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AUTHOR(S):

Watanabe, Hirotoshi; Domei, Takenori; Morimoto, Takeshi; Natsuaki, Masahiro; Shiomi, Hiroki; Toyota, Toshiaki; Ohya, Masanobu; ... Furukawa, Yutaka; Nakagawa, Yoshihisa; Kimura, Takeshi

CITATION:

Watanabe, Hirotoshi ...[et al]. Details on the effect of very short dual antiplatelet therapy after drug-eluting stent implantation in patients with high bleeding risk: insight from the STOPDAPT-2 trial. Cardiovascular intervention and therapeutics 2021, 36: 91-103

ISSUE DATE:

2021

URL:

http://hdl.handle.net/2433/261812

Details on the Effect of Very Short Dual Antiplatelet Therapy after Drug-eluting Stent Implantation in Patients with High Bleeding Risk; Insight from the STOPDAPT-2 Trial

First author: Hirotoshi Watanabe, H.W.

Short title: Detail of STOPDAPT-2 HBR subgroup analysis

Hirotoshi Watanabe[1], MD; Takenori Domei[2], MD; Takeshi Morimoto[3], MD; Masahiro Natsuaki[4], MD; Hiroki Shiomi[1], MD; Toshiaki Toyota[5], MD; Masanobu Ohya[6], MD; Satoru Suwa[7], MD; Kensuke Takagi[8], MD; Mamoru Nanasato[9], MD; Yoshiki Hata[10], MD; Masahiro Yagi[11], MD; Nobuhiro Suematsu[12], MD; Takafumi Yokomatsu[13], MD; Itaru Takamisawa[9], MD; Masayuki Doi[14], MD; Toshiyuki Noda[15], MD; Hideki Okayama[16], MD; Yoshitane Seino[17], MD; Tomohisa Tada[18], MD; Hiroki Sakamoto[18], MD; Kiyoshi Hibi[19], MD; Mitsuru Abe[20], MD; Kazuya Kawai[21], MD; Koichi Nakao[22], MD; Kenji Ando[2], MD; Kengo Tanabe[23], MD; Yuji Ikari[24], MD; Keiichi Igarashi Hanaoka[25], MD; Yoshihiro Morino[26], MD; Ken Kozuma[27], MD; Kazushige Kadota[6], MD; Yutaka Furukawa[5], MD; Yoshihisa Nakagawa[28], MD; and

Takeshi Kimura[1], MD. On behalf of the STOPDAPT-2 investigators.

Affiliations

[1]Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. [2]Department of Cardiology, Kokura Memorial Hospital, Kitakyusyu, Japan. [3]Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan. [4]Department of Cardiovascular Medicine, Saga University, Saga, Japan. [5]Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan. [6]Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan. [7]Department of Cardiology, Juntendo University Shizuoka Hospital, Izunokuni, Japan. [8]Department of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan. [9]Department of Cardiology, Sakakibara Heart Institute, Fuchu, Japan. [10]Department of Cardiology, Minamino Cardiovascular Hospital, Hachioji, Japan. [11]Department of Cardiology, Sendai Cardiovascular Center, Sendai, Japan. [12]Department of Cardiology, Saiseikai Fukuoka General Hospital, Fukuoka, Japan. [13]Department of Cardiology, Mitsubishi Kyoto Hospital, Kyoto, Japan. [14]Department of Cardiology, Kagawa Prefectural Central Hospital, Takamatsu, Japan. [15]Department of Cardiology, Gifu Prefectural General Medical Center, Gifu, Japan. [16]Department of Cardiology,

Ehime Prefectural Central Hospital, Matsuyama, Japan. [17]Department of Cardiology, Hoshi General Hospital, Koriyama, Japan. [18]Department of Cardiology, Shizuoka General Hospital, Shizuoka, Japan. [19]Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan. [20]Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan. [21]Department of Cardiology, Chikamori Hospital, Kochi, Japan. [22]Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, Kumamoto, Japan. [23]Division of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan. [24]Department of Cardiology, Tokai University Hospital, Isehara, Japan. [25]Hanaoka Seishu Memorial Cardiovascular Clinic, Sapporo, Japan. [26]Department of Cardiology, Iwate Medical University Hospital, Morioka, Japan. [27]Department of Cardiology, Teikyo University Hospital, Tokyo, Japan. [28]Department of Cardiovascular Medicine, Shiga University of Medical Science, Otsu, Japan.

Correspondence to: Takeshi Kimura

Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine

54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507 Japan

TEL: +81-75-751-4254 FAX: +81-75-751-3289

Email: taketaka@kuhp.kyoto-u.ac.jp

Total Word Counts: 5862 words

(Title 25; Abstract 245; Text and Acknowledgement 2969; and Reference, Legends, Tables 2623)

Journal Subject Terms: antiplatelet therapy; high bleeding risk; coronary artery disease; percutaneous coronary intervention.

Funding: STOPDAPT-2 is funded by Abbott Vascular Japan, Co., Ltd

Abstract

Previously we briefly reported the effect of 1-month dual antiplatelet therapy (DAPT) for patients with high bleeding risk (HBR) receiving percutaneous coronary intervention (PCI) in the STOPDAPT-2 trial, but full analysis data has not been available. We conducted post-hoc subgroup analysis regarding the effect of very short DAPT for HBR patients in STOPDAPT-2 trial. The primary endpoint was a 1-year composite of cardiovascular (cardiovascular death, myocardial infarction, definite stent thrombosis, or stroke) and bleeding (TIMI major/minor bleeding) outcomes. Major secondary endpoints were 1-year cardiovascular composite endpoint and bleeding endpoint. HBR was defined by the academic research consortium (ARC) HBR criteria. Among the 3009 study patients, 1054 (35.0%) were classified as HBR and 1955 (65.0%) were as non-HBR. There were no significant interactions between HBR/non-HBR subgroups and the assigned DAPT group on the primary endpoint (HBR; 3.48% vs. 5.98%, HR 0.57, 95%CI 0.32-1.03, and non-HBR; 1.81% vs. 2.36%, HR 0.78, 95%CI 0.42-1.45; P for interaction=0.48), the major secondary cardiovascular endpoint (HBR; 3.07% vs. 4.03%, HR 0.77, 95%CI 0.40-1.48, and non-HBR; 1.41% vs. 1.61%, HR 0.89, 95%CI 0.43-1.84; P for interaction=0.77), and the major secondary bleeding endpoint (HBR; 0.41% vs. 2.71%, HR 0.15, 95%CI 0.03-0.65, and

non-HBR; 0.40% vs. 0.85%, HR 0.48, 95%CI 0.14-1.58; P for interaction=0.22). In conclusion, the effects of 1-month DAPT for the primary and major secondary endpoints were consistent in HBR and non-HBR patients without any significant interactions. The benefit of 1-month DAPT in reducing major bleeding was numerically greater in HBR patients.

(245/250 words)

Keywords: antiplatelet therapy, coronary stent, bleeding, high bleeding risk, and percutaneous coronary intervention.

Clinical trial registration: Short and Optimal duration of Dual Antiplatelet Therapy after everolimus-eluting cobalt-chromium stent-2 [STOPDAPT-2]; NCT02619760

TEXT

The current US and European guidelines recommend DAPT for at least 12 months in acute coronary syndrome, and for at least 6 months in stable coronary artery disease, if not at high bleeding risk (HBR)[1,2]. In HBR patients, the updated European guideline recommended shorter DAPT for 6 months in acute coronary syndrome and for 1 month in stable coronary artery disease[2]. There were 3 clinical trials comparing different devices with abbreviated DAPT durations targeting HBR patients, such as LEADERS FREE (the Prospective randomized comparison of the BioFreedom biolimus A9 drug-coated stent versus the gazelle BMS in patients at high bleeding risk), ZEUS (The Zotarolimus- eluting Endeavor sprint stent in Uncertain DES Candidates), and SENIOR (SYNERGY II Everolimus elutiNg stent In patients Older than 75 years under-going coronary Revascularization associated with a short dual antiplatelet therapy)[3-5]. However, no previous study has compared different DAPT durations in HBR patients, and thus, the optimal DAPT duration after PCI using DES in HBR patients has not been yet adequately defined. We previously reported the result of the STOPDAPT-2 (Short and optimal duration of dual antiplatelet therapy after everolimus-eluting cobalt-chromium stent) trial, and the result showed the benefit of 1-month DAPT over 12-month DAPT with reduction of bleeding events without increase in

cardiovascular events in an all-comer population[6]. This strategy might be particularly beneficial in HBR patients to reduce bleeding events. Therefore, we conducted a post-hoc subgroup analysis of the STOPDAPT-2 trial based on the recently proposed ARC (academic research consortium) HBR criteria[7]. Recently, we published a brief report of this STOPDAPT-2 HBR substudy[8]. However, the important information, whole baseline characteristics and outcomes or time-to-event curves were missing in the brief report, and herein, we report the full analysis data and the additional analysis about the bleeding site and provide further discussion.

Methods

Study population

STOPDAPT-2 is a prospective, multicenter, open-label, adjudicator blinded randomized clinical trial conducted in Japan. The main objective of the STOPDAPT-2 study was to test the non-inferiority of 1 month of DAPT followed by clopidogrel monotherapy compared to 12 months of DAPT with aspirin and clopidogrel in terms of the primary cardiovascular and bleeding composite endpoint in patients receiving PCI with exclusive use of cobalt-chromium everolimus-eluting stent (CoCr-EES). The design, patient enrollment,

and main results at 1-year follow-up of the STOPDAPT-2 were previously reported in detail[6]. In brief, a total of 3045 patients with successful CoCr-EES implantation and without the plan of staged procedure were enrolled and randomized in a 1-to-1 ratio either to the 1-month DAPT group or 12-month DAPT group. During the initial 1-month (30- to 59-day), all the patients were to receive DAPT with aspirin 81-200 mg/day and P2Y12 receptor blockers (clopidogrel 75mg/day or prasugrel 3.75 mg/day at the discretion of the attending physicians). In the 1-month DAPT group, antiplatelet therapy was switched to clopidogrel monotherapy at 1-month, while in the 12-month DAPT group, patients were to receive DAPT with aspirin and clopidogrel up to 12-month. The study basically adopted an “all-comer” design with exclusion criteria limited only to the use of oral anticoagulants, history of intracranial hemorrhage, or known intolerance to clopidogrel. After exclusion of 36 participants who withdrew consent, the final analysis set included 3009 patients comprising 1500 patients in the 1-month DAPT group and 1509 patients in the 12-month DAPT group (Figure 1). Kyoto University Certified Review Board approved the study protocol and written informed consents were obtained from all patients.

Application of ARC-HBR definition

In the present analysis, patients were divided into HBR or non-HBR based on the ARC-HBR definitions[7]. Patients were regarded as HBR if having at least one major criterion or two minor criteria. We modified the ARC-HBR definitions, because some criteria of ARC-HBR were not exactly captured in the STOPDAPT-2 trial; medication of oral anticoagulants at discharge from the index hospitalization was regarded as major criterion of long-term oral anticoagulation. The usage of oral anticoagulants was one of the exclusion criteria, but some patients receiving anticoagulation were enrolled (protocol violation) and included in analysis; all previous bleeding history was regarded as minor criterion, because we did not have information on the timing, requirement of hospitalization or transfusion, and recurrence for previous history of spontaneous bleeding; liver cirrhosis was considered as major criterion regardless of the presence of portal hypertension; malignancy was excluded from the criteria for HBR, because we did not have information whether it was active or not; history of stroke was regarded as minor criterion, because we did not have information on its timing; history of intracranial bleeding was regarded as major criteria regardless of its etiology, although we did not have information whether it was traumatic or spontaneous; planned major surgery was included as major criteria, regardless of whether the procedure was deferrable or

not. The information on bleeding diathesis, brain arterio-venous malformation, and recent major trauma or surgery (major criteria), use of non-steroid anti-inflammatory drugs or steroids (minor criteria) were not captured in this trial, and these criteria were regarded as absent. There were missing values for serum creatinine in 10 patients, for platelet counts in 11 patients, and for hemoglobin in 6 patients, and these patients were regarded as not having those HBR criteria such as chronic kidney disease, thrombocytopenia, and anemia.

We also assessed thrombotic and bleeding risks of the individual patients by using the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) thrombotic/bleeding risk scores, and Coronary REvascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) thrombotic/bleeding risk scores[9,10]. Further, we also evaluated the high-risk features of stent-driven recurrent ischemia derived from the 2017 European Society of Cardiology (ESC) focused update on DAPT[2].

Outcome measures and definitions

The primary endpoint of the STOPDAPT-2 was a composite of cardiovascular and bleeding outcomes, that is a composite of death from cardiovascular cause, myocardial infarction (MI), definite stent thrombosis, ischemic or hemorrhagic stroke, and bleeding

defined as Thrombolysis in Myocardial Infarction (TIMI) major or minor criteria[11]. The major secondary cardiovascular endpoint was a composite of death from cardiovascular cause, MI, definite stent thrombosis, and ischemic or hemorrhagic stroke, and the major secondary bleeding endpoint was the bleeding defined as TIMI major or minor. Other secondary endpoints were described in the supplemental appendix. Bleeding events were also adjudicated and classified with the Bleeding Academic Research Consortium (BARC) criteria or Global Utilization of Streptokinase and TPA For Occluded Arteries (GUSTO), and classified by locations or causes (intracranial, gastrointestinal, related with surgery, or others)[12,13]. The definitions of MI, and stent thrombosis were derived from ARC, and stroke was adjudicated if the neurological dysfunction lasted longer than 24 hours[14]. The independent clinical event committee adjudicated the clinical events with blinded fashion about the assigned group. Persistent DAPT discontinuation was defined as discontinuation of either aspirin or $P2Y_{12}$ receptor blockers according to the study protocol or discontinuation lasting for >60 days in consistent with our previous studies[15,16].

Statistical Analysis

Categorical variables were presented as number and percentage and were compared

with χ^2 test. Continuous variables were expressed as mean +/- standard deviation (SD) or median with interquartile range (IQR) and were compared using the Student *t* test or Wilcoxon rank-sum test depending on their distributions. The cumulative incidence was estimated with the Kaplan-Meier method and compared with log-rank test. Absolute difference of incidence rate was calculated as the event rate in the 1-month DAPT group minus the event rate in the 12-month DAPT group. The hazard ratios (HR) for the endpoint events were calculated by the Cox's proportional hazard model with 95% confidential interval (CI) calculated from Wald's statistics.

Because the present study was post-hoc subgroup analysis, we did not make any power calculation for the primary and major secondary endpoints, and all reported P values were 2 tailed. P values <0.05 were considered statistically significant. All analysis was performed with JMP version 14.0 software (SAS Institute Inc., Cary, NC).

Results

HBR definitions and classification

Among the 3009 study patients, there were 1054 patients (35.0%) with HBR (1-month DAPT group: N=496, and 12-month DAPT group: N=558), and 1955 patients

(65.0%) with non-HBR (1-month DAPT group: N=1004, and 12-month DAPT group: N=951). Patients who met the ARC-HBR major criteria were not commonly found in this randomized trial except for the small proportion patients with severe anemia (8.7%) and end-stage CKD (5.5%), while the ARC-HBR minor criteria were much more prevalent including age >=75 years old (31.5%), moderate CKD (29.4%), and moderate anemia (21.6%) (Supplemental Table 1).

Baseline characteristics, and medications

When we compared HBR patients with non-HBR patients, patient characteristics were totally different (Table 1). HBR patients were older, more often women, and less often current smokers, and had lower body mass index than non-HBR patients. HBR patients more often presented as stable coronary artery disease, and more often had prior PCI, and prior first-generation DES implantation than non-HBR patients. Besides those included in the ARC-HBR criteria, HBR patients more often had comorbidities such as hypertension, diabetes, heart failure, peripheral artery disease, malignancy, left ventricular dysfunction, and mitral regurgitation than non-HBR patients. HBR patients compared with non-HBR patients more often had intermediate/high PARIS and CREDO-Kyoto thrombotic and bleeding risk scores, as well as high-risk features of stent-driven recurrent ischemia derived from the 2017

ESC focused update on DAPT. Procedural characteristics were also different between HBR and non-HBR patients, with higher prevalence of femoral approach, longer stenting, targets of left main coronary artery and right coronary artery, and multivessel targets in HBR patients. However, the SYNTAX (Synergy between percutaneous coronary intervention with taxus and cardiac surgery) score evaluated in 20 % of randomly selected patients were comparable between HBR and non-HBR patients[17]. Regarding medications at discharge, HBR patients more often received clopidogrel as the P2Y12 receptor blocker within 1-month than non-HBR patients. Statins were less often prescribed in HBR patients than in non-HBR patients, while the prevalence of proton pump inhibitor use was high and not different between HBR and non-HBR patients (Table 1).

Baseline characteristics and medications were well balanced between the 1-month DAPT and 12-month DAPT groups regardless of HBR and non-HBR patients (Supplemental Table 2).

In the entire study population, DAPT was actually stopped in 150 patients (10.0%) during the first 30 days, in 752 patients (50.1%) during the first 37 days, in 1090 patients (72.7%) during the first 44 days, in 1286 patients (85.7%) during the first 51 days, and in 1428 patients (95.2%) during the first 60 days in the 1-month DAPT group, while DAPT was

maintained in 1331 patients (88.2%) for 335 days, and in 848 patients (56.2%) for 365-day in the 12-month DAPT group. The patterns of DAPT discontinuation were similar in HBR and non-HBR patients (Supplemental Figure).

Clinical outcomes

In HBR patients, the primary endpoint occurred in 17 patients (3.48%) in the 1-month DAPT group and in 33 patients (5.98%) in the 12-month DAPT (absolute difference -2.50%, 95%CI -5.06% to 0.06%, HR 0.57, 95%CI 0.32-1.03, P=0.06) (Figure 2a, 3, and Table 2a). In non-HBR patients, the primary endpoint occurred in 18 patients (1.81%) in the 1-month DAPT group and in 22 patients (2.36%) in the 12-month DAPT group (absolute difference -0.55%, 95%CI -1.83% to 0.73%, HR 0.78, 95%CI 0.42-1.45, P=0.43) (Figure 2a and Table 2b). There was no significant interaction between HBR/non-HBR subgroups and the effect of 1-month DAPT relative to 12-month DAPT on the primary endpoint (P for interaction=0.48).

The major secondary cardiovascular endpoint occurred in 15 patients (3.07%) in the 1-month DAPT group and in 22 patients (4.03%) in the 12-month DAPT group in HBR patients (absolute difference -0.96%, 95%CI -3.21% to 1.29%, HR 0.77, 95%CI 0.40-1.48, P=0.43) (Figure 2b and Table 2a). In non-HBR patients, the major secondary cardiovascular

endpoint occurred in 14 patients (1.41%) in 1-month DAPT group and in 15 patients (1.61%) in the 12-month DAPT group (absolute difference -0.20%, 95%CI -1.28% to 0.88%, HR 0.89, 95%CI 0.43-1.84, P=0.75) (Figure 2b, 3, and Table 2b). There was no significant interaction between HBR/non-HBR subgroups and the effect of 1-month DAPT relative to 12-month DAPT on the major secondary cardiovascular endpoint (P for interaction=0.77).

The rate of the major secondary bleeding endpoint was significantly lower in the 1-month DAPT group (2 patients, 0.41%) than in the 12-month DAPT group (15 patients, 2.71%) in HBR patients (absolute difference -2.30%, 95%CI -3.77% to -0.83%, HR 0.15, 95%CI 0.03-0.65, P=0.01) (Figure 2c and Table 2a). In non-HBR patients, the major secondary bleeding endpoint occurred in 4 patients (0.40%) in the 1-month DAPT group and in 8 patients (0.85%) in the 12-month DAPT group (absolute difference -0.45%, 95%CI -1.16% to 0.26%, HR 0.48, 95%CI 0.14-1.58, P=0.22) (Figure 2c and Table 2b). There was no significant interaction between HBR/non-HBR subgroups and the effect of 1-month DAPT relative to 12-month DAPT on the major secondary bleeding endpoint (P for interaction=0.22). However, the benefit of 1-month DAPT over 12-month DAPT in reducing major bleeding was numerically greater in HBR patients than in non-HBR patients.

In HBR patients, intracranial hemorrhage occurred in no patient (0%) in the

1-month DAPT group and in 3 patients (0.54%) in the 12-month DAPT group (Figure 3, and Table 2).

Discussion

The main findings of the present post-hoc subgroup analysis of the STOPDAPT-2 trial based on the ARC-HBR criteria were the followings; 1) The effects of 1-month DAPT relative to 12-month DAPT for the primary and major secondary endpoints were consistent in HBR and non-HBR patients without any significant interactions; 2) The benefit of 1-month DAPT over 12-month DAPT in reducing major bleeding was numerically greater in HBR patients than in non-HBR patients.

Recently, there is an increasing attention on HBR patients who undergo PCI. HBR patients were often excluded or underrepresented in the randomized trials, and therefore, the optimal antithrombotic management after PCI in HBR patients has not been yet well established. Furthermore, HBR patients had not been well defined, and the definitions of HBR patients were different among the HBR trials[3-5]. The ARC-HBR has been proposed to standardize the definition of HBR from the literature review and by the consensus of experts[7]. In the ARC-HBR initiative, HBR was arbitrarily defined as a BARC 3 or 5 bleeding >=4% at

1-year or a risk of an intracranial hemorrhage >=1% at 1-year. In the present analysis, the prevalence of ARC-HBR patients were high (35%) even if we excluded those with very high bleeding risk such as those with use of oral anticoagulants and/or history of intracranial hemorrhage. The rate of major bleeding with 12-month DAPT was substantially higher in HBR patients than in non-HBR patients. In HBR patients, 1-month DAPT compared with 12-month DAPT was associated with significantly lower risk for major bleeding, and the benefit of 1-month DAPT over 12-month DAPT in reducing major bleeding was numerically greater in HBR patients than in non-HBR patients. Therefore, 1-month DAPT is an attractive DAPT regimen particularly in HBR patients. In the previous HBR trials, the 1-year rates of major bleeding remained high even with the abbreviated DAPT regimen (LEADERS FREE: 7.2%, ZEUS: 3.5-5%, and SENIOR: 3-4%)[3-5], while the 1-year rate of major bleeding with 1-month DAPT in HBR patients was extremely low (0.41%) in the present study. In the previous HBR trials, aspirin monotherapy was generally used after stopping DAPT. One of the reasons for this very low rate of major bleeding in the present study might be related to the use of clopidogrel monotherapy[18,19]. However, we did not test aspirin monotherapy after stopping DAPT at 1-month. Further research would be important to define the optimal antiplatelet monotherapy after stopping DAPT in HBR patients.

One of the most important issues related to the adoption of very short DAPT duration in HBR patients would be whether it might result in an increase in the cardiovascular events. It is well known that HBR patients also have higher risk for ischemic cardiovascular events[10]. Indeed, more than 70% of HBR patients in this study also had high-risk features of stent-driven recurrent ischemia defined in the ESC focused update of DAPT guideline[2]. However, in the present study, 1-month DAPT in HBR patients was not associated with an increase in cardiovascular event rates, but was associated with a numerical decrease in cardiovascular event rates. Despite the positive results in the STOPDAPT-2 trial, 1-month DAPT has not been yet the generally accepted regimen after PCI using DES. Nevertheless, 1-month DAPT followed by clopidogrel monotherapy would be an important option in patients with very high bleeding risk, considering the substantial mortality impact and iatrogenic nature of the bleeding events[20,21].

There are several important limitations in current analysis. First, the majority of patients enrolled in the STOPDAPT-2 trial had low/intermediate ischemic risk. The benefit of very short DAPT should be confirmed in other populations such as patients with acute coronary syndrome or with complex coronary artery disease. Furthermore, the STOPDAPT-2 trial enrolled those patients who did not have procedural complications, leading to

underestimation of the rate of major bleeding at 1-year. Second, the present post-hoc subgroup analysis related to HBR/non-HBR patients was totally underpowered and exploratory. Therefore, the favorable results of 1-month DAPT in HBR patients should be regarded as hypothesis generating. Third, there were some uncaptured data for ARC-HBR criteria. Fourth, it is well known that Japanese patients with coronary artery disease had lower ischemic risk as compared with US/European patients[22-24]. In addition, the vast majority of patients in this study underwent PCI guided by intracoronary imaging devices, which were rarely used in US and Europe. Therefore, we should be cautious about extrapolating the current study results outside Japan.

Conclusion

In this post-hoc subgroup analysis of the STOPDAPT-2 trial based on the ARC-HBR criteria, the effects of 1-month DAPT relative to 12-month DAPT for the primary and major secondary endpoints were consistent in HBR and non-HBR patients without any significant interactions. The benefit of 1-month DAPT over 12-month DAPT in reducing major bleeding was numerically greater in HBR patients than in non-HBR patients.

Acknowledgements

We appreciate the members of Research Institute for Production Development handling a series of large clinical trials and the co-investigators for exaggeratedly enrolling patients, collecting follow-up data, or adjudicating clinical events.

Funding

STOPDAPT-2 was funded by Abbott Vascular Japan. The study sponsor is not involved in the implementation of the study, data collection, event fixation and statistical analysis. However, approval of the study sponsor should be obtained for presentation in scientific meetings and submission of papers.

Conflict of interests

Koichi Nakao has received a speaker honorarium from Sanofi and Daiichi-Sankyo. Kenji Ando has received a speaker honorarium from Japan Lifeline, Medtronic Japan, Terumo, and Biotronik Japan. Kengo Tanabe has received a speaker honorarium from Kaneka Medix. Yuji Ikari received a research grant from Abbott Vascular Japan. Yoshihisa Nakagawa has received a speaker honorarium from Daiichi-Sankyo, Bayer Yakuhin, and Bristol-Myers Squibb. Takeshi Kimura serves as a advisory role to Abbott Vascular japan and received a research

grant from Daiichi-Sankyo. Others have no conflict of interest

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Figure legends

Figure 1. Study flow

HBR is defined by ARC-HBR definition.

ARC=Academic Research Consortium, DAPT=dual antiplatelet therapy, and HBR=high bleeding risk.

Figure 2. Clinical Outcomes at 1-year stratified by HBR and non-HBR: 1-momth versus 12-month DAPT

Time-to-event curves up to 1-year for (a) primary endpoint, (b) major secondary cardiovascular endpoint, and (c) major secondary bleeding endpoint stratified by HBR and non-HBR.

CI=confidence interval, HBR=high bleeding risk, HR=hazard ratio, MI=myocardial infarction, PCI=percutaneous coronary intervention, and TIMI=Thrombolysis in Myocardial Infarction.

Figure 3. Bleeding sites in HBR patients and non-HBR patients

Cumulative 1-year incidences of TIMI major or minor bleeding, and its breakdown classified

by the bleeding sites in HBR patients and non-HBR patients.

DAPT=dual antiplatelet therapy, GI=gastrointestinal, HBR=high bleeding risk,

ICH=intracranial hemorrhage, and TIMI=Thrombolysis in Myocardial Infarction.

Tables

Table 1. Background differences between HBR patients and non-HBR patients

	HBR N=1054	Non-HBR N=1955	P value
Base background			
Age, years	75.8±8.6	64.8±9.7	<0.001
>=75	708 (67.2)	239 (12.2)	<0.001
Men	736 (69.8)	1601 (81.9)	<0.001
BMI, kg/m^2	23.5±3.5	24.7±3.5	<0.001
<25	721 (68.4)	1094 (56.0)	<0.001
Presentation			
Acute coronary syndrome	310 (29.4)	838 (42.9)	<0.001
STEMI	139 (13.2)	422 (21.6)	<0.001
NSTEMI	41 (3.9)	139 (7.1)	<0.001
Unstable angina	130 (12.3)	277 (14.2)	0.16
Stable coronary artery disease	744 (70.6)	1117 (57.1)	<0.001

Past history			
Prior PCI	464 (44.0)	568 (29.1)	<0.001
Prior first-generation DES	60 (5.7)	52 (2.7)	<0.001
Prior CABG	35 (3.3)	24 (1.2)	<0.001
Prior myocardial infarction	164 (15.6)	242 (12.4)	0.016
Prior stroke	149 (14.1)	37 (1.9)	<0.001
Prior ischemic stroke			
Prior hemorrhagic stroke	8 (0.8)	0 (0)	<0.001
Prior bleeding	42 (4.0)	5 (0.3)	<0.001
Congestive heart failure	141 (13.4)	81 (4.1)	<0.001
Atrial fibrillation	33 (3.1)	24 (1.2)	<0.001
Severe anemia	263 (25.0)	0 (0)	<0.001
Thrombocytopenia	31 (2.9)	0 (0)	<0.001
COPD	41 (3.9)	43 (2.2)	0.009
Liver cirrhosis	10 (1.0)	0 (0)	<0.001
Malignancy	147 (14.0)	109 (5.6)	<0.001

Peripheral artery disease	134 (12.7)	62 (3.2)	<0.001
Moderate CKD	595 (56.5)	288 (14.7)	<0.001
Severe CKD	166 (15.8)	0 (0)	<0.001
eGFR<30 and not on dialysis	64 (6.1)	0 (0)	<0.001
Dialysis	102 (9.7)	0 (0)	<0.001
Hypertension	855 (81.1)	1366 (69.9)	<0.001
Dyslipidemia	765 (72.6)	1479 (75.7)	0.07
Diabetes mellitus	466 (44.2)	693 (35.5)	<0.001
Insulin-treated	95 (9.0)	107 (5.5)	<0.001
Current smoking	145 (13.8)	565 (28.9)	<0.001
Left ventricular ejection fraction	58.7±10.9	60.3±10.0	<0.001
<40%	55 (5.7)	60 (3.3)	0.004
Mitral regurgitation with grade 3/4	43 (4.1)	32 (1.6)	<0.001
PARIS thrombotic risk score	3.4±1.6	2.2±1.5	<0.001
Low	328 (31.1)	1159 (59.3)	<0.001
Intermediate	430 (40.8)	666 (34.1)	

High	296 (28.1)	130 (6.7)	
PARIS bleeding risk score	7.3±2.4	4.1±1.9	<0.001
Low	83 (7.9)	775 (39.6)	<0.001
Intermediate	468 (44.4)	1090 (55.8)	
High	503 (47.7)	90 (4.6)	
CREDO-Kyoto thrombotic risk score	2.4±1.7	0.6±0.8	<0.001
Low	380 (36.1)	1718 (87.9)	<0.001
Intermediate	447 (42.4)	229 (11.7)	
High	227 (21.5)	8 (0.4)	
CREDO-Kyoto bleeding risk score	1.2±1.5	0.3±0.7	<0.001
Low	497 (47.2)	1495 (76.5)	<0.001
Intermediate	381 (36.2)	418 (21.4)	
High	176 (16.7)	42 (2.2)	
High-risk features of stent-driven recurrent ischemia †	807 (76.6)	486 (24.9)	<0.001

Procedural background

Invasive FFR	162 (15.4)	253 (12.9)	0.07
Radial approach	785 (74.5)	1711 (87.5)	<0.001
Brachial approach	96 (9.1)	64 (3.3)	<0.001
Femoral approach	179 (17.0)	203 (10.4)	<0.001
Number of lesions	1.11±0.36	1.15±0.40	0.01
SYNTAX scores*	10.2±6.6	10.4±7.1	0.75
Minimal stent diameter, mm	2.96±0.47	2.98±0.49	0.23
<3.0	445 (42.2)	792 (40.5)	0.36
Total stent length, mm	31.6±17.7	29.7±16.2	0.003
>=28	574 (54.5)	955 (48.9)	0.003
Target vessel			
LMCA	44 (4.2)	36 (1.8)	<0.001
LAD	546 (51.8)	1136 (58.1)	0.001
CX	195 (18.5)	378 (19.3)	0.58
RCA	342 (32.5)	504 (25.8)	<0.001
Graft	5 (0.5)	1 (0.1)	0.01

Target of CTO	38 (3.6)	84 (4.3)	0.35
Target of bifurcation	283 (26.9)	486 (24.9)	0.23
Bifurcation with 2 stents	7 (0.7)	7 (0.4)	0.25
Target of 2 vessels or more	98 (9.3)	118 (6.0)	0.001
Target of 3 vessels	5 (0.5)	6 (0.3)	0.48
Use of intravascular ultrasound	907 (86.1)	1649 (84.4)	0.21
Use of optical coherence tomography	141 (13.4)	302 (15.5)	0.12
Medication at discharge			
Aspirin	1051 (99.7)	1955 (100)	0.01
P2Y12 receptor blockers	1053 (99.9)	1954 (99.95)	0.66
Clopidogrel	713 (67.7)	1139 (58.3)	<0.001
Prasugrel	337 (32.0)	814 (41.6)	<0.001
Ticlopidine	3 (0.3)	1 (0.1)	0.1
Cilostazol	3 (0.3)	3 (0.2)	0.45
Oral anticoagulants	13 (1.2)	0 (0)	<0.001
Beta blockers	464 (44.0)	851 (43.5)	0.79

ACE inhibitors or ARB	668 (63.4)	1205 (61.6)	0.35
Statins	853 (80.9)	1782 (91.2)	<0.001
Proton pump inhibitors	818 (77.6)	1565 (80.1)	0.12

Values are means ± SD or number (%). ACE=angiotensin converting enzyme, ARB=angiotensin 2 receptor blockers, BMI=body mass index, CABG=coronary artery bypass grafting, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, CREDO-Kyoto=Coronary REvascularization Demonstrating Outcome study in Kyoto, CTO=chronic total occlusion, CX= left circumflex coronary artery, DAPT=dual antiplatelet therapy, DES=drug eluting stents, eGFR=estimated glomerular filtration rate, FFR=fractional flow reserve, HBR=high bleeding risk, LAD=left anterior descending coronary artery, LMCA=left main coronary artery, NSTEMI=Non ST-segment elevation myocardial infarction, PARIS=Patterns of Non- Adherence to Anti-Platelet Regimen in Stented Patients, PCI=percutaneous coronary intervention, RCA=right coronary artery, SD=standard deviation, STEMI=ST-segment elevation myocardial infarction, and SYNTAX=Synergy Between Percutaneous Coronary Intervention With Taxus.

*SYNTAX scores were calculated at core laboratory of angiogram for randomly selected 571 patients.

† High-risk features of stent-driven recurrent ischemia were derived from 2017 ESC focused update of on DAPT[2].

Table 2. Clinical outcomes stratified by HBR and non-HBR

(a) HBR stratum

	No. (event %)		Hazard ratio	
	1M-DAPT (N=496)	12M-DAPT (N=558)	(95% CI)	P value
Primary endpoint				
Cardiovascular death, MI, Definite ST, Stroke, or TIMI major or minor bleeding	17 (3.48%)	33 (5.98%)	0.57 (0.32-1.03)	0.06
Major secondary endpoints				
Cardiovascular death, MI, Definite ST, or Stroke	15 (3.07%)	22 (4.03%)	0.77 (0.40-1.48)	0.43
TIMI major or minor bleeding	2 (0.41%)	15 (2.71%)	0.15 (0.03-0.65)	0.01
Other endpoints				
Death	13 (2.67%)	12 (2.16%)	1.22 (0.56-2.67)	0.62

Cardiac death	5 (1.02%)	6 (1.09%)	0.94 (0.29-3.08)	0.92
Cardiovascular death	5 (1.02%)	8 (1.44%)	0.70 (0.23-2.15)	0.54
Non-cardiovascular death	8 (1.66%)	4 (0.73%)	2.25 (0.68-7.48)	0.18
MI	6 (1.24%)	3 (0.55%)	2.25 (0.56-9.01)	0.25
Large MI (CKMB>=10*ULN)	1 (0.21%)	0 (0.00%)	-	-
Small MI (CKMB<10*ULN)	5 (1.04%)	2 (0.36%)	2.82 (0.55-14.52)	0.22
MI without CKMB elevation	0 (0.00%)	1 (0.18%)	-	-
MI without measurement of CKMB	0 (0.00%)	0 (0.00%)	-	-
Definite ST	0 (0.00%)	0 (0.00%)	-	-
Definite or Probable ST	1 (0.20%)	0 (0.00%)	-	-
Stroke	5 (1.03%)	12 (2.24%)	0.47 (0.16-1.33)	0.15
Ischemic	5 (1.03%)	11 (2.07%)	0.51 (0.18-1.47)	0.21
Hemorrhagic	0 (0.00%)	1 (0.18%)	-	-
Bleeding				
TIMI major	0 (0.00%)	10 (1.81%)	-	-
TIMI minor	2 (0.41%)	5 (0.91%)	0.45 (0.09-2.31)	0.34

BARC 3 or 5	3 (0.61%)	18 (3.26%)	0.19 (0.05-0.63)	0.007
BARC 5	1 (0.20%)	3 (0.54%)	0.38 (0.04-3.61)	0.4
BARC 5b	1 (0.20%)	2 (0.36%)	0.56 (0.05-6.21)	0.64
BARC 5a	0 (0.00%)	1 (0.18%)	-	-
BARC 3	2 (0.41%)	15 (2.72%)	0.15 (0.03-0.65)	0.01
BARC 3c	0 (0.00%)	2 (0.37%)	-	-
BARC 3b	0 (0.00%)	7 (1.27%)	-	-
BARC 3a	2 (0.41%)	7 (1.27%)	0.32 (0.07-1.54)	0.16
GUSTO moderate/severe	2 (0.41%)	15 (2.72%)	0.15 (0.03-0.65)	0.01
GUSTO severe	1 (0.20%)	7 (1.27%)	0.16 (0.02-1.30)	0.09
GUSTO moderate	1 (0.20%)	8 (1.45%)	0.14 (0.02-1.12)	0.06
Intracranial bleeding	0 (0.00%)	3 (0.54%)	-	-
Gastrointestinal bleeding	3 (0.61%)	13 (2.35%)	0.26 (0.07-0.90)	0.03
Revascularization	41 (8.58%)	38 (7.10%)	1.21 (0.78-1.89)	0.39
TLR	15 (3.10%)	10 (1.88%)	1.70 (0.76-3.78)	0.19
CD-TLR	10 (2.07%)	7 (1.32%)	1.61 (0.61-4.23)	0.33

Non-TLR	30 (6.31%)	30 (5.59%)	1.12 (0.68-1.86)	0.65
CABG	2 (0.44%)	2 (0.37%)	1.13 (0.16-8.01)	0.9
Death or MI	17 (3.48%)	15 (2.70%)	1.28 (0.64-2.56)	0.49
Cardiovascular death or MI	10 (2.05%)	11 (1.99%)	1.02 (0.43-2.41)	0.96
MACE (Cardiac death, MI, or CD-TLR)	15 (3.08%)	14 (2.58%)	1.21 (0.58-2.50)	0.61

(b) Non-HBR stratum

Patients without HBR	**1M-DAPT (N=956)**	**12M-DAPT (N=890)**	**Hazard ratio (95% CI)**	**P Value**
Primary endpoint				
Cardiovascular death, MI, Definite ST, Stroke, or TIMI major or minor bleeding	18 (1.81%)	22 (2.36%)	0.78 (0.42-1.45)	0.43
Major secondary endpoints				
Cardiovascular death, MI,	14 (1.41%)	15 (1.61%)	0.89 (0.43-1.84)	0.75

Definite ST, or Stroke				
TIMI major or minor bleeding	4 (0.40%)	8 (0.85%)	0.48 (0.14-1.58)	0.22
Other endpoints				
Death	8 (0.81%)	6 (0.64%)	1.27 (0.44-3.66)	0.66
Cardiac death	3 (0.30%)	2 (0.22%)	1.43 (0.24-8.54)	0.7
Cardiovascular death	4 (0.40%)	3 (0.32%)	1.27 (0.28-5.67)	0.75
Non-cardiovascular death	4 (0.40%)	3 (0.32%)	1.27 (0.28-5.68)	0.75
MI	7 (0.71%)	8 (0.87%)	0.83 (0.30-2.30)	0.72
Large MI (CKMB>=10*ULN)	4 (0.41%)	2 (0.21%)	1.90 (0.35-10.39)	0.46
Small MI (CKMB<10*ULN)	2 (0.20%)	3 (0.33%)	0.63 (0.11-3.80)	0.62
MI without CKMB elevation	1 (0.10%)	1 (0.11%)	0.96 (0.06-15.28)	0.97
MI without measurement of CKMB	0 (0.00%)	2 (0.21%)	-	-
Definite ST	2 (0.20%)	1 (0.11%)	1.90 (0.17-20.97)	0.6
Definite or Probable ST	3 (0.30%)	1 (0.11%)	2.85 (0.30-27.39)	0.36
Stroke	3 (0.30%)	4 (0.42%)	0.71 (0.16-3.18)	0.66

Ischemic	3 (0.30%)	4 (0.42%)	0.71 (0.16-3.18)	0.66
Hemorrhagic	0 (0.00%)	0 (0.00%)	-	-
Bleeding				
TIMI major	3 (0.30%)	6 (0.64%)	0.48 (0.12-1.90)	0.29
TIMI minor	1 (0.10%)	2 (0.21%)	0.48 (0.04-5.24)	0.54
BARC 3 or 5	5 (0.50%)	9 (0.96%)	0.53 (0.18-1.57)	0.25
BARC 5	0 (0.00%)	0 (0.00%)	-	-
BARC 5b	0 (0.00%)	0 (0.00%)	-	-
BARC 5a	0 (0.00%)	0 (0.00%)	-	-
BARC 3	5 (0.50%)	9 (0.96%)	0.53 (0.18-1.57)	0.25
BARC 3c	2 (0.20%)	2 (0.21%)	0.95 (0.13-6.76)	0.96
BARC 3b	1 (0.10%)	4 (0.42%)	0.24 (0.03-2.12)	0.2
BARC 3a	2 (0.20%)	3 (0.32%)	0.63 (0.11-3.79)	0.62
GUSTO moderate/severe	4 (0.40%)	8 (0.85%)	0.48 (0.14-1.58)	0.22
GUSTO severe	3 (0.30%)	4 (0.43%)	0.71 (0.16-3.19)	0.66
GUSTO moderate	1 (0.10%)	4 (0.42%)	0.24 (0.03-2.12)	0.2

Intracranial bleeding	2 (0.20%)	2 (0.21%)	0.95 (0.13-6.76)	0.96
Gastrointestinal bleeding	3 (0.30%)	6 (0.64%)	0.47 (0.12-1.90)	0.29
Revascularization	57 (5.87%)	38 (4.18%)	1.45 (0.96-2.18)	0.08
TLR	20 (2.03%)	13 (1.43%)	1.48 (0.73-2.97)	0.27
CD-TLR	16 (1.62%)	12 (1.32%)	1.28 (0.60-2.70)	0.52
Non-TLR	41 (4.24%)	30 (3.28%)	1.31 (0.82-2.10)	0.26
CABG	4 (0.41%)	3 (0.32%)	1.27 (0.28-5.68)	0.75
Death or MI	15 (1.51%)	14 (1.51%)	1.02 (0.49-2.11)	0.96
Cardiovascular death or MI	11 (1.11%)	11 (1.19%)	0.95 (0.41-2.20)	0.91
MACE (Cardiac death, MI, or CD-TLR)	23 (2.32%)	18 (1.97%)	1.22 (0.66-2.27)	0.52

BARC=the Bleeding Academic Research Consortium, CABG=Coronary Artery Bypass Grafting, CD-TLR=Clinically-driven Target Lesion Revascularization, CKMB=Creatine Kinase-MB, DAPT=Dual Antiplatelet Therapy, GUSTO=Global Utilization of Streptokinase and TPA For Occluded Arteries, HBR= High bleeding risk, MACE=Major Adverse Cardiac Event, MI=Myocardial Infarction, ST=Stent thrombosis, TIMI=Thrombolysis in Myocardial

Infarction, TLR=Target Lesion Revascularization, and ULN=Upper limit of Normal.

Figures.

Figure 1.

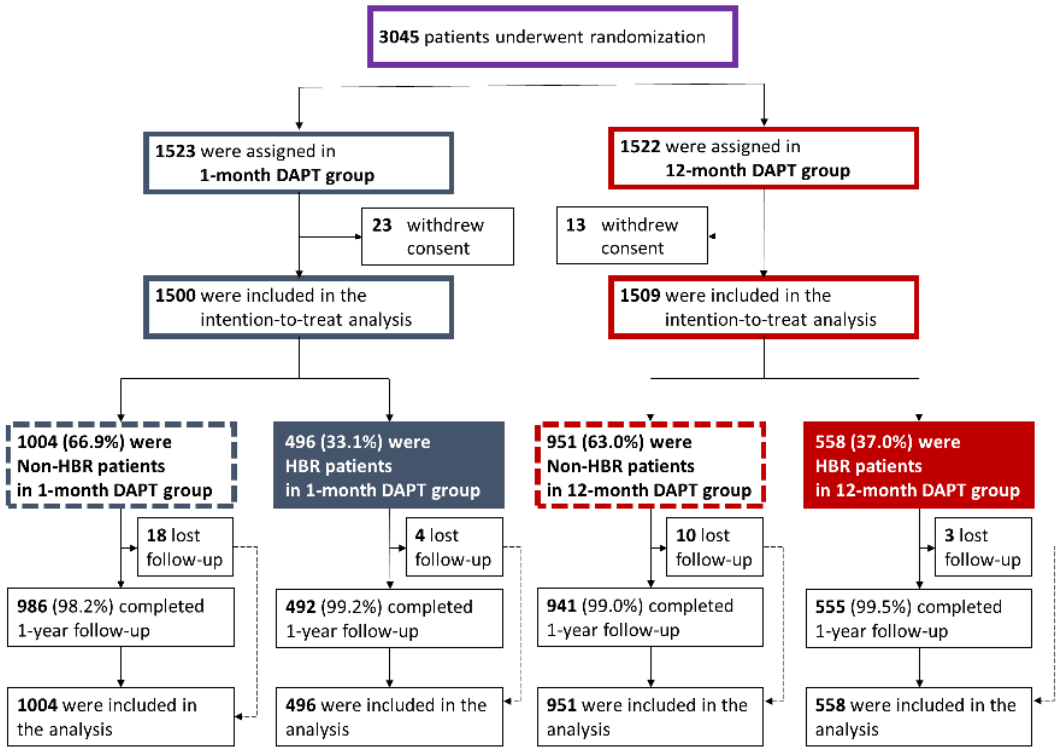
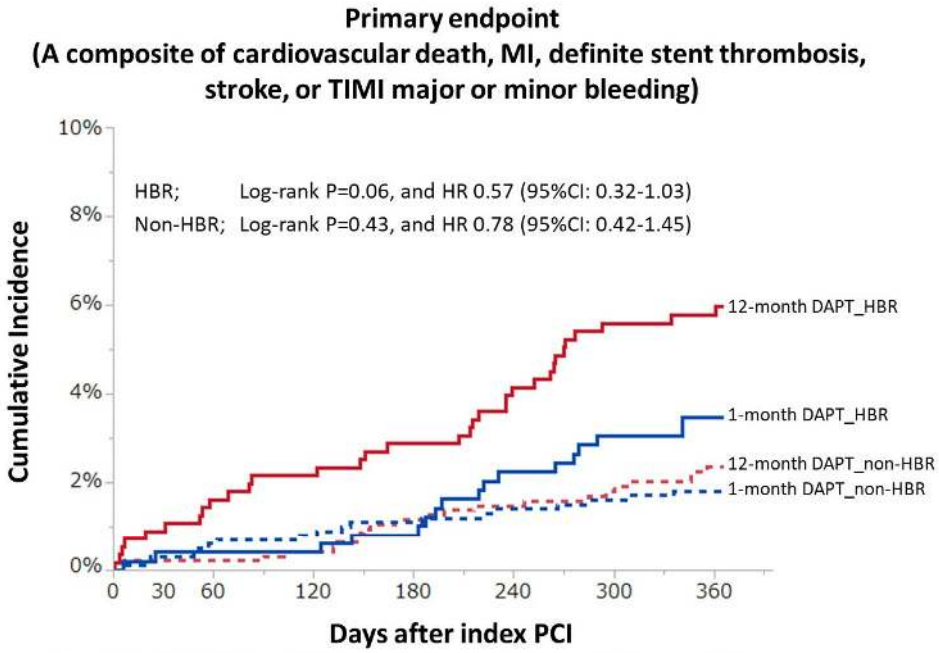


Figure 2.

(a)



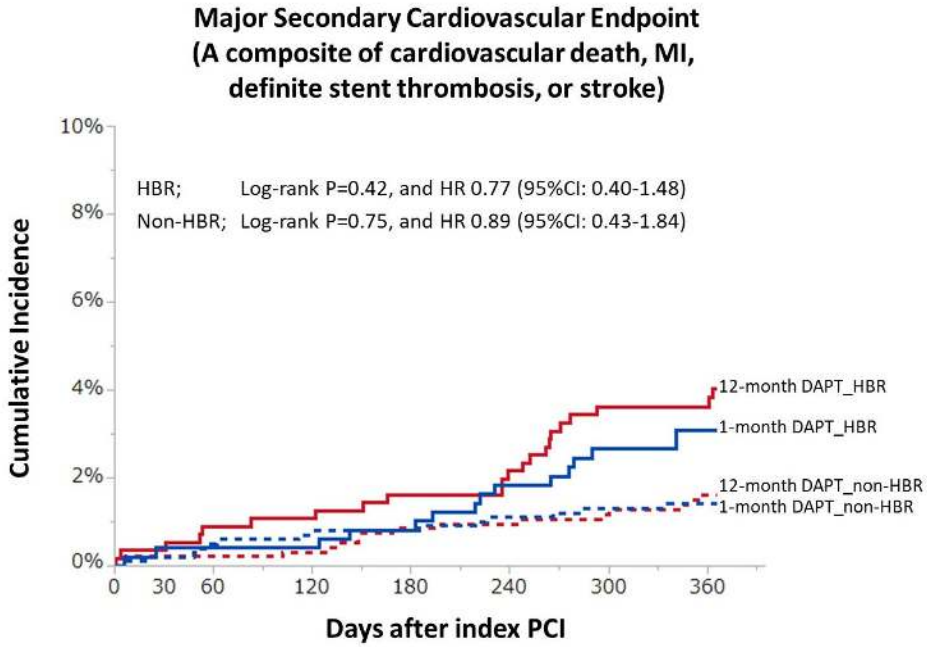
HBR patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		5	9	12	16	23	31	33
Number of patients at risk	558	553	546	543	538	530	521	424
Cumulative incidence (%)		0.9	1.6	2.2	2.9	4.1	5.6	6.0
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	2	2	4	11	15	17
Number of patients at risk	496	493	490	488	486	478	471	385
Cumulative incidence (%)		0.4	0.4	0.4	0.8	2.2	3.1	3.5

Non-HBR patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	2	4	11	14	18	22
Number of patients at risk	951	948	940	938	931	928	921	735
Cumulative incidence (%)		0.2	0.2	0.4	1.2	1.5	1.9	2.4
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		3	6	8	11	14	16	18
Number of patients at risk	1004	1001	989	987	982	975	970	766
Cumulative incidence (%)		0.3	0.6	0.8	1.1	1.4	1.6	1.8

(b)



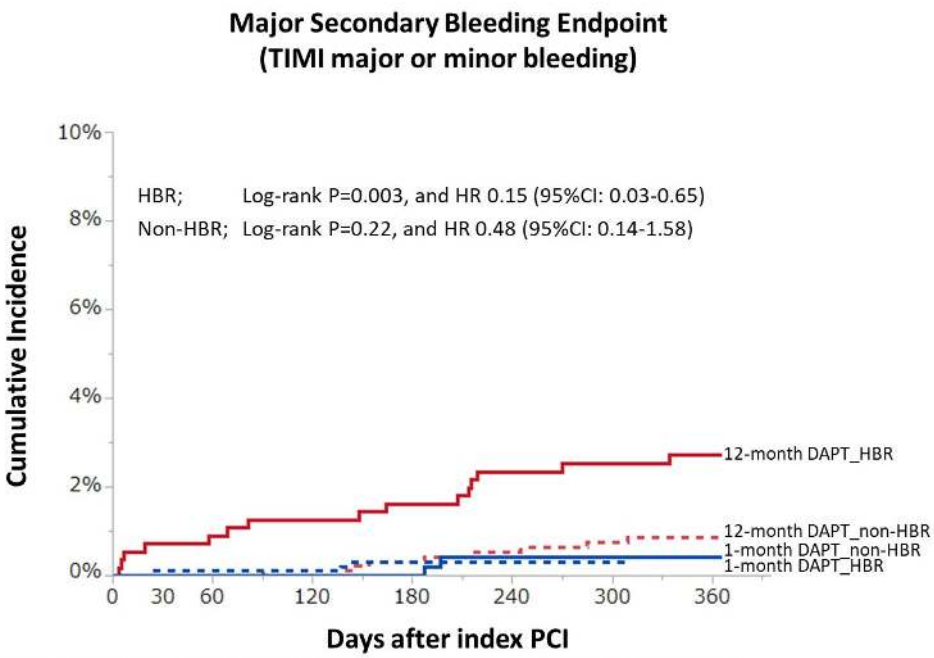
HBR patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	5	6	9	12	20	22
Number of patients at risk	558	556	550	549	545	540	531	431
Cumulative incidence (%)		0.4	0.9	1.1	1.6	2.2	3.6	4.0
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	2	2	4	9	13	15
Number of patients at risk	496	493	490	488	486	480	473	387
Cumulative incidence (%)		0.4	0.4	0.4	0.8	1.8	2.7	3.1

Non-HBR patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	2	3	8	9	12	15
Number of patients at risk	951	948	940	939	934	933	927	741
Cumulative incidence (%)		0.2	0.2	0.3	0.9	1.0	1.3	1.6
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		2	5	7	8	11	13	14
Number of patients at risk	1004	1002	990	988	985	978	973	770
Cumulative incidence (%)		0.2	0.5	0.7	0.8	1.1	1.3	1.4

(c)



HBR patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		4	5	7	9	13	14	15
Number of patients at risk	558	554	549	546	542	536	532	436
Cumulative incidence (%)		0.7	0.9	1.3	1.6	2.4	2.5	2.7
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		0	0	0	0	2	2	2
Number of patients at risk	496	494	491	489	489	483	479	393
Cumulative incidence (%)		0.0	0.0	0.0	0.0	0.4	0.4	0.4

Non-HBR patients

12-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		0	0	1	3	5	7	8
Number of patients at risk	951	950	942	941	938	935	930	744
Cumulative incidence (%)		0.0	0.0	0.1	0.3	0.5	0.7	0.9
1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		1	1	1	3	3	3	4
Number of patients at risk	1004	1001	992	992	988	984	978	773
Cumulative incidence (%)		0.1	0.1	0.1	0.3	0.3	0.3	0.4

Figure 3.