Sex-based outcomes of dual-antiplatelet therapy after percutaneous coronary intervention: a pairwise and network meta-analysis

Short title: *Agbaedeng et al., sex differences in DAPT outcome*

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ABSTRACT

Background Although dual antiplatelet therapy (DAPT) improves the outcomes of patients undergoing percutaneous coronary intervention (PCI), sex-specific differences in efficacy and safety of DAPT remain unresolved. We compared sex differences for DAPT outcomes and DAPT durations (1–3-month [short-term], 6-month [mid-term], and >12-month [extended] versus 12-month).

Methods We searched databases through 31st December 2023 for trials reporting DAPT after PCI. The endpoints were major adverse cardiovascular and cerebrovascular events (MACCE), net-adverse clinical and cerebrovascular events (NACCE), and any bleeding. Extracted data were pooled in a frequentist network and pairwise, random-effects meta-analysis.

Results Twenty-two trials (99,591 participants, 25.2% female) were included. Female sex significantly associated with a higher 1-year MACCE risk (hazard ratio 1.14 [95% confidence interval 1.02–1.28]) and bleeding (1.13 [1.00–1.28]), but not NACCE (1.12 [0.96–1.31]). In sub-analyses, the association between female sex and MACCE was related to use of clopidogrel as the second anti-platelet (1.11 [1.03–1.20]), whereas higher bleeding events were related to newer P2Y12 inhibitors (P2Y12i)'s (1.58 [1.01–2.46]). For DAPT duration, short-term DAPT followed by P2Y12i monotherapy was non-inferior for MACCE in females and males (0.95 [95% CI 0.83–1.10 and 0.96 [0.80–1.16]) but tended to be superior in males for NACCE vs. 12-month DAPT (0.96 [0.91–1.01]); mid-term DAPT tended to be associated with a lower bleeding risk in males (0.43 [0.17–1.09]).

Conclusions Female sex is associated with higher MACCE and bleeding when newer P2Y12i agents are used. Short-term DAPT followed by P2Y12i monotherapy is safe and effective in both sexes undergoing PCI.

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Keywords: dual antiplatelet therapy, DAPT; sex difference; percutaneous coronary intervention, PCI; network meta-analysis

Key Points

- Female sex is associated with ischaemic and bleeding events post PCI
- Short-term dual-antiplatelet therapy (DAPT) is noninferior to 12-month DAPT in preventing ischaemic and bleeding events in both sexes
- Sex dimorphism in DAPT outcome should be considered in guideline recommendations

1. INTRODUCTION

Dual antiplatelet therapy (DAPT) is recommended for patients undergoing percutaneous coronary intervention (PCI). However, the optimal duration of these combinatorial therapies remains uncertain. Depending on the clinical indication, current strategies usually involve 3–12 month treatment with aspirin plus P2Y12 inhibitor (P2Y12i [i.e., clopidogrel, prasugrel, or ticagrelor]) [1, 2]. The 2017 European Society of Cardiology guidelines recommend DAPT for 6 months following PCI with drug-eluting stent (DES) in patients with stable coronary disease, with the potential for extension in those at a low bleeding risk or early discontinuation (at 3 months) in those with a high bleeding risk [1]. For patients with acute coronary syndromes (ACS), a minimum of 12 months of DAPT is recommended, which could be extended in those at a lower risk of bleeding or abbreviated in those at a high risk of bleeding [1, 2]. However, current guideline recommendations are mostly based on trials with underrepresentation of females [3]. Thus, current DAPT recommendations fail to account for the unique differences in females and males.

There are indeed major biological and clinical sex differences between females and males that may warrant reconsideration of DAPT recommendations. Both preclinical and clinical studies show that females have greater susceptibility to endothelial dysfunction and platelet reactivity [4, 5]. Females also have smaller arteries than males, and those presenting with coronary artery disease (CAD) tend to be older, present more frequently with non-ST-segment elevation ACS, and have a higher burden of comorbidities [6-8]. Overall, females have worse short- and long-term prognosis from CAD and poorer outcomes related to major bleeding and major adverse cardiovascular and cerebrovascular events (MACCE) after PCI [9-11]. These data are accompanied by the fact that females are more likely to be undertreated with PCI, receive DAPT and more specifically to be prescribed more potent P2Y12i, such as prasugrel [3]. Moreover, in the PARIS (Patterns of Non-Adherence to

Antiplatelet Regimens in Stented Patients) study, females also had higher rates of early DAPT cessation compared to males.[12] These important observations underscore the need to evaluate whether there were sex-specific differences in outcomes with DAPT in contemporary randomised controlled trials (RCTs). We therefore performed this trial-level meta-analysis (MA) to compare DAPT outcomes in females versus males, with additional focus on how this was affected by different durations of DAPT.

2. METHODS

2.1 Registration and Reporting

This systematic review and meta-analysis was prospectively registered on PROSPERO (**ID: CRD42021278663**) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13].

2.2 Data Sources and Searches

We searched MEDLINE, Embase, and Web of Science Core Collection to identify relevant studies published through 1st January 2023. Relevant key terms relating to "sex" and "dual antiplatelet therapy" AND "percutaneous coronary intervention" were employed (**Supplementary Methods S1**). Furthermore, the reference lists of relevant articles and reviews were manually searched for additional data sources.

2.3 Eligibility Criteria and Study Selection

After removing duplicates, two investigators (TAA & JJN) screened the titles and abstracts of retrieved references independently for eligibility. The exclusion criteria included: case reports and series, conference abstracts, editorials, *in vitro* and *in vivo* animal studies and non-randomised trials. References of RCTs reporting patients on DAPT post-PCI were included

for full-text review. Following this, full texts were subsequently evaluated by two independent investigators (TAA, JJN) for final eligibility. The following exclusion criteria were applied: non-PCI based revascularisation; DAPT usage before PCI; aged <18 years or ≥80 years; or no data on sex. Studies with sample size ≥500 patients and complete data for sex, DAPT duration, and clinical outcome following PCI were included. Any discrepancies were resolved by consensus.

2.4 Data Extraction and Quality Assessment

Two investigators (TAA and JJN) independently extracted data using a preconceived data form on trial characteristics, participant characteristics (i.e., age, gender, diagnosis, comorbidities, type of stent, antiplatelet regimen used), maximum follow-up duration, prevalence of comorbidities, crude effect size estimates, number of events and non-events, and sample size. Discrepancies were resolved by discussion. DAPT strategies were defined as: short-term DAPT, DAPT given for 1–3 months post-PCI followed by either aspirin or a newer P2Y12i agent; mid-term DAPT, DAPT given for up to 6 months post-PCI; standard DAPT; DAPT given for 12 months; or extended DAPT; DAPT given for >12 months, respectively. DAPT was classified into three groups: clopidogrel-based DAPT, when clopidogrel was the only P2Y12i used in the strategy; newer P2Y12i-based DAPT, when prasugrel or ticagrelor was the only P2Y12i agent used; or mixed DAPT, when either clopidogrel or a newer P2Y12i agent was used.

Potential risk of bias (RoB) was assessed across five different domains of bias using the Cochrane Risk of Bias Tool version 2.0 [14]. The RoB tool consists of five domains of bias, addressing all crucial mechanisms through which bias can be introduced into trial evidence. The domains are labelled using descriptions of the causes of bias addressed, which

are in turn assessed using signalling questions. The RoB per domain is categorised as low, unclear, or high.

2.5 Outcomes and End Points

The co-primary end points were major adverse cardiovascular and cerebrovascular events (MACCE), any bleeding, and net adverse clinical and cerebrovascular events (NACCE). MACCE was defined as a composite of all-cause death, myocardial infarction (MI), cardiovascular (CV) death, stroke or transient ischaemic accident (TIA), and definite or probable stent thrombosis (ST). NACCE was defined a composite of MACCE and any bleeding. The secondary ischaemic end points included: all-cause death, MI, stroke, CV death, stent thrombosis, stroke/TIA, definite or probable ST, repeat revascularisation. Secondary bleeding end points included: Bleeding Academic Research Consortium (BARC) grade 3 or 5 bleeding. Complete definitions of primary outcomes are provided in **Supplemental Table S1**.

2.6 Data Synthesis and Analysis

We performed pairwise, random-effects meta-analyses comparing events in females versus males. Heterogeneity was assessed using the X^2 test on Cochrane's Q statistic, quantified by I^2 values (values of <25%, 50–75%, and >75% represent low, moderate, and high heterogeneity, respectively) [15]. Results are presented as forest plots, either individually or summarised by subgroups for the type of outcome or duration of DAPT.

Additionally, we performed random-effects, frequentist NMA in females and males for different DAPT durations, summarising this as hazard ratio (HR) and 95% confidence interval (95% CI). All HRs were measured as 1-year event rates (**Supplemental Data**). The effectiveness and safety of treatments were assessed using the P-score metric, which was

calculated from the risk estimates and corresponding standard errors as previously described [16]. The P-score metric serves as a treatment rank and measures the extent of certainty that one intervention is better than another, which is averaged over all competing interventions. P-score values can vary between 0.0 and 1.0, with a higher value indicating the likelihood that an intervention is highly effective. We then examined the consistency between direct and indirect sources of evidence by the network splitting method (**Supplemental Table S2**). All statistical tests were two-tailed, with significance defined as 95% confidence intervals (95% CI) not crossing 1.0. All analyses were conducted using *netmeta* and *meta* packages in R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

3.1 Literature Synthesis and Characteristics

Of 697 records obtained from database and supplementary searches, 22 trials involving 99,591 participants (25,106 females, 25.2%) met our inclusion criteria (**Supplemental Figure S1**) [17-38]. All trials were included in the pairwise meta-analysis of sex differences. Thirteen trials contributed data for the network meta-analysis (**Figure 1**). The characteristics of the included trials are shown in **Table 1** and the distribution of demographic and comorbidity characteristics is presented in **Supplemental Tables S3**.

3.2 Risk of Bias

The RoB of included trials is shown in **Supplemental Table S4**. Of these, 81.8% and 18.2% of trials had low RoB or some concerns due to randomisation, respectively; 27.3%, 54.5%, and 18.2% had low, some concerns, or high RoB, respectively, due to assignment to intervention; 68.2%, 27.3%, and 4.5% had low, some concerns, or high RoB, respectively, due to adherence to assigned intervention; 77.3% and 22.7% had low RoB or some concerns

due to missing outcome data; 86.4% and 13.6% had low RoB or some concerns due to measurement of outcomes; and 81.8% and 18.2% had low RoB or some concerns due to selection of reported results.

3.3 Pairwise Meta-Analysis

3.3.1 Primary Outcome

Results for overall sex differences in primary outcomes are presented in **Figure 2**. Compared to males, female sex was significantly associated with higher 1-year risk of MACCE (HR 1.14 [95% CI 1.02–1.28]) and any bleeding (1.13 [1.00–1.28]), but not NACCE (1.12 [0.96–1.31]). The association between female sex and primary endpoints were significant for MACCE (1.15 [1.04–1.26]) during only at 24-month follow-up and any bleeding during at 12-month follow-up (1.31 [1.02–1.68]).

In subgroup analyses, compared to males, female sex was associated with a 11% increased risk of MACCE in patients on clopidogrel-based DAPT (1.11 [1.03–1.20]), but not for ticagrelor-based (1.14 [0.81–1.61]), mixed DAPT (1.13 [0.94–1.38]), or newer P2Y12i's (1.11 [0.78–1.58]), **Table 2**. No significant association was observed between female sex and 1-year risk of NACCE in any subgroup analysis of NACCE, **Table 2**. For bleeding, female sex was significantly associated with increased risk of any bleeding in DAPT based on any newer P2Y12i, ticagrelor-based (1.58 [1.01–2.46]), trials that de-escalated DAPT to newer P2Y12i monotherapy (1.58 [1.01–2.46]), and ACS cohorts (1.58 [1.01–2.46]). Meta-regression should no significant effect of radial access on primary outcomes (**Supplemental Figure S2**).

3.3.2 Secondary Outcomes

Results of overall sex differences for secondary outcomes are summarised in **Figure 3**. Compared to males, female sex was significantly associated with 1-year increased risk of stroke (1.18 [1.01–1.37]) and major bleeding (1.20 [1.01–1.42]), but with a lower risk of any revascularisation (0.97 [0.95–0.99]). However, female sex was not significantly associated with all-cause mortality, CV mortality, MI, any ST, definite ST, BARC major bleeding, or minor bleeding.

3.3.3 Publication Bias and Heterogeneity

We found evidence of significant heterogeneity in the pairwise meta-analyses for MACCE, NACCE, and any bleeding (P <0.05, **Table 2, Supplemental Figures S3–S5**). The *Egger's Regression* tests showed the presence of publication bias in the analysis of MACCE and any bleeding (*Egger's P* = 0.008 and 0.036), but not for NACCE (**Table 2**).

3.4 Network Meta-analysis

3.4.1 MACCE

When compared to 12-month DAPT in female participants, there were no significant differences in the risk of MACCE for short-term DAPT followed by P2Y12i monotherapy (HR 0.95 [95% CI 0.83–1.10]), short-term DAPT followed by aspirin monotherapy (0.69 [0.45–1.06]), mid-term DAPT (1.12 [0.90–1.39]), extended DAPT (1.06 [0.95–1.18]), or P2Y12i monotherapy (1.11 [52–2.36]), **Figure 4a.**. In males, compared to 12-month DAPT, no significant association was seen when short-term DAPT followed by P2Y12i monotherapy (0.96 [0.80–1.16]), short-term DAPT followed by aspirin monotherapy (1.16 [0.83–1.62]), mid-term DAPT (1.05 [0.84–1.31]), extended DAPT (1.07 [0.93–1.23]), or P2Y12i monotherapy (1.19 [0.67–2.11]).

3.4.2 NACCE

When compared to 12-month DAPT in female participants, there were no significant differences in the risk of NACCE for short-term DAPT followed by P2Y12i (0.86 [0.63–1.17]) or aspirin monotherapies (0.88 [0.63–1.23]), mid-term DAPT (0.98 [0.68–1.42]), and extended DAPT (0.99 [0.56–1.72]). In males, compared to 12-month DAPT, there was a trend for short-term DAPT followed by P2Y12i monotherapy to be associated with reduced 1-year risk of NACCE (0.96 [0.92–1.01]), while no significant difference was found for short-term DAPT followed by aspirin monotherapy (0.98 [0.87–1.12]), mid-term DAPT (0.94 [0.76–1.17]), or extended DAPT (1.14 [0.88–1.47]).

3.4.3 Any Bleeding

When compared to 12-month DAPT in female participants, there were no significant differences in the risk of any bleeding for P2Y12i monotherapy (0.41 [0.15–1.14]), short-term DAPT followed by P2Y12i (0.92 [0.59–1.45]) or aspirin monotherapies (0.86 [0.51–1.45]), mid-term DAPT (0.99 [0.43–2.28]), and extended DAPT (0.89 [0.51–1.55]). In males, compared to 12-month DAPT, mid-term DAPT tended to be associated with a lower bleeding risk (0.43 [0.17–1.09]), whereas there were no significant differences in the risk of any bleeding for P2Y12i monotherapy (0.65 [0.28–1.48]), short-term DAPT followed by P2Y12i (0.74 [0.46–1.17]) or aspirin monotherapies (0.77 [0.48–1.24]), and extended DAPT (0.80 [0.42–1.51]).

3.4.4 Ranking of Treatment Strategies

Rankograms of the various DAPT strategies are shown in **Figure 5**. Short-term DAPT followed by aspirin and P2Y12i monotherapies were ranked the best strategies for reducing MACCE in females (P-score 0.94) and males (P score 0.75); short-term DAPT followed by

P2Y12i monotherapy in females (P-score 0.65) and 12-month DAPT males (P-score 0.67) was ranked second best; and the least effective strategy was mid-term DAPT in females (P-score 0.21) and short-term DAPT followed by aspirin monotherapy in males (P-score 0.31). For NACCE, short-term DAPT followed by P2Y12i monotherapy was ranked the best strategy in females (P-score 0.69) and mid-term DAPT in males (P-score 0.73); the second-best strategies were short-term DAPT followed by aspirin and P2Y12i monotherapies in females (P-score 0.63) and males (P-score 0.72); and the least effective strategies were 12-month DAPT in females (P-score 0.33) and extended DAPT followed by aspirin monotherapy in males (P-score 0.11). For any bleeding, P2Y12i monotherapy was ranked the best strategy in females (P-score 0.92) and mid-term DAPT in males (P-score 0.87); the second-best strategies were short-term DAPT followed by aspirin monotherapy in females (P-score 0.51) and P2Y12i monotherapy in males (P-score 0.63); and the least effective strategies were 12-month DAPT in females (P-score 0.31) and males (P-score 0.24).

3.4.5 Network Consistency and Heterogeneity

The network meta-analyses showed consistency between direct and indirect evidence for all outcomes (P >0.05, **Table S4**). Heterogeneity was not observed for MACCE in females (I^2 =0.6%) and NACCE in males (I^2 =0%). However, moderate heterogeneity was detected for MACCE in females (I^2 =48%), NACCE in females (I^2 =34.2%), and any bleeding in females and males (I^2 =36.8% and 74.4%). The comparison-adjusted funnel plots are shown in **Supplemental Figures S5–S11**.

4. DISCUSSION

It remains unclear what the optimal duration of DAPT after PCI is, and whether the same approach is appropriate for both sexes. The present meta-analysis of 22 trials involving

99,591 patients who underwent PCI examined for sex-specific differences in outcomes of DAPT post-PCI (**Graphical Abstract**). The principal findings are that female sex is associated with an increased risk of MACCE, particularly in clopidogrel-based DAPT, and increased risk of bleeding, especially in P2Y12i-based DAPT. For DAPT strategies, short-term DAPT followed by P2Y12i monotherapy is noninferior for MACCE compared to 12-month DAPT in females but was superior in males, whereas extended DAPT tended to have a higher risk of MACCE in males. In both females and males, short-term (either followed by P2Y12i or aspirin monotherapy), mid-term, and extended DAPT were noninferior to 12-month DAPT for 1-year risk of MACCE, NACCE, and any bleeding. When these strategies were ranked, short-term DAPT showed the most effectiveness for MACCE and NACCE in both sexes, whereas P2Y12i monotherapy and mid-term were the most effective for any bleeding.

De-escalation of DAPT to P2Y12i monotherapy ≤3 months after PCI is a relatively recent concept, with only a few trials reporting this strategy. The SMART-CHOICE (Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents) trial tested a hypothesis of de-escalation of short-term DAPT (aspirin plus clopidogrel for 3 months) to clopidogrel monotherapy vs. 12-month DAPT, showing that P2Y12i monotherapy after short-term DAPT results in non-inferior rates of MACCE. The GLOBAL LEADERS trial (a superiority trial exploring 1-month DAPT followed by ticagrelor monotherapy versus 12-month DAPT followed by aspirin monotherapy in patients undergoing PCI with DES) showed that de-escalation of short-term DAPT to ticagrelor monotherapy was not superior to 12-month DAPT in preventing all-cause mortality or new Q-wave MI two years after PCI.[39] The TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial demonstrated the superiority of de-escalation of 3-month DAPT

(ticagrelor plus aspirin) to ticagrelor monotherapy for BARC 2, 3, or 5 bleeding events over 12-month DAPT without increased risk of ischaemic events [40]. In the present analysis, we found that de-escalation of short-term and mid-term DAPT strategies were the most effective strategy for both ischaemic endpoints (MACCE) and net clinical benefit (NACCE) in both males and females. Indeed, short-term DAPT significantly reduced risk of MACCE compared to 12-month DAPT in males. Although these data may indicate potential sexual dimorphism in MACCE risk in short-term (1 to 3 months) DAPT followed by newer P2Y12i monotherapy, our data should be interpreted with caution, given the smaller sample size for females, which may have prevented statistically significance being reached.

Our pairwise analysis showed that female sex is associated with increased MACCE risk, particularly in clopidogrel-based DAPT, and risk for any bleeding, major bleeding, and bleeding in trials of newer P2Y12i agents in DAPT. Indeed, the superiority of newer, more potent P2Y12i's over clopidogrel has been reported previously [34, 41]. The TRITON-TIMI 38 trial, a trial of ACS patients undergoing PCI, demonstrated a reduced risk of ischaemic events in prasugrel-based DAPT compared to clopidogrel-based DAPT, although there was a higher risk of major bleeding [34]. However, this trial had variable follow-up times, ranging from 6 to 15 months, which may have confounded the effects of the drugs. For instance, the Elderly ACS 2 trial, which compared low-dose prasugrel-based DAPT to clopidogrel-based DAPT, reported temporal patterns in the effects of prasugrel vs. clopidogrel [41]. The clopidogrel arm had higher ischaemic event rates than the low-dose prasugrel arm in the subacute phase (4–30 days), but without a difference in bleeding rates. In the late phase (1–12 months), although ischaemic events were still high with clopidogrel, bleeding rates were higher with low-dose prasugrel. Moreover, registry data showed that ticagrelor could substantially reduce the risk of MACCE without increasing the risk of major bleeding compared to clopidogrel in patients with stable CAD undergoing complex PCI.[42] These

findings are consistent with ours, which show greater MACCE risk in females more than males driven by clopidogrel but not newer P2Y12i, whereas newer P2Y12i's are associated with higher risk of bleeding in females compared to males.

In pairwise meta-analysis of secondary outcomes, we show that female sex is associated with an increased risk of stroke and reduced risk of any revascularisation compared to male sex. This may be related to sex-related differences in baseline characteristics as females tend to be older, have higher comorbidity burden, and reduced functional status than males [3, 43]. However, baseline characteristics alone fail to explain the increased any bleeding risk in females observed herein.

Our results compare very well and extend the findings from previous meta-analyses. Consistent with our results, the network meta-analysis of Khan *et al*. showed that short-term DAPT followed by P2Y12i monotherapy was non-inferior to 12-month DAPT for MI, MACCE, and mortality [44]. They showed a reduction in ischaemic risk that was associated with newer P2Y12i's and bleeding risk associated with clopidogrel. Similar findings were noted in other network meta-analyses [45, 46], although their definitions of short-term DAPT varied (≤6 months [45] and <12 months [46], respectively). However, these meta-analyses did not provide sex-based comparisons on DAPT outcomes. A recent meta-analysis by Schreuder *et al.* showed no differences between potent P2Y12i and clopidogrel-based DAPT for efficacy and safety endpoints in either females and males, recommending the use of potent P2Y12i DAPT in both sexes [47]. Unlike our meta-analysis, the authors included trials that enrolled both patients undergoing PCI and no revascularisation.

Potential pathophysiological mechanisms underlying these differences in DAPT outcomes between women and men include platelet biology and effects of sex hormones. In a surgical cohort, women were shown to have a higher platelet count and on-treatment platelet reactivity compared to men [4, 5, 48]. This coupled with the loss of protective effects of

oestrogen due to its depletion in older, post-menopausal women , the primary female population in DAPT trials, might lead to increased thrombotic states and greater ischaemic events. Data also show that the effect of sex hormones might be related to the physiological balance between testosterone and oestrogen-related steroid hormones (e.g., 17β-oestradiol, E2): T/E2 ratio. Lower sex-specific T/E2 ratio was associated with greater risk of all-cause mortality after 23.7 months of follow-up in patients with ischaemic heart disease [49]. Differential drug distribution might also explain the observed outcomes. For instance, females also have higher activity of the ticagrelor-metabolising cytochrome P450 (CYP) isoform 3A4 (CYP3A4) and lower P-glycoprotein (P-gp) expression, a key transporter of ticagrelor across the intestinal wall, than men [50, 51]. Together with higher rates of early DAPT cessation in females compared to males [12], this could lead to reduced duration of effect of DAPT in females. Moreover, the higher burden of comorbidities in females might blunt the effect of DAPT [6-8].

The present study has several limitations. The evidence generated from the network meta-analysis was from aggregate, study-level data only, not patient-level data. Second, the time of randomisation varied across the included trials; randomisation occurred at the time of PCI or several months post-procedure. Third, network meta-analysis could not be performed for key ischaemic and bleeding endpoints due to the paucity of data and the low number of trials reporting these events, thereby limiting the generalisability of our findings. The number of females included in the trials was low, ranging from 19.4% to 36.3%, which may have limited the statistical power of the present analyses and its generalisability. Fourth, we could not distinguish the outcomes based on the clinical indication for PCI, which in turn affects the recommended duration of DAPT. Finally, given that aggregate/summary level comparisons were conducted in our meta-analysis, it was not possible to perform covariate adjustment to assess the contributions of the comorbidity differences between females and males.

Despite these limitations, there are several strengths in the current network meta-analysis. First, we have incorporated the most recent clinical trials that assessing the efficacy and safety of DAPT. Second, our findings can help guide patient management; physicians might consider using P2Y12i monotherapy over aspirin-based monotherapy for early de-escalation of DAPT. Third, newer P2Y12i DAPT might be preferred to clopidogrel-based DAPT, given the effectiveness and safety of the former strategy. In females, who may have an inherently higher risk of bleeding, it may paradoxically be better to use newer, more potent P2Y12i's for short-term DAPT rather than clopidogrel. However, for prolonged DAPT, switching to clopidogrel may offer a more optimal strategy, as it has lower bleeding rates than potent P2Y12i's. However, some caution should be observed with this, as the present analysis showed that extended DAPT beyond the standard 12 months could lead to excess MACCE risk in males. Future trials should also explore potential usefulness of risk scores in assessing optimal strategies [52].

5. CONCLUSION

Our data suggest that there may be sexual dimorphism in outcomes associated with DAPT. Female sex increases the risk of MACCE and bleeding events in newer P2Y12i-based DAPT. Additionally, short-term DAPT is non-inferior to 12-month DAPT for MACCE and NACCE in females and males. These findings warrant the need for large-scale, sex-based trials of DAPT effectiveness to define the optimal treatment strategies in both females and males.

DISCLOSURES

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DATA AVAILABILITY STATEMENT: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL: Due to the publicly available data used in this meta-analysis, institutional review board approval was not required.

CONSENT TO PARTICIPATE: Not applicable.

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Table 1. Characteristics of included trials

Trial	Year	Country (sites | country)	Design	Population	Follow-up	Procedure	Comparison	SAPT	P2Y12i	Participants (% female)
REDUCE	2021	Netherlands (NR)	RCT	ACS: STEMI, NSTEMI, Unstable Angina	24-month	PCI with COMBO stent	3-month DAPT (Pras + ASA) vs. 12-month DAPT	Aspirin	Prasugrel	1496 (20.1)
PRODIGY	2016	Italy (3 | 1)	RCT (open-label)	All-comers	24-month	PCI with both BMS and DES	6-month DAPT (CLOP + ASA) vs. 24-month DAPT	Aspirin	Clopidogrel	1970 (30.4)
RESET	2012	Korea (26 |1)	RCT (open-label)	Angina or AMI (≥50% stenosis)	12-month	PCI with DES	3-month DAPT (CLOP + ASA) vs. 12-month DAPT	Aspirin	Clopidogrel	2117 (36.3)
ISAR-SAFE	2015	Multinational (40 | 12)	RCT (double-blind, placebo-controlled)	CAD	9-month	PCI with DES	6-month DAPT (CLOP + ASA) vs. 12-month DAPT	Aspirin	Clopidogrel	4005 (19.4)
DAPT	2014	Multinational (452 | 11)	RCT (placebo-controlled)	CAD	30-month	PCI with DES	30-month DAPT (CLOP or Pras + ASA) vs. 12-month DAPT	Aspirin	Clopidogrel or Prasugrel	9961 (25.4)
SECURITY	2016	Multinational (NR)	RCT	Angina (stable or unstable) with diabetes	24-month	PCI with 2nd Gen DES	6-month DAPT (CLOP + ASA) vs. 12-month DAPT	Aspirin	Clopidogrel	429 (27.0)
TWILIGHT	2021	Multinational (187 | 11)	RCT (double-blind, placebo-controlled)	High-risk patients	12-month	PCI with DES	TIC SAPT vs. TIC DAPT (TIC + ASA)	Ticagrelor	Ticagrelor	7119 (23.9)
SMART-CHOICE	2019	Korea (33 | 1)	RCT (open-label)	CAD with ≥1 stenosis of ≥50%	12-month	PCI with DES	P2Y12i SAPT (CLOP, Pras, or TIC) vs. 12-month DAPT (P2Y12i + ASA)	Clopidogrel or new P2Y12i	Clopidogrel or new P2Y12i	2993 (26.6)
I-LOVE-IT 2	2016	Multinational (32 | 1)	RCT (assessor-blind)	Stable CAD + ACS	12-month	PCI with DES	6-month DAPT (CLOP + ASA) vs. 12-month DAPT	Aspirin	Clopidogrel	1829 (32.1)
ARCTIC	2014	France (38 | 1)	RCT (open-label)	CAD	12-month	PCI with DES	18-month DAPT (CLOP or Pras + ASA) vs. 12-month DAPT	Aspirin	Clopidogrel or Prasugrel	1259 (19.5)
DES LATE	2014	Korea (24 | 1)	RCT (open-label)	NR	24-month	PCI with DES	12-month DAPT (CLOP + ASA) vs. 36-month DAPT	Aspirin	Clopidogrel	5045 (30.6)
TICO	2020	Korea (38 | 1)	RCT (unblinded)	ACS: STEMI, NSTEMI, Unstable Angina	12-month	PCI with DES	3-month DAPT (ASA + TIC) vs. 12-month DAPT	Ticagrelor	Ticagrelor	3056 (20.5)
LEADERS FREE	2020	Multinational (68 | 20)	RCT (double-blind)	CAD	24-month	PCI with both BMS and DES	PCI with BA9 DCS + 1-month DAPT (ASA + CLOP) vs. PCI with BMS + 1-month DAPT	Aspirin	Clopidogrel	2432 (30.3)
PROTECT	2016	Multinational (196 | 36)	RCT (open-label)	Broad CAD	60-month	PCI with DES	3-month DAPT (CLOP or Ticlid + ASA) vs. 12-month DAPT	Aspirin	Clopidogrel or Ticlopidine	8709 (23.7)
DAPT	2018	Multinational (452 | 11)	RCT (double-blind, placebo-controlled)	CAD	30-month	PCI with DES	30-month DAPT (CLOP or Pras + ASA) vs. 12-month DAPT	Aspirin	Clopidogrel or Prasugrel	11648 (25.1)
GLOBAL LEADERS	2020	Multinational (130 | 18)	RCT (open-label)	All-comers	24-month	PCI with DES	1-month DAPT (TIC + ASA) followed by 23-month TIC SAPT vs. 12-month DAPT (CLOP + ASA) followed by 12-month ASA SAPT	Ticagrelor	Clopidogrel or Ticagrelor	15968 (23.3)
SORT OUT V	2013	Denmark (3 | 1)	RCT	All-comers	12-month	PCI with DES	N-BES + 12-month DAPT (CLOP or Pras + ASA) vs. C-SES + 12-month DAPT	Aspirin	Clopidogrel or Prasugrel	2468 (24.6)
TRITON-TIMI 38	2007	Multinational (707 | 30)	RCT (double-dummy, double-blind)	ACS: STEMI, NSTEMI, Unstable Angina	15-month	PCI with both BMS and DES	15-month DAPT (Pras + ASA) vs. 15-month DAPT (CLOP + ASA)	None	Prasugrel vs Clopidogrel	13608 (26.0)
SMART-DATE	2018	Korea (31 | 1)	RCT (open-label)	ACS: STEMI, NSTEMI, Unstable Angina	18-month	PCI with DES	6-month DAPT (CLOP + ASA) vs. 12-month DAPT (ASA + CLOP)	Aspirin	Clopidogrel or new P2Y12i	2712 (24.6)

STOPDAPT-2 ACS	2022	Japan (96 | 1)	RCT (open-label)	ACS: STEMI, NSTEMI, Unstable Angina	12-month	PCI with DES	1-month DAPT (CLOP or Pras + ASA) vs. 12-month DAPT (CLOP + ASA)	Clopidogrel	Clopidogrel or new P2Y12i	4136 (20.7)
MASTER DAPT	2024	Multinational (150 | 30)	RCT (open-label)	All-comers with HBR	12-month	PCI with DES	1-month DAPT (CLOP or Pras or TIC + ASA) vs. 12-month DAPT (CLOP or Pras or TIC + ASA)	ASA	Clopidogrel or new P2Y12i	4579 (30.7)
HOST-IDEA	2023	Korea (37 | 1)	RCT (open-label)	Stable CAD, unstable angina, NSTEMI	12-month	PCI with DES	3-to-6-month DAPT (CLOP or TIC Pras + ASA) vs. 12-month DAPT (CLOP or TIC Pras + ASA)	Mixed	Clopidogrel or new P2Y12i	2013 (26.1)

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; ASA, acetylsalicylic acid (aspirin); BMS, bare-metal stent; CAD, coronary artery disease; CLOP, clopidogrel; DES, drug-eluting stent; NSTEMI; non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; Pras, prasugrel; RCT, randomised clinical trial; SAPT, single antiplatelet therapy; STEMI, ST segment elevation myocardial infarction; TIC, ticagrelor; Ticlid, ticlopidine

Table 2. Summary of Subgroup-based Sex Differences in Primary Outcomes of DAPT

Subgroup	Trials (N)	Participants		Associated Risk		Heterogeneity		*Egger's* test (*P*-value)
		Females	Male	HR	95% CI (LL–UL)	I^2	*P*-value	
MACCE								
• Overall	17	19,259	58,393	1.14	1.02–1.28	76.5%	<.001	0.007
Type of P2Y12i								
- CLOP/new P2Y12i DAPT	9	12,672	39,226	1.16	0.94–1.45	83.5%	<.001	0.118
- CLOP DAPT	5	2,881	7,412	1.11	1.03–1.20	0.0%	0.485	0.063
- New P2Y12i DAPT	3	3,706	11,755	1.11	0.78–1.58	70.9%	0.032	0.785
- Ticagrelor DAPT	2	2,003	6,645	1.20	0.60–2.38	85.4%	0.009	ND
Post-DAPT Monotherapy								
- Aspirin	10	10,070	28,506	1.20	1.01–1.43	82.3%	<.001	0.014
- New P2Y12i	3	5,717	18,899	1.14	0.81–1.60	71.3%	0.031	0.889
- Ticagrelor DAPT	3	5,717	18,899	1.14	0.81–1.60	71.3%	0.031	0.889
PCI population								
- All-comers	11	13,503	39,827	1.20	1.03–1.41	82.4%	<.001	0.007
- ACS	5	5,230	17,079	1.06	0.88–1.26	58.8%	0.046	0.773
NACCE								
• Overall	12	9,330	28,441	1.12	0.96–1.31	74.4%	<.001	0.273
Type of P2Y12i								
- CLOP DAPT	6	1,763	5,331	1.17	0.89–1.52	79.0%	<.001	0.368
- New P2Y12i DAPT	2	436	1,844	1.29	0.60–2.75	94.7%	<.001	ND
Post-DAPT Monotherapy								
- Aspirin	7	2,521	7,025	1.10	0.88–1.38	78.4%	<.001	0.455
- New P2Y12i	2	4,019	13,478	1.38	0.75–2.54	93.0%	<.001	ND
- Ticagrelor DAPT	2	4,019	13,479	1.38	0.75–2.54	93.0%	<.001	ND
PCI population								
- All-comers	7	7,396	21,517	1.08	0.95–1.21	68.2%	0.004	0.609
- ACS	3	1,292	5,124	1.18	0.73–1.92	89.4%	<.001	0.556
Any Bleeding								
• Overall	8	8,776	26,135	1.13	1.00–1.28	60.4%	0.014	0.036
Type of P2Y12i								
- CLOP/new P2Y12i DAPT	4	5,576	16,285	1.07	0.97–1.18	0.0%	0.627	0.397
- CLOP DAPT	2	1,197	3,205	1.02	0.87–1.18	49.1%	0.161	ND
- New P2Y12i DAPT	2	2,003	6,645	1.58	1.01–2.46	67.3%	0.080	ND
- Ticagrelor DAPT	2	2,003	6,645	1.58	1.01–2.46	67.3%	0.080	ND
Post-DAPT Monotherapy								
- Aspirin	4	5,530	15,099	1.03	0.95–1.11	8.9%	0.348	0.569
- New P2Y12i	2	2,003	6,645	1.58	1.01–2.46	67.3%	0.080	ND
- Ticagrelor DAPT	2	2,003	6,645	1.58	1.01–2.46	67.3%	0.080	ND
PCI population								
- All-comers	5	5,917	16,210	1.03	0.95–1.11	0.0%	0.428	0.341
- ACS	3	2,859	9,925	1.53	1.11–2.11	35.5%	0.212	0.493

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; CLOBi, clopidogrel; DAPT, dual-antiplatelet therapy; HR, hazard ratio; LL, lower limit of the 95% confidence interval; MACCE, major adverse cardiovascular and cerebrovascular events; NACCE, net clinical and cerebrovascular events; ND, not determined; P2Y12i, P2Y12 inhibitor agent; PCI, percutaneous coronary intervention; UL, upper limit of the 95% confidence interval

FIGURE LEGENDS

Figure 1. Network of Dual Antiplatelet Therapy (DAPT) Comparisons

The thickness of the lines reflects the number of trials comparing the two treatments. Extended DAPT (ASA) represents de-escalation of DAPT beyond 12 months followed by aspirin monotherapy. Short-term DAPT (ASA) represents de-escalation of DAPT at short-term followed by aspirin monotherapy. Short-term DAPT (P2Y12i) represents de-escalation of DAPT at short-term followed by P2Y12 inhibitor monotherapy. Plot was generated in R and formatted in Adobe Illustrator.

Abbreviation: ASA, acetylsalicylic acid (aspirin); DAPT, dual antiplatelet therapy, P2Y12i, P2Y12 inhibitor

Figure 2. Pairwise Meta-analysis of Primary Endpoints in Females versus Males

Forest plots showing pooled comparisons of 1-year risk of primary endpoints in females vs. males at various DAPT durations.

Abbreviation: same as before

Figure 3. Pairwise Meta-analysis of Secondary Endpoints in Females versus Males

Forest plots showing pooled comparisons of 1-year risk of secondary endpoints in females vs. males at various DAPT durations.

Abbreviation: Any ST, any stent thrombosis (probable and/or definite); BARC, Bleeding Academic Research Consortium; CV death, cardiovascular death; definite ST, definite stent thrombosis; MI, myocardial infarction; rest are same as before. * Major bleeding defined according to **Table S1** in the **Data Supplement**.

Figure 4. Network Meta-analysis of Primary Endpoints in Females and Males

Network forest plots showing pooled comparisons of different DAPT duration versus (vs.) 12-month DAPT for major adverse cardiovascular and cerebrovascular events, MACCE, (**a.**),

net adverse clinical and cerebrovascular events, NACCE, (**b.**), and any bleeding (**c.**) in females and males.

Abbreviation: CI, confidence interval; RR, risk ratio; the rest same as before

Figure 5. Rankograms for Primary Endpoints in Females and Males

P-score based rankograms of effectiveness of different durations of DAPT for MACCE, NACCE, and any bleeding in females (*top*) and males (*bottom*).

Abbreviation: same as before

Graphical Abstract — Sex Differences in Outcomes of Clinical Trials of Dual Antiplatelet Therapy (DAPT) after Percutaneous Coronary Interventions (PCI)