% CI 0.53–1.01; I2 = 6%) were lower with abbreviated compared with standard DAPT (**Figure 3**).

The rate of MCRB and major bleeding at 12 months in the control group was 5.32% (95%CI 3.54% to 7.98%) and 3.10% (95%CI 2.23% to 4.30%), respectively in the ARC-HBR identified HBR population. Abbreviated DAPT significantly reduced both MCRB (RR 0.52, 95% CI 0.35–0.77; I2 = 18%) and major bleeding (RR 0.47, 95% CI 0.24–0.91; I2 = 32%) compared with a

standard DAPT regimen also in the ARC-HBR identified HBR population. (**Figure 4A-B**).

Ischemic endpoints

No significant difference for composite efficacy endpoints of all-cause death, MI and stroke (i.e. MACE 1) (RR 0.97, 95% CI 0.74–1.26; I2 = 38%) or cardiovascular death, MI and stroke (i.e. MACE 2) (RR 0.92, 95% CI 0.77–1.10; I2 = 0%) was observed between abbreviated and standard DAPT regimens (**Figure 1 and Figure 2C-D**). Cardiovascular mortality was significantly lower in HBR patients with abbreviated compared with standard DAPT regimens (RR 0.79, 95% CI 0.65–0.95; I2 = 0%), whereas all-cause mortality did not differ (RR 0.91, 95% CI 0.68–1.23; I2 = 24%) (**Figure 1 and Figure 2E-F**). Similarly, definite stent thrombosis, definite or probable stent thrombosis, MI or stroke rates were similar with abbreviated compared with standard DAPT (**Figure 1 and Supplementary Figure 5**). Funnel plots for ischemic endpoints are presented in **Supplementary Figure 4 C-D**.

At landmark analysis, accounting only for events which occurred during the SAPT versus DAPT phases of the included studies, MACE 1 and MACE 2 were similar in the two treatment arms (**Figure 3**). Consistent results for the ischemic endpoints were observed in the ARC-HBR identified HBR population (**Figure 4**).

Sensitivity analyses

Leave-one-out study analyses for MCRB, major bleeding and MACE are presented in **Supplementary Table 6**. When only studies with central events adjudication were included, results remained consistent to the main analysis, confirming lower MCRB (RR 0.73, 95% CI 0.61–0.87; I2 = 0%), major bleeding (RR 0.79, 95% CI 0.62–0.99; I2 = 0%) and cardiovascular death (RR 0.81, 95% CI 0.66–0.99; I2 = 0%) with abbreviated DAPT, and no difference in MACE according to multiple definitions (**Supplementary Figure 6**).

Subgroup analyses:

Subgroup analysis according to clinical presentation, type of antiplatelet therapy continuation after short DAPT discontinuation and type of drug eluting stent implanted were performed. Abbreviated DAPT was associated with a reduction of MCRB and major bleeding irrespective of clinical presentation (test for subgroup differences in MCRB: $p_{int} = 0.62$;– test for subgroup differences in major bleeding: $p_{int} = 0.17$) (**Figure 5**). No difference was observed between abbreviated and standard DAPT irrespective of clinical presentation with respect to MACE 1 ($p_{int} = 0.70$) or MACE 2 ($p_{int} = 0.91$) definitions (**Figure 5**). Treatment effect was similar, irrespective of clinical presentation, also for the other reported endpoints.

With respect to type of antiplatelet therapy administered after short DAPT discontinuation, abbreviated DAPT was consistently associated with lower MCRB and major bleeding in patients who continued aspirin or a P2Y12i after DAPT discontinuation (test for subgroup differences in MCRB: $p_{int} = 0.43$ – test for subgroup differences in major bleeding: $p_{int} = 0.83$), with no difference for MACE 1 ($p_{int} = 0.55$), MACE 2 ($p_{int} = 0.59$) or other explored endpoints (**Supplementary Figure 7**).

The subgroup analysis according to the type of drug-eluting stent (DES) implanted in the experimental arm showed that abbreviated DAPT was associated with a borderline interaction for MCRB ($p_{int} = 0.06$) and a significant quantitative interaction for major bleeding ($p_{int} = 0.02$), whereas a borderline qualitative interaction for MACE 1 ($p_{int} = 0.12$) and all-cause mortality ($p_{int} = 0.08$), but not for MACE 2 ($p_{int} = 0.23$) and cardiovascular mortality ($p_{int} = 0.85$) was observed (**Supplementary Figure 8**).

Discussion

The main findings of the present analysis are summarized as follows:

- Abbreviated DAPT for one or three-month was associated with lower major or clinically relevant nonmajor bleeding, major bleeding and cardiovascular mortality compared to

standard DAPT in HBR patients treated with PCI.

- Abbreviated DAPT was similarly effective compared with standard DAPT for the prevention of MACE, stent thrombosis and other ischemic events, irrespective of clinical presentation and type of antiplatelet agent administered after short DAPT discontinuation.
- These findings remained consistent irrespective of the HBR definition, either based on PRECISE-DAPT score or the ARC-HBR framework, as endorsed by guidelines.

The present collaborative meta-analysis including data from all-randomized trials available in the field, is the largest source of information to date for HBR patients, enabling greater statistical power to assess safety and effectiveness of an abbreviated DAPT course compared with a standard DAPT regimen for this selected patient population. Compared with prior studies, the current analysis has the strength of exclusively including data from randomized clinical trials, avoiding potential biases introduced by observational data. In addition, data of relevant subgroups were obtained, which allowed assessing the effect of an abbreviated DAPT with respect to clinical presentation. Finally, a landmark analysis was performed, censoring all events occurring during the initial DAPT phase and accounting only for events occurring after the treatment differed in the two study groups, and confirms the robustness of the observations in the main analysis.

Current guidelines recommend 3 or 6 months DAPT in HBR patients undergoing PCI for ACS or CCS, based on prior RCT, or even shorter treatment courses, based on consensus opinion.[1,6] Recently, the MASTER-DAPT was the first randomized trial to demonstrate that among HBR patients undergoing coronary stenting with a bioresorbable polymer-based sirolimus-eluting stent, abbreviating DAPT to 1 month, was non-inferior to a standard DAPT for 6 months or more in terms of net adverse clinical events or major adverse cardiac or cerebral event, and superior

in terms of MCRB.[10] Another recent analysis of the XIENCE 28 and XIENCE 90 studies, compared, through propensity-stratified analyses, the outcomes of HBR patients treated with one-month or three-months DAPT after PCI with a durable polymer everolimus-eluting stent. No difference for any of the ischemic endpoints explored was observed, including stent thrombosis, which was low in both DAPT treatment arms.[28] In line with these studies, the current meta-analysis confirmed, with a higher level of precision, that an abbreviated DAPT reduces bleeding, with a favorable impact on cardiovascular mortality, and was not associated with higher risk of ischemic events. Hence, the current study reinforces the position held by guidelines that DAPT duration should be minimized to 1 and up to 3 months in HBR patients.[1,6]

An important clinical conundrum is the optimal DAPT duration in patients who are both HBR and at high ischemic risk, such as those presenting with ACS. The recent STOP-DAPT2-ACS, that randomized 4,136 patients to 1-2 months DAPT or a longer DAPT course for 12 months after PCI for ACS, and who were not selected based on HBR criteria, failed to demonstrate the noninferiority of the abbreviated DAPT regimen for the primary endpoint of net adverse clinical events.[18] While a significant reduction of bleeding events was observed in the shorter DAPT arm, a numerical increase of ischemic events raised concern about the feasibility of a very-short DAPT in ACS patients, followed by clopidogrel monotherapy.[18] Whether HBR status modify these outcomes, and what should be the best strategy in patients both at high risk of ischemic and bleeding events was an important gap in evidence. A prior analysis suggested that despite the concomitant presence of high ischemic risk features, such as complex PCI or ACS, a shorter treatment with DAPT for 3-6 months was associated with superior net clinical benefit in HBR.[5] Current meta-analysis extends these findings showing that further reducing DAPT to one- or three- month(s) after coronary stenting in HBR patients is beneficial, with a reduction of adverse events and no additional ischemic liability in the ACS subgroup. This finding reinforces

the concept that DAPT duration should be adjusted based on patients' characteristics, and that bleeding rather than ischemic risk should be prioritized in HBR patients.[5]

Major bleeding is associated with an immediate and sustained increased risk of mortality, similar or greater than recurrent myocardial infarction, and this is of even greater relevance among HBR patients in whom these complications are more frequent.[29] We observed that abbreviated DAPT was associated with lower cardiovascular mortality. This is in line with prior results of the CHARISMA trial in which a prolonged DAPT course in asymptomatic patients was associated with more than 3-fold increased MI risk and cardiovascular death.[30] Apart from the direct fatal consequences of bleeding in critical organs, such as intracranial hemorrhage, qualifying for cardiovascular death adjudication, multiple indirect pathways effecting the cardiovascular system could justify bleeding related mortality. Bleeding reduces blood oxygen carrying/delivery capacity leading to myocardial hypoperfusion, precipitating myocardial ischemia, and is associated to increased platelet activation and aggregability which may predispose to coronary thrombotic events.[31] In addition, blood transfusion could further worsen these conditions, as stored red blood cells have reduced deformability, reduced nitrous oxide delivery, which may promote vasoconstriction and microvascular plugging worsening myocardial ischemia.[32]

Importantly, bleeding events could have a negative impact on drug adherence, with the sudden disruption of key treatments such as antiplatelet agents, β-blockers and statin which may result in ischemic complications.[33] The PARIS study showed that an early discontinuation of antiplatelet agents was not associated to an excess of ischemic events when the decision was coordinated by the treating physician.[34] Instead, when DAPT was suddenly disrupted, as in the case of major bleeding, there was a dramatic increase of coronary ischemic events.[34] Interestingly, this pattern was evident in both HBR or non-HBR patients.[35] Finally, an excessive antithrombotic treatment in HBR patients may potentially trigger cardiovascular events in multiple districts through atherosclerotic plaque hemorrhage.[36]

Antiplatelet therapy has a key role in preventing both stent thrombosis and spontaneous atherothrombotic events in other non-stented coronary segments.[1] The introduction of refined DES platforms with thinner struts and more biocompatible polymers drastically reduced the risk of stent thrombosis allowing progressively shorter DAPT treatment. Contemporary generation DES with either durable or bioresorbable polymers or no polymer have demonstrated low rates of ischemic MACE in HBR patients despite very short DAPT, with consistently improved outcomes compared with bare metal stents.[37–39] Whether DES efficacy in an abbreviated DAPT setting is device- or class-specific remains unclear, and confirmation of each device performance is warranted. In the current meta-analysis, we observed a trend towards better response to abbreviated DAPT for all-cause death and ischemic events in the subgroup of patients treated with bioresorbable or no-polymer DES. While this limited evidence for a possible stent type and DAPT duration interaction is merely hypothesis generating, it may suggest that biodegradable/no-polymer stents, with a reduced time-exposure to the potentially thrombogenic polymer material might be safer in an abbreviated DAPT environment. Yet, this observation needs confirmation in dedicated randomized studies.

The type of antiplatelet drug to be maintained after DAPT discontinuation is also a matter of debate. While aspirin was traditionally the treatment of choice after DAPT discontinuation and was recommended indefinitely for secondary prevention, several studies have challenged this practice, by testing a P2Y12 inhibitor monotherapy after a short course of DAPT.[9,15] Abbreviated DAPT followed by P2Y12 inhibitor monotherapy was associated with a reduction of major bleeding compared with prolonged DAPT.[40] In the current meta-analysis, no difference in terms of bleeding and ischemic protection by continuing single anti-platelet therapy with either aspirin or a P2Y12 receptor blocker was observed, confirming the feasibility of both strategies in HBR patients after an abbreviated DAPT course. These results are in line with prior studies that showed no difference among aspirin and a P2Y12 inhibitor in terms of bleeding during single

antiplatelet therapy.[41,42] However, given the short follow-up in the current study, the ability to observe a longer-term difference between the two single antiplatelet therapy treatment strategies is limited. The CAPRIE trial showed a modest 8.7% relative reduction of ischemic events with clopidogrel monotherapy compared to a single antiplatelet therapy with aspirin for secondary prevention in patients with established vascular disease, with greater benefit in higher risk subgroups, such as those with diabetes.[43] These results were also confirmed in a meta-analysis of 42,108 patients that observed a 19% risk reduction of myocardial infarction with P2Y12 inhibitor monotherapy compared to aspirin, with similar odds for stroke, all-cause and vascular death.[42] The HOST-EXAM trial showed that clopidogrel, compared to aspirin monotherapy, during the maintenance period after PCI, reduced the risk of the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to ACS, or BARC type 3 or greater bleeding by 27%, with a positive impact on both ischemic and bleeding risk.[44] Therefore, P2Y12 inhibitor monotherapy appears promising alternative to long-term treatment strategy after PCI. Based on the present analysis, the optimal antiplatelet monotherapy type for long-term risk prevention, that maximizes ischemic and bleeding risk in HBR patients after an initial short course of DAPT, remains unclear and further studies are needed in this field.

Limitations

Several important limitations of this analysis should be acknowledged.

First, the present aggregated-study meta-analysis cannot overcome the limitations from each individual trial, as for instance the lack of a placebo-controlled design in the majority of studies included. Nevertheless, study quality was high with blinded adjudication of events by an independent clinical event committee assuring low probability of performance bias.

Second, abbreviated DAPT entailed different types of single antiplatelet therapy upon DAPT withdrawal (i.e. aspirin, clopidogrel, prasugrel or ticagrelor monotherapy) which in some instances were based on physician preference.[10,13] We tried to overcome this limitation with a

dedicated subgroup analysis that explored statistical heterogeneity for a continuation with aspirin or a P2Y12 inhibitor. A more granular evaluation based on the type of P2Y12 inhibitor used (i.e. clopidogrel, prasugrel or ticagrelor) would have been desirable but not applicable in our case. As the choice of the P2Y12 inhibitor type was not randomized and based on physician preference the impact of unmeasured confounders would bias this comparison. However, in the current study that entailed a randomized DAPT duration, P2Y12i type was balanced in the two treatment arms, limiting the potential of this element to bias the study results. A prior analysis showed that P2Y12i monotherapy continuation with either ticagrelor or clopidogrel after short DAPT provided consistent results versus DAPT continuation up to 15 months.[45] Yet, dedicated randomized clinical trials to test the impact of different antiplatelet monotherapy types in this setting will be useful in the future.

Third, specific HBR features (e.g. history of prior intracranial bleeding, recent prior stroke, active bleeding or bleeding within 1-2 months from study inclusion) were exclusion criteria in many of the included studies. Yet, the application of two standardized and guideline-endorsed bleeding definitions for HBR identification yielded consistent results.[4,8] Need for urgent surgery, another element proposed in the HBR-ARC definition, was also an exclusion criterion in many of these trials, therefore our results cannot be extended to this patient population. Patients with OAC were also excluded from the current analysis despite being a recognized HBR criterion.[4] While concurrent treatment with OAC is frequent, presenting in up to 10% of patients undergoing PCI, OAC per se is different from other HBR criteria.[4] OAC drives a higher risk for bleeding due to its biological effect on systemic coagulation, but it also affect the ischemic risk, reducing the risk of stent-related and non-stent related ischemic events.[46] In this regard, current treatment recommendation for OAC patients undergoing PCI diverge from those in the general PCI population: in the European guidelines peri-procedural treatment with DAPT followed immediately after by P2Y12 inhibitor monotherapy is recommended for OAC patients whereas such an approach has not been tested in randomized studies in patients without indication for

OAC;[47] in addition, while PCI patients generally are treated with single antiplatelet therapy indefinitely after stenting, lifelong antiplatelet therapy is not recommended in most OAC patients due to the high bleeding risk from this combination.[48] Thus, DAPT duration recommendations in OAC-treated patients should be derived from separate study meta-analyses.

Fourth, randomized clinical trials, with their inherent higher selection based on protocol inclusion/exclusion criteria, tend to select a lower risk population compared with real-world patients. Yet, conclusion derived from observational data are limited by unmeasured confounders, hence in order to evaluate the impact of DAPT duration, randomized trials are needed for unbiased estimates.

Fifth, treatment decision of DAPT duration in patients with prior stent thrombosis is currently a clinical conundrum. Stent thrombosis was an exclusion criterion in many PCI trials, and since these events are rare, especially with modern DES, clinical decisions in this setting are uncertain.

Finally, we did not prespecify to assess the consistency of the treatment effects of a short versus standard DAPT regimen in patients who underwent complex PCI. However, subgroup analyses from some of the included studies yielded reassuring results.[49,50]

Conclusions

In the present large-scale, collaborative meta-analysis based on the totality of the available evidence for HBR patients undergoing PCI, an abbreviated DAPT regimen of either 1 or 3 month(s), followed by single antiplatelet therapy, was associated with lower bleeding, with a favorable effect on cardiovascular mortality, without increasing ischemic events or stent thrombosis. One-month or three-month DAPT courses after PCI appears an appealing treatment option in HBR patients to optimize outcomes. Further studies are required to determine how to individualize the decision between 1-month and 3-month DAPT, and the role of single antiplatelet therapy after DAPT.

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Figure Legend:

Structured Graphical Abstract. Impact of abbreviated vs. standard DAPT in patients at high bleeding risk undergoing coronary stenting.

Figure 1. Forest plot for the explored clinical endpoints comparing abbreviated vs. standard dual antiplatelet therapy duration. Relative risks for the random-effects model are presented. CI: Confidence Interval; DAPT: Dual Antiplatelet Therapy.

Figure 2. Forest plot for individual endpoints. Major or clinically relevant non-major bleeding (A); Major Bleeding (B); All-cause death, myocardial infarction or stroke (MACE 1)(C) cardiovascular death, myocardial infarction or stroke (MACE 2)(D), all-cause death (E) and cardiovascular death (F). CI: Confidence Interval; RR: Relative Risk.

Figure 3. Landmark analysis for clinical events occurring after treatment divergence in the two study arms. Relative risks for the random-effects model are presented. CI: Confidence Interval; DAPT: Dual Antiplatelet Therapy.

Figure 4. Forest plot for individual endpoints in the Academic Research Consortium High Bleeding Risk (ARC-HBR) identified high bleeding risk population. Major or clinically relevant non-major bleeding (A); Major Bleeding (B); Major Adverse Cardiovascular Events (C) Net Adverse Clinical Events (D), All-cause death (E) and Cardiovascular death (F). CI: Confidence Interval; RR: Relative Risk.

Figure 5. Subgroup analysis based on clinical presentation at the time of percutaneous coronary intervention. Treatment effects and interaction p values are presented for subgroups of patients with acute coronary syndrome and chronic coronary syndrome.
Relative risks and interaction testing for the random-effects model are presented. CV: cardiovascular; MACE: major adverse cardiovascular events; MB: major bleeding; MCRB: major or clinically relevant non-major bleeding; NACE: net adverse clinical events;