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ORIGINAL ARTICLE

Case-fatality rate of major bleeding events in patients on dual antiplatelet therapy after percutaneous coronary intervention: A systematic review and meta-analysis

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Abstract

Background: Assessment of the case-fatality rate (CFR) of major bleeding on dual antiplatelet therapy (DAPT) may improve balancing risks and benefits of different durations of DAPT following percutaneous coronary intervention (PCI).

Objectives: To determine the CFR of major bleeding in patients on DAPT after PCI and to compare rates among different durations of DAPT.

Methods: Medline, Embase, and CENTRAL were searched from inception to August 2021 for randomized trials that reported fatal bleeding among patients who were randomized to ≥1 month of DAPT following PCI. Summary estimates for CFRs of major bleeding were calculated using the random-effects inverse-variance method. Statistical heterogeneity was evaluated using the I^2 statistic.

Results: Of 2777 citations obtained by the search, 15 (48%) of 31 potentially eligible studies were excluded because fatal bleeding was not reported, leaving 16 studies that were included in the analysis. Overall, there were 823 major bleeding events including 91 fatal events in 48,884 patients who were assigned to receive DAPT during study follow-up. The CFR of major bleeding was 10.8% (95% confidence interval [CI], 7.1–16.2; I^2 = 50%) in the entire study population, and 13.8% (95% CI, 6.5–27.1; I^2 = 28%), 11.2% (95% CI, 6.7–18.0; I^2 = 0%), and 5.8% (95% CI, 3.0–11.1; I^2 = 0%) in

those on short-term (≤6 months; $n = 16{,}553$), standard-term (12 months; $n = 19{,}453$), and long-term DAPT (>12 months; $n = 10{,}238$), respectively.

Conclusion: Fatal bleeding is not reported in many studies evaluating DAPT after PCI. The CFR of major bleeding on DAPT is substantial and may be higher in the first 12 months of DAPT than during long-term DAPT.

KEYWORDS
bleeding, case-fatality rate, drug-eluting stent, dual antiplatelet therapy, meta-analysis, percutaneous coronary intervention

Essentials

- We aimed to assess the proportion of fatal relative to major bleeds on dual antiplatelets (DAPT).
- We did a meta-analysis of trials evaluating DAPT after percutaneous coronary intervention (PCI).
- Fatal bleeding is not reported in many studies evaluating DAPT after PCI.
- The proportion of fatal relative to major bleeds on DAPT is substantial (10.8%).

1 | INTRODUCTION

Deciding on the optimal duration of dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor inhibitor after implantation of drug-eluting stents (DES) in patients with coronary artery disease is challenging. Extending DAPT beyond the standard 12-month duration decreases the risk of major cardiovascular events but increases the risk of bleeding.[1] Although the benefit in terms of cardiovascular mortality, myocardial infarction, and revascularization was evaluated in several meta-analyses, the effect of different durations of DAPT on the risk of bleeding and its clinical consequences, in particular fatal events, have received less attention.[2] Furthermore, evaluation of the safety of different durations of DAPT is hampered by heterogenous bleeding definitions across studies.

Assessment of the case-fatality rate of major bleeding may help improve balancing risks and benefits of different durations of DAPT because not only the absolute risk of major bleeding but also its fatality should be considered when individualizing the duration of DAPT. The case-fatality rate also allows to measure the impact of bleeding events during different treatment periods, which may be important because a major bleed in the first months of DAPT may have different consequences compared with a major bleed after the initial 12 months of DAPT. Furthermore, the case-fatality rate of major bleeding provides an objective measure of bleeding severity, when comparing results among studies using different bleeding definitions.

In this systematic review and meta-analysis, we therefore aimed to determine the case-fatality rate of major bleeding events after percutaneous coronary intervention (PCI) with DES, to evaluate case-fatality rates across different durations of DAPT and bleeding definitions, and to compare the risk of fatal bleeding in patients receiving short-, standard-, and long-term DAPT.

2 | METHODS

2.1 | Literature search and eligibility criteria

Medline, Embase, and Cochrane Central Register of Controlled Trials were searched without language restriction from inception to August 11, 2021, for relevant studies combining terms for "randomized controlled trial," "percutaneous coronary intervention," "drug-eluting stent," "dual antiplatelet therapy," "aspirin," "clopidogrel," "prasugrel," and "ticagrelor." The search strategy (Table S1) was reviewed by an information specialist according to the guideline for Peer Review of Electronic Search Strategies.[3] To identify additional studies, we consulted content experts and searched references of included studies.

Randomized controlled trials comparing different durations or agents of DAPT in DES-treated patients with coronary artery disease were eligible. Studies were included if they fulfilled the following three criteria: (1) the study prospectively enrolled patients with coronary artery disease who underwent implantation of DES; (2) participants were randomized to receive any combination of aspirin and a $P2Y_{12}$ receptor inhibitor (i.e., clopidogrel, prasugrel, or ticagrelor) for at least 1 month; and (3) fatal bleeding events were reported or provided by the study investigators. The protocol of this study was registered with PROSPERO (CRD42020193341). Ethical approval was not sought because this meta-analysis was based on already published study-level data.

2.2 | Study selection, data extraction, and risk of bias assessment

Two investigators independently screened titles, abstracts, and subsequently full-text articles using Covidence systematic review software (www.covidence.org). Data extraction and assessment for risk of bias

were performed in duplicate by two investigators using the revised Cochrane Collaboration's method for assessing risk of bias in randomized trials (RoB 2).[4] Standardized forms were used to extract data including study and participant characteristics, definitions of major bleeding, and study outcomes. Disagreements at screening, data extraction, or risk of bias assessment were resolved through discussion or by consulting a third author. In case relevant information in an eligible study was not available, the principal investigator of the study was contacted to provide the data of interest. A reminder to share data was sent 3 weeks after the initial invitation to collaborate. If the author did not respond, the study was excluded before performing the analysis in August 2021.

2.3 | Study outcomes

The primary study outcome was fatal bleeding. Bleeding events were classified as "major bleeding" based on the primary bleeding definition of the individual studies (Table S2). The case-fatality rate of major bleeding was defined as the proportion of fatal bleeding events relative to the total number of major bleeding events.

We specified secondary outcomes in the study protocol but decided to omit meta-analyses on these outcomes, because our systematic review did not identify more data than already meta-analyzed in previous studies.[1,5]

2.4 | Statistical analysis

Duration of DAPT was categorized as short term (i.e., ≤6 months), standard term (i.e., 12 months), and long term (i.e., >12 months). Summary estimates (i.e., proportion for case-fatality rates and risk ratios for treatment comparisons) were calculated using the random effects inverse-variance method. A continuity correction of 0.5 was used in studies with zero cell frequencies. The Sidik-Jonkman estimator for between-study variance and the method by Hartung and Knapp were used to adjust test statistics and confidence intervals for treatment comparisons.[6] For the calculation of case-fatality rates, a logit transformation was conducted before pooling proportions and the Wilson score method was used to calculate 95% confidence intervals (CIs).

Patients who were assigned to DAPT during the study follow-up were considered in the analysis of case-fatality rates; those on antiplatelet monotherapy were excluded. For example, if a study randomized patients 12 months after DES insertion to aspirin monotherapy versus DAPT, only patients assigned to the DAPT arm were considered for the analysis of case-fatality rates. Study arms and follow-up periods that were considered for the analysis of case-fatality rates of major bleeding are depicted in Figure 1.

Subgroup analyses were performed by primary bleeding definition, duration of DAPT, and type of $P2Y_{12}$ receptor inhibitor (i.e., studies or study arms in which >90% of patients received clopidogrel vs. heterogenous use of $P2Y_{12}$ receptor inhibitors vs. use of prasugrel or ticagrelor in all patients). For the estimation of case-fatality rates by duration of DAPT, only studies reporting events for a specific DAPT period were considered (i.e., first 12 months vs. beyond 12 months after DES insertion). For example, the long-term DAPT arm of the PRODIGY study was not included for the estimation of the case-fatality rate of major bleeding on long-term DAPT because the study only reported bleeding events for the entire period of months 2–24 after DES insertion (Figure 1).

In sensitivity analyses, we excluded trials at high risk of bias and studies or study arms in which $P2Y_{12}$ inhibitors other than clopidogrel were used for DAPT in ≥10% of patients.

Statistical heterogeneity was evaluated using the I^2 statistic and by providing 95% prediction intervals.[7,8] Small-study bias was evaluated using the Egger regression test. A p value <.05 was considered to indicate statistical significance. All analysis were performed in R, version 3.6.3, using the *meta* package for meta-analysis.[9]

3 | RESULTS

Of the 2777 citations identified from the systematic literature search, 175 studies were assessed as full texts and 31 considered potentially relevant (Figure S1; Table S3). Fatal bleeding was reported in the primary publication of 15 (48%) potentially relevant studies.[10–24] After contacting corresponding authors for unreported data on fatal bleeds, a total of 16 studies were included in the review,[10–25] whereas the remaining 15 studies were excluded because information required for our analysis was unavailable or not provided (Table S3). All excluded studies assessed bleeding as their primary safety outcome but did not report the number of fatal bleeding events in the primary trial publication or secondary publications identified by our search (Table S3).

3.1 | Characteristics of included studies and bias assessment

The 16 included studies enrolled a total of 62,648 patients. Mean age ranged from 59 to 69 years (median 64 years); 16,985 (27%) were female. Among the 16 studies included in the analysis, two (n = 3352) compared different $P2Y_{12}$ receptor inhibitors,[10,11] seven (n = 33,668) evaluated short-term versus standard-term DAPT,[12–17,25] five (n = 20,351) long-term versus standard-term DAPT,[18–22] and two (n = 5277) short-term vs long-term DAPT[23,24] (Figure 1; Table 1). Most patients (57% [27,983/48,884]) who were allocated to DAPT during study follow-up received aspirin plus clopidogrel (Table 1). In the GLOBAL LEADERS study,[12] all patients on short-term DAPT and 4146 (52%) on standard-term DAPT received ticagrelor; in the TICO study,[17] all patients on DAPT received ticagrelor. The PRASFIT-Elective study randomized patients to prasugrel plus aspirin (n = 370) or clopidogrel plus aspirin for 6 months (n = 372).[10] The TROPICAL ACS study randomized patients to aspirin plus prasugrel (n = 1306) or aspirin plus deescalation from prasugrel to clopidogrel based on platelet function testing 14 days after hospital discharge (798 received clopidogrel [61%] and 506

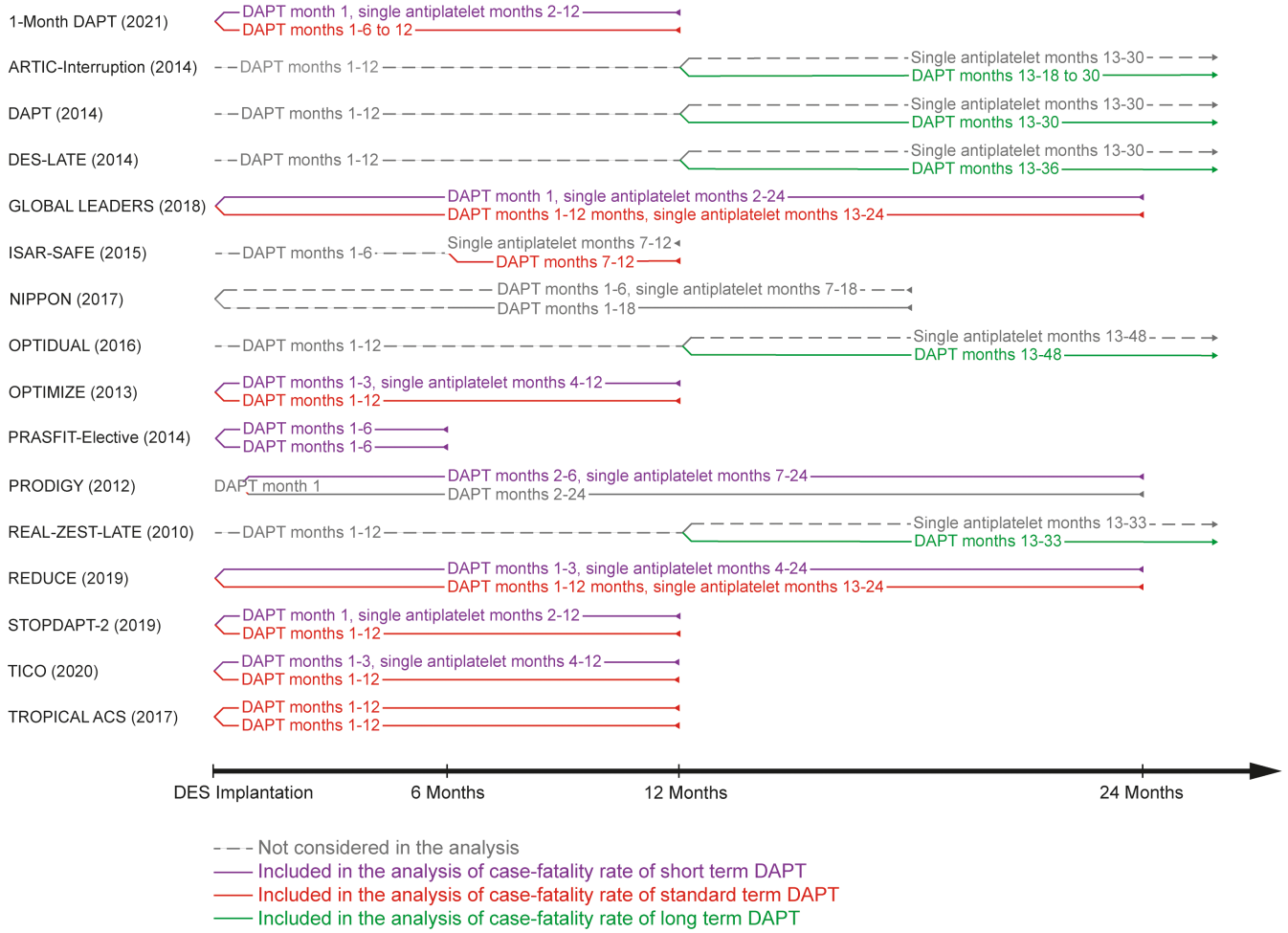

FIGURE 1 Study arms and follow-up periods considered for the calculation of case-fatality rates of major bleeding. The bifurcations indicate the time of randomization and start of follow-up. We considered patients allocated to 18 months of DAPT in the NIPPON trial and 24 months of DAPT in the PRODIGY trial for the overall case-fatality rate of major bleeding; neither treatment arm was considered for the calculation of the case-fatality rate of major bleeding by treatment duration, because outcomes were not specifically reported according to our predefined groups by duration of DAPT. DAPT, dual antiplatelet therapy.

[39%] continued prasugrel).[11] The ARCTIC-Interruption,[19] DAPT,[18] NIPPON,[24] and REDUCE trials[15] left the choice of $P2Y_{12}$ receptor inhibitor at the treating physician's discretion; clopidogrel use ranged from 40% to 98% (Table 1).

The overall risk of bias for the bleeding results was assessed as "low" in nine studies, as "some concerns" in three studies and as "high" in four studies (Figure 2). The main reason for bias was nonadherence to the assigned DAPT regimen (domain 2 of the RoB 2). The remaining domains were assessed as "low risk" in all studies, except for one study in which the randomization procedure was not described and no protocol, prespecified statistical analysis plan, or study registration were available.

3.2 | Fatal bleeding

A total of 98 (0.2%) fatal bleeds occurred in 59,296 patients who were included in the 14 studies that evaluated different durations of DAPT, and one (0.03%) fatal bleed occurred in 3352 patients who were included in the two studies[10,11] evaluating different $P2Y_{12}$ receptor inhibitors. Of the studies evaluating different DAPT durations, 12 studies assessed either short- or extended-term DAPT versus standard-term DAPT (n = 54,019; fatal bleeds, 82 [0.2%]). Compared with patients allocated to standard-term DAPT, the risk of fatal bleeding did not differ in those allocated to long-term DAPT (risk ratio, 1.09; 95% CI, 0.35–3.42; I^2 = 0%; 95% prediction interval, 0.09–13.3; Figure S2) or short-term DAPT (risk ratio, 0.70; 95% CI, 0.36–1.39; I^2 = 0%; 95% prediction interval, 0.19–2.57; Figure S3).

3.3 | Case-fatality rate of major bleeding

A total of 823 major bleeds including 91 fatal events occurred in 48,884 patients who were assigned to receive short-term, standard-term, or long-term DAPT during the follow-up period. The overall case-fatality rate of major bleeding was 10.8% (95% CI, 7.1–16.2; I^2 = 50%;

TABLE 1 Characteristics of the trials included in the meta-analysis

Study (first author, year)	Funding source	Design	Setting	DAPT duration	Use of clopidogrel for DAPT	Time point of rando-mization	Follow-up duration after randomization	Major bleeding definition
1-Month DAPT (Hong, 2021)[14]	Industrial	Randomized, open-label, noninferiority trial	Multicenter Asia	1 month (n = 1507); 6–12 months (n = 1513)	1405/1507 (93%); 1421/1513 (94%)	At DES insertion	12 month	STEEPLE major bleed
ARCTIC-Interruption (Collet, 2014)[19]	Industrial and nonindustrial	Randomized, open-label, superiority trial	Multicenter Europe	12 month (n = 624); 18–30 months (n = 635)	NA; 569/635 (90%)	12 month after DES insertion	Median of 17 month	STEEPLE major bleed
DAPT (Mauri, 2014)[18]	Industrial and nonindustrial	Randomized, double-blind, superiority trial	Multicenter worldwide	12 month (n = 4941); 30 month (n = 5020)	NA; 3275/5020 (65%)	12 month after DES insertion	18 month	GUSTO severe or moderate
DES-LATE (Lee, 2014)[20]	Nonindustrial	Randomized, open-label, superiority trial	Multicenter Asia	12 month (n = 2514); 36 months (n = 2531)	NA; 2531/2531 (100%)	12–18 months after DES	24 month	TIMI major bleed
GLOBAL LEADERS (Vranckx, 2018)[12]	Industrial	Randomized, open-label, superiority trial	Multicenter worldwide	1 month (n = 7980); 12 month (n = 7988)	0/7980 (0%); 3842/7988 (48%)	At DES insertion	24 month	BARC 3 or 5
ISAR-SAFE (Schulz-Schupke, 2015)[13]	Industrial and nonindustrial	Randomized, double-blind, noninferiority trial	Multicenter worldwide	6 month (n = 1997); 12 month (n = 2003)	NA; 2003/2003 (100%)	6 month after DES insertion	9 month	TIMI major bleed
NIPPON (Nakamura, 2017)[24]	Industrial and nonindustrial	Randomized, open-label, noninferiority trial	Multicenter Asia	6 month (n = 1654); 18 month (n = 1653)	1619/1654 (98%); 1605/1653 (97%)	At DES insertion	Median of 435 d	Modified REPLACE-2 major bleed
OPTIDUAL (Helft, 2016)[21]	Industrial and nonindustrial	Randomized, open-label, superiority trial	Multicenter Europe	12 month (n = 690); 48 month (n = 695)	NA; 695/695 (100%)	12 month after DES insertion	36 month	ISTH major bleed
OPTIMIZE (Feres, 2013)[25]	Industrial	Randomized, open-label, noninferiority trial	Multicenter South America	3 month (n = 1563); 12 month (n = 1556)	1563/1563 (100%); 1556/1556 (100%)	At DES insertion	12 month	Modified REPLACE-2 major bleed
PRASFIT-Elective (Isshiki, 2014)[10]	Industrial	Randomized, double-blind trial	Multicenter Asia	6 month (n = 370); 6 month (n = 372)	0/370 (0%); 372/372 (100%)	At DES insertion	6 month	TIMI major bleed
PRODIGY (Valgimigli, 2012)[23]	Nonindustrial	Randomized, open-label, superiority trial	Multicenter Europe	6 month (n = 983); 24 month (n = 987)	983/983 (100%); 987/987 (100%)	1 month after insertion	24 month	BARC 3 or 5
REAL-ZEST-LATE (Park, 2010)[22]	Nonindustrial	Randomized, open-label, superiority trial	Multicenter Asia	12 month (n = 1344); 33 month (n = 1357)	NA; 1357/1357 (100%)	12 month after DES insertion	Median of 19 month	TIMI major bleed
REDUCE (De Luca, 2019)[15]	Industrial	Randomized, open-label, noninferiority trial	Multicenter Europe and Asia	3 month (n = 751); 12 month (n = 745)	308/751 (41%); 301/745 (40%)	At DES insertion	24 month	BARC 3 or 5[a]
STOPDAPT-2 (Watanabe, 2019)[16]	Industrial	Randomized, open-label, noninferiority trial	Multicenter Asia	1 month (n = 1500); 12 month (n = 1509)	903/1500 (60%); 1509/1509 (100%)	At DES insertion	12 month	TIMI major bleed
TICO (Kim, 2020)[16]	Industrial	Randomized, open-label, superiority trial	Multicenter Asia	3 month (n = 1527): 12 month (n = 1529)	0/1527 (0%); 0/1529 (0%)	At DES insertion	12 month	TIMI major bleed
TROPICAL ACS (Sibbing, 2017)[11]	Industrial and nonindustrial	Randomized, open-label, noninferiority trial	Multicenter Europe	12 month (n = 1306); 12 month (n = 1304)	0/1306 (0%); 798/1304 (61%)	At DES insertion	12 month	BARC 3 or 5

Abbreviations: DAPT, dual antiplatelet therapy; DES, drug-eluting stent; NA, not applicable.

[a]Major bleeding was defined as BARC 2, 3, or 5 bleeds in the original trial. For this meta-analysis, only BARC 3 or 5 bleeds were considered to be a major bleed.

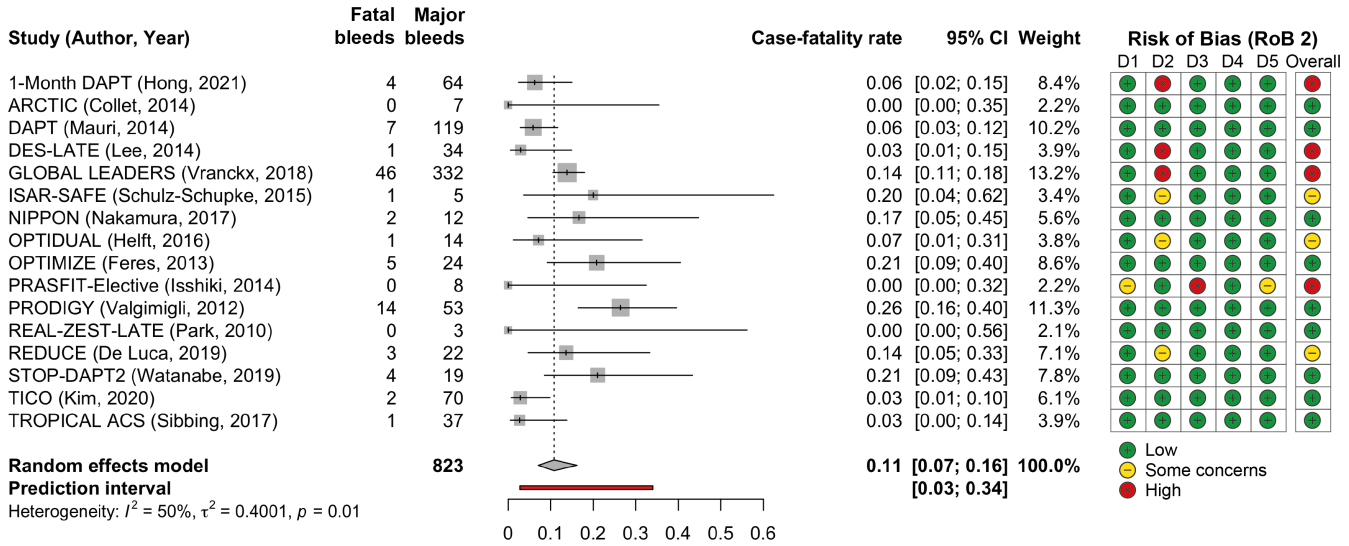

FIGURE 2 Case-fatality rate of major bleeding in patients on DAPT after PCI with DES. Risk of bias legend: D1, bias arising from the randomization process; D2, bias because of deviation from the intended intervention; D3, bias because of missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of the reported result

95% prediction interval, 2.7–34.0; Figure 2). The case-fatality rate of major bleeding in patients on short-term DAPT (n = 16,553), standard-term DAPT (n = 19,453), and long-term DAPT (n = 10,238) was 13.8% (95% CI, 6.5–27.1; I^2 =28%), 11.2% (95% CI, 6.7–18.0; I^2 =0%), and 5.8% (95% CI, 3.0–11.1; I^2 =0%), respectively (Figure 3; p = 0.63 and p = 0.12 for subgroup difference between short- and standard-term DAPT and between standard- and long-term DAPT, respectively).

Six different major bleeding definitions were used across the 16 included studies (Table 1). The case-fatality rate of major bleeding did not differ statistically significantly across bleeding definitions, but few studies constituted each subgroup (Figure 4).

The case-fatality rates of major bleeding did not differ according to the type of $P2Y_{12}$ receptor inhibitor (Figure S4).

Small-study bias was not evident for case-fatality rates of major bleeding (Egger test, p = .16). However, reporting bias cannot be excluded, because fatal bleeding was not reported in 48% of potentially relevant studies.

3.4 | Sensitivity analysis

When studies at high risk of bias or those using a $P2Y_{12}$ inhibitor other than clopidogrel in ≥10% of patients were excluded in sensitivity analyses, the overall case-fatality rate of major bleeding, as well as the subgroup estimates did not change meaningfully (Figures S5–S10).

4 | DISCUSSION

Our meta-analysis of 16 studies demonstrates that the case-fatality rate of major bleeding is substantial (10.8%). It may be especially high in the first 12 months of DAPT (13.8% for short-term DAPT and 11.2% for standard-term DAPT) and decrease during long-term DAPT (5.8%). Whether the case-fatality rate of major bleeding varies across different bleeding definitions remains uncertain, mainly because of the numerous definitions that were used with subsequently low events per subgroup. Our findings suggest that future studies should assess whether the case-fatality rate of major bleeding should be considered in the risk–benefit equation for different DAPT durations and be used by clinicians to improve individualized management of patients who undergo PCI, when combined with cardiovascular mortality and major bleeding rates. Furthermore, fatal bleeding was underreported, and reporting of such events should be encouraged in future research on DAPT to allow assessment of treatment effects on the most severe form of bleeding.

The consequences of major bleeding have received little attention in previous meta-analysis of DAPT following PCI.[2] In an individual participant data meta-analysis of randomized controlled trials evaluating DAPT for miscellaneous indications (i.e., acute coronary syndrome, high risk of cardiovascular disease, lacunar stroke, atrial fibrillation, PCI), patients on DAPT had an increased risk of fatal bleeding compared with those who received aspirin plus placebo (hazard ratio, 1.42; 95% CI, 1.04–1.95).[26] In contrast, a meta-analysis of 33,435 patients with previous myocardial infarction showed that long-term DAPT, compared with standard-term DAPT, was not associated with an increased risk of fatal bleeding (risk ratio 0.91; 95% CI, 0.53–1.58), but a higher risk of major bleeding (risk ratio, 1.73; 95% CI, 1.19–2.50).[27] Our study of DES-treated patients supports findings that long-term DAPT, compared with standard-term DAPT, is not associated with an increased risk of fatal bleeding (risk ratio, 1.09; 95% CI, 0.35–3.42) in DES-treated patients with coronary artery disease. However, our and other studies are underpowered to adequately assess differences of this rare outcome, despite evaluating data of close to 60,000 patients. Similarly, previous meta-analyses failed to show differences in cardiovascular

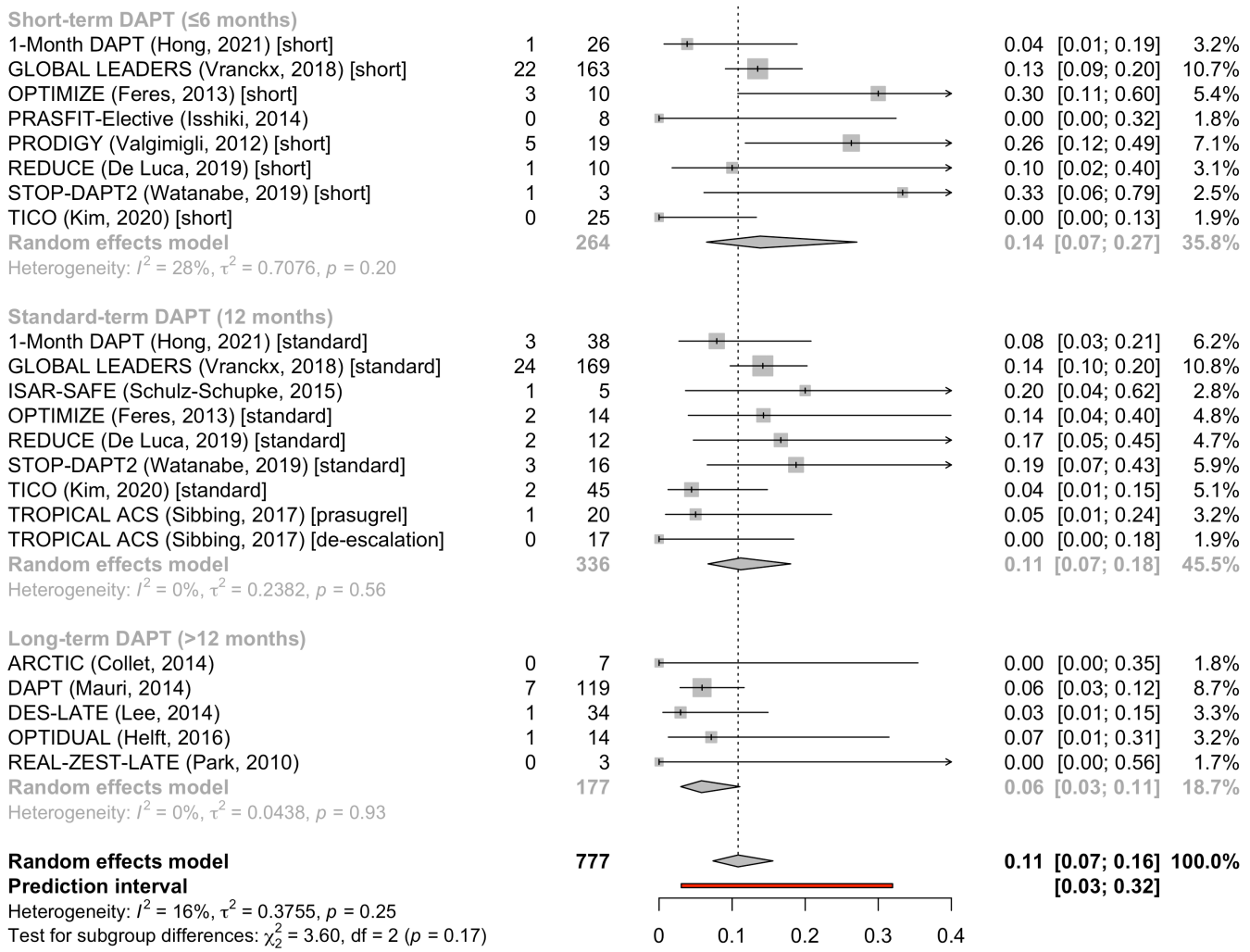

FIGURE 3 Case-fatality rate of major bleeding by duration of DAPT. CI, confidence interval

death rates between different durations of DAPT,[1,5] and the effect of different DAPT durations on all-cause mortality is uncertain.[1,5] As such, comparing rates of cardiovascular and major bleeding events and differentially weigh these surrogate outcomes of death by using case-fatality rates may help estimating mortality differences between different durations of DAPT. In this regard, our study provides important additional information. The overall case-fatality rate of major bleeding in patients on DAPT was substantial and with 10.8% comparable to the case-fatality rate of major bleeding in patients on direct oral anticoagulants (8%–10%) or vitamin K antagonists (8%–11%).[28,29] This risk is important to consider when counseling patients on safety measures to reduce the risk of bleeding (e.g., avoid contact sports, wearing helmets) and when evaluating the indication for a proton pump inhibitor. Furthermore, the case-fatality rates may be lower during long-term DAPT than in the first 12 months of DAPT following PCI. Similarly, in some randomized controlled trials evaluating DAPT in patients with clinically evident cardiovascular disease, the bleeding excess for DAPT versus antiplatelet monotherapy was confined to the first year,[30–32] whereas in other trials it was not.[18,23] Combined with our results, these findings may indicate that patients who are going to bleed on DAPT tend to bleed early and that the risk of such a bleed to be fatal may be more pronounced in the first 12 months. Patients who do not experience a bleeding event that led to cessation of treatment during the first 12 months (so-called stress test)[33] and continued DAPT beyond 12 months may have a lower risk of adverse bleeding outcomes. This hypothesis may particularly apply to patients who experience an extracranial bleeding event because occurrence of intracranial hemorrhage is more stochastic.[34]

Heterogenous bleeding definitions limit between-study comparisons and meta-analysis of different DAPT durations. Importantly, there is more than fourfold difference in the frequency of major bleeding events across different definitions,[35] and, as such, bleeding definitions influence the assessment of the net clinical benefit and decisions regarding the optimal duration of DAPT in clinical practice. Although our analysis was underpowered to detect a statistically significant difference in case-fatality rates of major bleeding according to bleeding definitions, point estimates of case-fatality

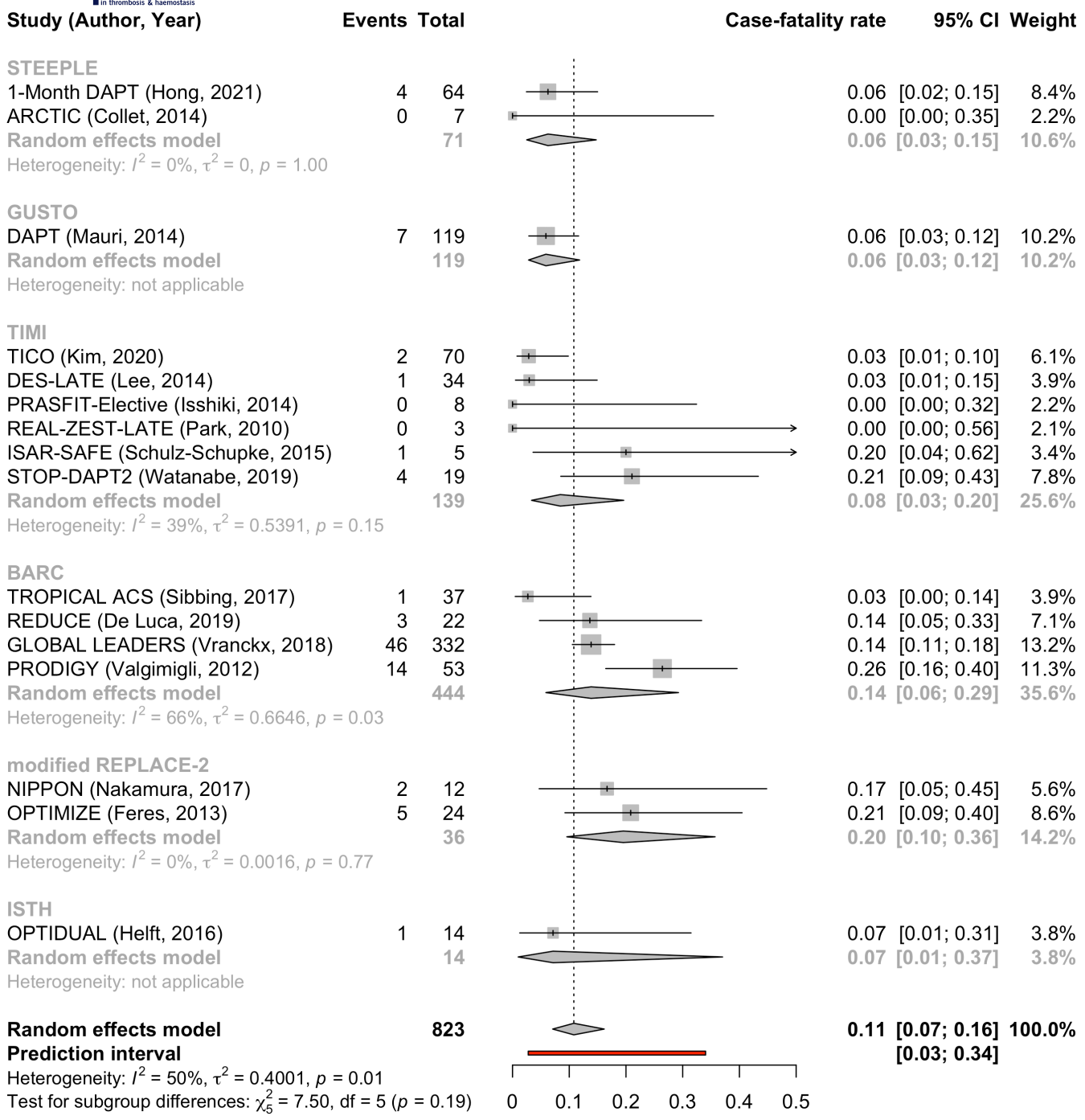

FIGURE 4 Case-fatality rate of major bleeding by bleeding definition. CI, confidence interval

rates ranged from 0% to 26%, highlighting the potential influence of different definitions on the fatality of bleeding events.

Following insertion of DES, the 2016 American College of Cardiology and American Heart Association guidelines recommend at least 6 months of DAPT in patients with stable ischemic heart disease and at least 12 months of DAPT in patients with acute coronary syndromes.[36] The guidelines provide conditional recommendations for short-term DAPT and long-term DAPT depending on bleeding risk, which is determined based on clinical parameters (e.g., prior bleeding on DAPT, oral anticoagulant use). A recent individual patient-data meta-analysis, including 14,963 patients from eight randomized controlled trials, supports the approach to guide duration of DAPT based on the risk of bleeding.[37] Our results indicate that not only the risk of major bleeding, but also its case-fatality rate should be considered in the risk–benefit equation in future studies because it may help estimating mortality differences, when combined with cardiovascular mortality rates, and because case-fatality rates may differ based on the duration of DAPT.

There are potential limitations to this study. First, 15 of 31 (48%) potentially relevant studies did not report fatal bleeding events. Second, we pooled trials with heterogeneous populations

that varied in study design, treatment strategy, and major bleeding definitions. To address heterogenous study designs, we considered only study arms that represent specific DAPT periods for the calculation of case-fatality rates (Figure 1). Furthermore, we performed subgroup and sensitivity analyses, which did not demonstrate meaningful differences in case-fatality rates by type of $P2Y_{12}$ receptor inhibitor or after exclusion of studies at high risk of bias. Overall, there was moderate statistical heterogeneity associated with the overall case-fatality rate of major bleeding ($I^2 = 50\%$; 95% prediction interval, 2.7%–34%), which could largely be explained by different durations of DAPT ($I^2 = 0\%$ for subgroups of standard-term and long-term DAPT; $I^2 = 28\%$ for subgroup of short-term DAPT). Third, inherent to the available data, different bleeding classifications were used to define major bleeding. Albeit our analysis did not suggest a statistically significant difference of case-fatality rates of major bleeding according to bleeding definitions, few studies constituted each subgroup which precludes a firm conclusion. Similarly, the subgroup analysis by duration of DAPT was underpowered and does not allow firm conclusions. Fourth, 13 (81%) studies used an open-label design, which may result in ascertainment and detection bias of bleeding events. However, most open-label trials used a central adjudication committee that was blinded to the treatment allocation of study participants and fatal bleeding is unlikely to be prone to these biases. Fifth, the introduction of reversal agents for ticagrelor may decrease case-fatality rates of major bleeding in the future.[38] Sixth, the use of proton pump inhibitors may affect the risk of major bleeding on DAPT but the proportion of patients on a proton pump inhibitor during follow-up was rarely reported in the included studies, prohibiting a meaningful subgroup analysis by proton pump inhibitor use. Seventh, few studies provided data on race of the participants preventing the evaluation of differences in case-fatality rates by race. Finally, patients enrolled in trials that evaluate long-term DAPT might be at a lower risk of bleeding than those enrolled in trials evaluating shorter duration of DAPT. Whether this potential difference in the baseline risk of major bleeding affects the severity or consequences of a major bleeding event cannot be excluded. We did not request individual patient data, which would have allowed us to adjust estimates by various risk factors.

In conclusion, almost one-half of studies that evaluated DAPT after PCI did not report on fatal bleeding. The case-fatality rate of major bleeding on DAPT is substantial and may be higher in the first 12 months of DAPT than during long-term DAPT.

AUTHOR CONTRIBUTIONS

Study concept and design: T. T., N. K., G. L. G., and L. A. C. Study selection, data extraction, and assessment of risk of bias: T. T., A. P., and L. A. C. Data analysis: T. T. Drafting of the manuscript: T. T., N. K., and L. A. C. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the manuscript: All authors. T. T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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