JACC: ADVANCES VOL. 4, NO. 2, 2025

ORIGINAL RESEARCH

Sex Differences in the Safety and Efficacy of Different Durations of DAPT After PCI

Dae Yong Park, MD,[a,*] Shiwani Mahajan, MD, MHS,[a,*] Emily Fishman, MD,[b] Alexander P. Ambrosini, MD,[b] Laura M. Romero Acero, MD,[c] Jiun-Ruey Hu, MD, MPH,[d] Greta Campbell, BA,[e] Golsa Babapour, MD,[a] Michelle D. Kelsey, MD,[f] Pamela S. Douglas, MD,[g] Aakriti Gupta, MD, MSc,[d] Jennifer Frampton, DO, MPH,[a] Michael G. Nanna, MD, MHS[a]

ABSTRACT

BACKGROUND Randomized controlled trials (RCTs) have examined the clinical impact of abbreviating the duration of dual antiplatelet therapy (DAPT) and have reported outcomes in men and women.

OBJECTIVES The authors examined the safety and efficacy of different durations of DAPT following percutaneous coronary intervention (PCI) in men and women.

METHODS We searched Cochrane, Embase, MEDLINE, PubMed, Scopus, and Web of Science databases for RCTs that compared any 2 of 1, 3, 6, or 12 months of DAPT after PCI and reported outcomes in men and women. We performed a systematic review and network meta-analysis to examine sex-based differences in net adverse clinical events (NACE), major adverse cardiovascular events (MACE), and bleeding.

RESULTS Fifteen RCTs were included, comprising 44,610 men (74.7%) and 15,132 women (25.3%). No difference in NACE or MACE was observed between 1, 3, 6, or 12 months of DAPT in both sexes. In both men and women, 1 and 3 months of DAPT were each associated with lower risk of bleeding compared with 12 months of DAPT. In women, 3 months of DAPT was associated with a lower risk of bleeding compared with 6 months. Similar results were found in sensitivity analysis of acute coronary syndrome-only trials.

CONCLUSIONS No significant sex-based differences in NACE or MACE were observed with different durations of DAPT after PCI, while a lower bleeding risk was observed with shorter DAPT (1-3 months) among both sexes. This suggests that shorter DAPT may be preferred in both sexes following PCI, especially in those with high bleeding risk.

From the [a]Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut, USA; [b]Department of Medicine, Yale New Haven Hospital, New Haven, Connecticut, USA; [c]Hospital de San Jose, Fundacion Universitaria de Ciencias de la Salud, Bogotá, Colombia; [d]Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA; [e]Department of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [f]Division of Cardiology, Department of Medicine, Duke University, Durham, North Carolina, USA; and the [g]Duke Clinical Research Institute, Duke University, Durham, North Carolina, USA. *Drs Park and Mahajan contributed equally to this work.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 6, 2024; revised manuscript received November 1, 2024, accepted December 5, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101543

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BARC = Bleeding Academic Research Consortium

DAPT = dual antiplatelet therapy

MACE = major adverse cardiovascular events

NACE = net adverse clinical events

P2Y12i = purinergic receptor P2Y G-protein coupled, 12 protein inhibitor

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

RR = risk ratio

SAPT = single antiplatelet therapy

Dual antiplatelet therapy (DAPT) with aspirin and a purinergic receptor P2Y, G-protein coupled, 12 protein (P2Y12) inhibitor is recommended after percutaneous coronary intervention (PCI) to reduce the risk of thrombotic events. However, the optimal duration of this therapy continues to be a subject of debate, especially among patients with acute coronary syndrome (ACS) vs chronic coronary syndrome.[1,2] Women are known to have poorer outcomes after cardiovascular events, as well as an increased risk of bleeding after PCI.[3,4] Female sex has been identified as an independent predictor of major bleeding in some studies,[3,5] though risk scores used to predict bleeding after PCI do not include sex in the risk model.[6,7] Early DAPT cessation has also been shown to be more common among women compared to men.[5] It remains unknown if there are sex-based differences in the safety and efficacy of different durations of DAPT following PCI.

Prolonged DAPT using potent P2Y12 inhibitors increases the risk of bleeding, while shorter durations raise concerns regarding efficacy in preventing potential recurrent ischemic events.[8] Prior studies evaluating sex differences in DAPT duration have demonstrated discordant results. For example, the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) trial [9] showed similar 2-year bleeding and ischemic outcomes among men and women with 6 months vs 24 months of DAPT after PCI, whereas the TICO trial [10] demonstrated a higher risk of net adverse clinical events (NACE) and major bleeding among women even after multivariable adjustment. Moreover, women remain underrepresented in cardiovascular trials evaluating optimal DAPT duration after PCI.[11-13] As such, individual studies are underpowered to examine the safety and efficacy of different durations of DAPT among women.

In order to clarify whether sex differences exist in the optimal duration of DAPT following PCI, we conducted a sex-specific systematic review and meta-analysis of randomized controlled trials (RCTs) to examine if there were sex-based differences in the safety and efficacy of different DAPT durations in patients who have undergone PCI for stable angina or ACS.

METHODS

This systematic review was implemented in accordance with a previously documented protocol at the Open Science Framework (DOI: 10.17605/OSF.IO/CGF76) and compliance with the reporting standards provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis group (Supplemental Table 1).[14] Our study was exempt by the Yale Institutional Review Board as we utilized data from previously published sources exclusively.

SEARCH STRATEGY AND INCLUSION CRITERIA. Two authors (D.P. and S.M.) carried out a thorough literature search across the Cochrane Library, Ovid Embase, Ovid MEDLINE, PubMed, Scopus, and the Web of Science Core Collection. The search encompassed articles from the inception of these databases up until June 4, 2024. This search was constructed using carefully selected terminology and keywords, along with synonyms related to topics such as DAPT, treatment duration, PCI, and RCT, mirroring the approach taken in a prior study.[15] The complete search strategies for all databases can be found in Supplemental Table 2. Upon compiling relevant studies, the reference lists of each study were cross-referenced to identify additional pertinent literature. Citations from the initial search were imported into EndNote 20 software to eliminate duplicate studies. The screening process included evaluating titles, abstracts, full manuscripts, and supplementary material to determine eligibility. The selected studies underwent a careful re-evaluation for accuracy, which was superintended by the corresponding author (M.N.). Any disagreements were settled through team discussions under the corresponding author's guidance.

Studies with the following criteria were included: 1) RCT; 2) comparison between any 2 of 1, 3, 6, or 12 months of DAPT; 3) reporting of outcomes associated with men and women; 4) follow-up duration ≥9 months from the index PCI; and 5) written in the English language. When ≥2 studies on the same RCT data were found, the earlier original paper was prioritized. DAPT was defined as the concomitant administration of aspirin and a P2Y12 inhibitor. For each included trial, we applied the Cochrane Collaboration's tool to appraise the risk of bias, and for each pooled outcome, we used the GRADE system to assess its quality.[16,17]

DATA ACQUISITION AND OUTCOMES OF INTEREST. From each individual trial, we collected details including the trial's acronym, year(s) of enrollment, the country where the study took place, the proportion of patients with ACS, the agent for single antiplatelet therapy (SAPT) used in the experimental (abbreviated DAPT) groups, the type of stents

employed, and the number of men and women included. Moreover, we organized baseline patient characteristics to facilitate study-level comparisons. The primary outcome of interest was NACE. Secondary outcomes comprised major adverse cardiovascular events (MACE) and bleeding. The definitions of the outcomes were based on the individual trial, and each of the outcomes reported in each trial can be found in Supplemental Table 3.

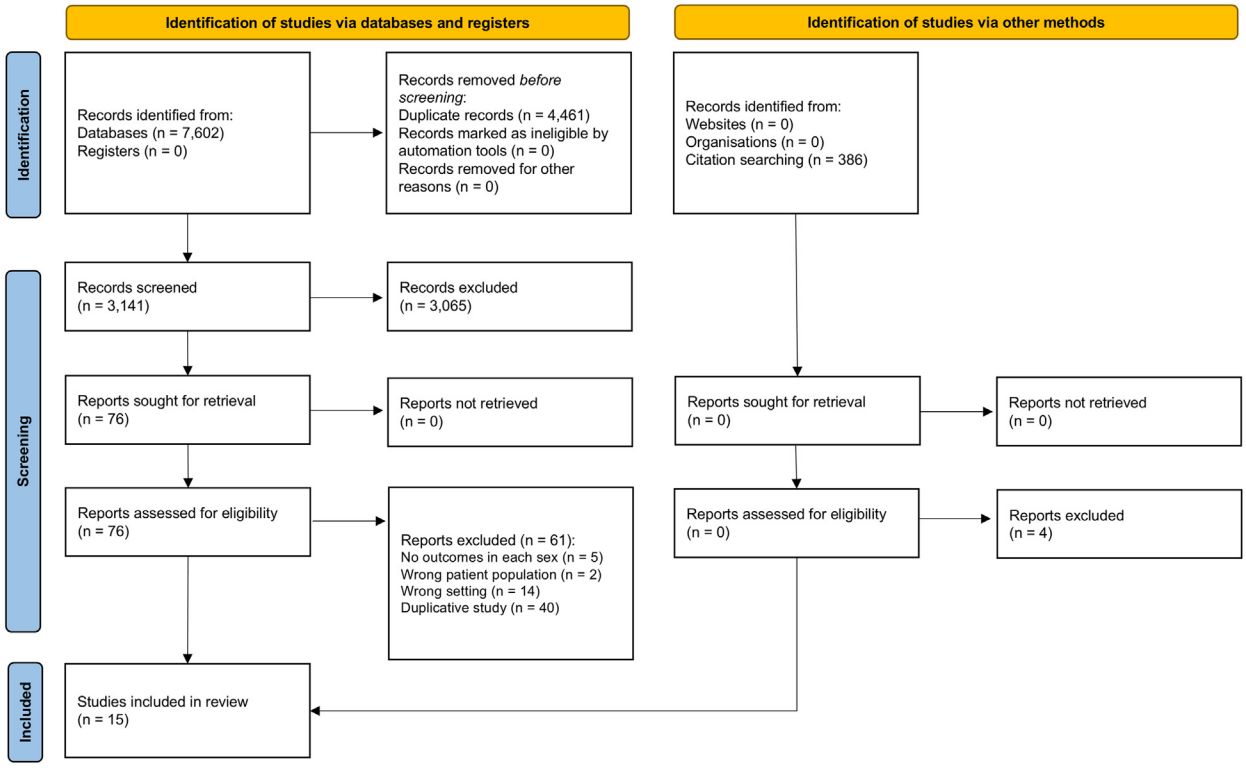
STATISTICAL ANALYSIS. To ensure uniformity across all studies, we computed risk ratios (RRs) comparing different durations of DAPT from the selected RCTs. Zero-cell correction was unnecessary since all the outcomes had at least 1 occurrence in all the studies. After we collected the outcomes from each trial, we performed a frequentist network meta-analysis with random effects model to determine pooled estimates by alternating the reference groups. Briefly, we compared the risk of our primary and secondary outcomes after 1 vs 3, 6, and 12 months of DAPT; 3 vs 6 and 12 months of DAPT; and 6 vs 12 months of DAPT. Pooled RRs with their respective 95% CI were generated. *P* values <0.05 were considered statistically significant, and *P* values <0.10 but >0.05 were considered marginally significant for hypothesis-generating purposes. Assumptions inherent in network meta-analysis were made, including transitivity, consistency, homogeneity, sufficiency of evidence, and additivity of treatment effects.[18] We evaluated inconsistencies between direct and indirect estimates by node-splitting analysis. We assessed the level of heterogeneity and incoherence in the network models by using the magnitude of the between-study variance Tau-squared and the I^2 statistic for incoherence. In each outcome, we computed P-scores for each duration of DAPT. P-scores indicate the level of certainty that a particular duration of DAPT is superior to others, weighted equally across all denominators.[19] A P-score of 0 signifies the poorest duration of DAPT, while a score of 1 represents the best duration of DAPT. The technical underpinnings of the frequentist network meta-analysis model we used have been previously described.[20] The statistical model specifications used can be found in Supplemental Table 4.

A sensitivity analysis was performed for the subset of trials that reported major bleeding, as defined by Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding or thrombolysis in myocardial infarction major bleeding. Two more sensitivity analyses were performed for the subset of trials that exclusively enrolled patients with ACS and those that used ticagrelor as the single antiplatelet agent. Finally, we performed a conventional pairwise meta-analysis based on the DerSimonian and Laird method to compare women and men who underwent a shortened duration of DAPT using a selection of trials that published post-hoc analysis on sex differences.[10,21-23] Because the baseline characteristics of women and men differed, we adjusted the outcomes for select covariates (hypertension, diabetes mellitus, dyslipidemia, and ACS) using multivariable Poisson regression and used the adjusted RRs for supplementary meta-analysis. All statistical analyses were performed using SAS, version 9.4 (SAS Institute) and R version 4.2.3 (R Foundation for Statistical Computing).

RESULTS

Fifteen RCTs with a total sample size of 59,742, including 44,610 men (74.7%) and 15,132 women (25.3%), were included in our study (**Figure 1**).[11-13,24-35] 7 trials, which included 16,024 men (35.9%) and 5,855 women (38.7%), compared 3 months with 12 months of DAPT (**Figure 2**).[13,24,27,28,31-33] 4 trials, which included 7,474 men (16.8%) and 2,467 women (16.3%), compared 6 months with 12 months of DAPT.[26,29,30,34] 3 trials, which included 17,941 men (40.2%) and 5,402 (35.7%) women, compared 1 month with 12 months of DAPT.[12,25,35] One trial, which included 3,171 men (7.1%) and 1,408 women (9.3%), compared 1 month with 6 months of DAPT.[11] The number of patients in each duration of DAPT is summarized in Supplemental Table 5. Two trials recruited participants with high risk of bleeding.[11,33] Years of recruitment ranged from 2008 to 2022 (**Table 1**). From the 15 selected trials, 8 were carried out in Asia, with 6 of them conducted in South Korea. One trial took place in Brazil. The remaining 6 trials were multinational collaborations that encompassed various countries spanning the Americas, Europe, and Asia. The proportion of ACS cases within the chosen trials ranged from 32.0% to 100%, with an unadjusted mean of 70.0%. When adjusted for sample size of each of the trials, ACS constituted 71.2% of the total trial population. Five trials exclusively enrolled patients with ACS.[12,24,26,31,35] Aspirin was the SAPT agent used in 7 trials, followed by 4 trials that administered ticagrelor and 2 trials that protocolized clopidogrel. One trial utilized both aspirin and clopidogrel, while another provided the prescribing physician with discretion over which antiplatelet agent to use. The stents deployed, and the baseline patient characteristics were variable among the trials (Supplemental Table 6). Of note, these characteristics represent all the patients, both men and women

FIGURE 1 PRISMA Flow Diagram of the Meta-Analysis



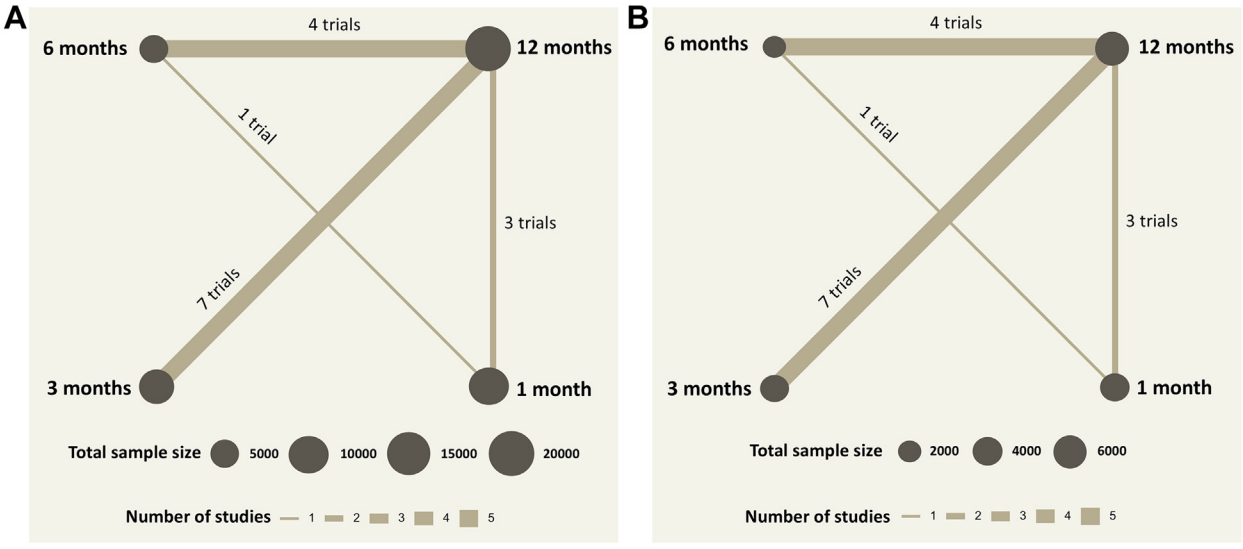
The flow diagram illustrates the process whereby studies were selected in the present network meta-analysis. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

combined, in each trial, as attributes stratified to men and women were unavailable in all but 3 trials. The definitions of NACE, MACE, and bleeding also differed from one trial to another (Supplemental Table 3).

The risk of bias was largely low in the included trials, apart from performance bias, which was high in 9 trials due to their open-label design (Supplemental Table 7). The quality of pooled outcomes was moderate owing to some biases and imprecisions (Supplemental Table 8). Heterogeneity observed in the frequent network models ranged from none to moderate (Supplemental Table 9). No statistically significant inconsistencies in the frequentist network models were observed with random effects applied (Supplemental Table 10). The full results of the node-splitting analysis of inconsistency can be found in the supplementary appendix (Supplemental Table 11, Supplemental Figure 1).

In men, no significant difference in the risk of NACE or MACE was observed between 1 month and 3, 6, or 12 months of DAPT; between 3 months and 6 or 12 months of DAPT; and between 6 and 12 months of DAPT (**Table 2**). DAPT for 1 month (RR: 0.56; 95% CI: 0.34-0.91; $P = 0.018$) and 3 months (RR: 0.54; 95% CI: 0.33-0.89; $P = 0.015$) were each associated with a lower risk of bleeding compared with 12 months of DAPT, but no difference was observed between 1 and 3 months of DAPT, 1 and 6 months of DAPT, 3 and 6 months of DAPT, and 6 and 12 months of DAPT. In women, similar to men, no significant difference in the risk of NACE or MACE was seen in all the combinations of 1, 3, 6, and 12 months of DAPT (**Central Illustration**). However, 1 month (RR: 0.86; 95% CI: 0.74-0.99; $P = 0.049$) and 3 months of DAPT (RR: 0.55; 95% CI: 0.35-0.86; $P = 0.008$) were each associated with lower risk of bleeding compared with 12 months of DAPT. In addition, 3 months of DAPT was associated with lower risk of bleeding compared with 6 months of DAPT (RR: 0.50; 95% CI: 0.27-0.90; $P = 0.022$) in women. No difference in the risk of bleeding was demonstrated between 1 and 3 months of DAPT and 6 and 12 months of DAPT. In men, P scores were the highest at 1 month of DAPT for the

FIGURE 2 Network Plot of the Included Randomized Controlled Trials



The network plot illustrates the number of trials that compared 1 month, 3 months, 6 months, and 12 months of dual antiplatelet therapy among (A) men and (B) women. The size of the circles and lines are proportional to the total sample size of men or women patients and the number of relevant trials, respectively.

outcomes NACE and bleeding, but at 3 months of DAPT for MACE. In women, P scores were the highest at 3 months of NACE and bleeding but at 1 month of DAPT for MACE (**Figure 3**).

In a sensitivity analysis of trials that reported major bleeding, 3 months of DAPT was associated with marginally lower risk of major bleeding compared with 12 months of DAPT in both men (RR: 0.60; 95% CI: 0.33-1.08; $P = 0.087$) and women (RR: 0.47; 95% CI: 0.21-1.09; $P = 0.078$) (Supplemental Table 12). A sensitivity analysis of trials that exclusively enrolled patients with ACS showed no difference in the risk of NACE and MACE among all the combinations of 1, 3, 6, and 12 months of DAPT in both men and women (Supplemental Table 13). In men, DAPT for 1 month was associated with significantly lower risk of bleeding compared with DAPT for 12 months (RR: 0.40; 95% CI: 0.26-0.61; $P < 0.001$), and DAPT for 3 months was associated with marginally lower risk of bleeding compared with DAPT for 12 months (RR: 0.60; 95% CI: 0.33-1.08; $P = 0.087$). In women, DAPT for 3 months was also associated with marginally lower risk of bleeding compared with DAPT for 12 months (RR: 0.47; 95% CI: 0.21-1.09; $P = 0.078$). Similar findings were observed in sensitivity analysis of trials that used ticagrelor as the single antiplatelet agent in men (Supplemental Figure 14). In women, however, 1 month of DAPT was associated with higher risk of NACE than 3 months of DAPT when ticagrelor was used. On the other hand, 3 months of DAPT was associated with lower risk of NACE and marginally lower risk of bleeding compared with 12 months of DAPT.

Four trials separately published post-hoc analysis based on sex differences. Three [10,22,23] of these trials shortened the duration of DAPT to 3 months, and the remaining 1 trial[21] shortened the duration to 1 month. Significant differences were observed between women and men at baseline (Supplemental Table 15). In the experimental groups who underwent shortened DAPT, no difference in the risk of all-cause mortality, MACE, and myocardial infarction was observed between women and men (Supplemental Figures 2 to 4). However, women had a higher risk of major bleeding compared with men despite undergoing a shortened duration of DAPT (Supplemental Figure 5). Findings were similar in the meta-analysis using RRs adjusted for differences in select covariates between women and men (Supplemental Figures 6 to 9).

DISCUSSION

The results of this systematic review and meta-analysis of RCTs demonstrate that there were no significant differences in the risk of NACE or MACE between different durations of DAPT (1, 3, 6, or 12 months) compared to a SAPT or usual care among

TABLE 1 Main Characteristics of the Included Trials

Trial	Year[a]	Country	ACS[b]	SAPT	Stent	Experimental			Control		
						Men	Women	DAPT	Men	Women	DAPT
ULTIMATE DAPT	2019-2022	Multinational	100%	Ticagrelor	SES, ZES, others	1,264	436	1 mo	1,257	443	12 mo
HOST-IDEA	2016-2021	South Korea	55.2%	Any[c]	SES	731	271	3 mo[d]	756	255	12 mo
MASTER DAPT	2017-2019	Multinational	48.3%	Clopidogrel, aspirin	SES	1,590	705	1 mo	1,581	703	6 mo
TICO	2015-2018	South Korea	100%	Ticagrelor	SES	1,204	323	3 mo	1,224	305	12 mo
SMART CHOICE	2014-2017	South Korea	58.2%	Clopidogrel	EES, SES	6,040	1,839	3 mo	6,100	1,828	12 mo
TWILIGHT	2015-2017	Multinational	64.8%	Ticagrelor	Second-generation DES[e]	1,087	408	3 mo	1,111	387	12 mo
STOPDAPT-2 ACS	2015-2017	Japan	100%	Clopidogrel	Cobalt-chromium EES	2,709	846	1 mo	2,712	852	12 mo
REDUCE	2014-2016	Multinational	100%	Aspirin	CD34+ antibody-coated SES	1,631	427	3 mo	1,649	429	12 mo
GLOBAL LEADERS	2013-2015	Multinational	50.6%	Ticagrelor	BES	602	127	1 mo	567	166	12 mo
SMART-DATE	2012-2015	South Korea	100%	Aspirin	ZES, EES, BES	1,016	341	6 mo	1,028	327	12 mo
IVUS-XPL	2010-2014	South Korea	49.0%	Aspirin	EES	611	298	6 mo	632	288	12 mo
ISAR-SAFE	2008-2014	Multinational	40.7%	Aspirin	EES, SES, ZES, BES, PES	470	229	6 mo	494	207	12 mo
I-LOVE-IT 2	2012-2013	China	81.8%	Aspirin	SES	1,611	386	6 mo	1,612	391	12 mo
OPTIMIZE	2010-2012	Brazil	32.0%	Aspirin	ZES	992	571	3 mo	982	574	12 mo
RESET	2009-2010	South Korea	54.6%	Aspirin	ZES	682	377	3 mo	665	393	12 mo

Individual trial name abbreviations are detailed in the list of abbreviations in the main text. [a]Enrollment years. [b]Average of the percentage of acute coronary syndrome in abbreviated and standard dual antiplatelet groups. [c]Any antiplatelet at the discretion of the ordering physician: aspirin (64.1%), clopidogrel (33.7%), ticagrelor (1.9%), prasugrel (0.3%) in the trial. [d]Median of 100 d with interquartile range 91 to 151 d. [e]Second-generation drug-eluting stent: durable polymer cobalt-chromium EES, durable polymer platinum-chromium EES, durable polymer ZES, durable polymer cobalt-chromium SES, biodegradable polymer DES, polymer-free DES, bioresorbable vascular scaffold, sirolimus-eluting self-apposing stent, tacrolimus-eluting carbostent.

ACS = acute coronary syndrome; BES = biolimus-eluting stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; EES = everolimus-eluting stent; GLOBAL LEADERS = Global Leaders Strategy With the Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus 2-Month Dual Antiplatelet Therapy in Patients Undergoing PCI; HOST-IDEA = Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Coronary Intervention With Next-Generation Drug-Eluting Stent Platforms and Abbreviated Dual Antiplatelet Therapy; I-LOVE-IT 2 = Is There a Life for DES After Discontinuation of Clopidogrel: Multicenter Study of the Endeavor Zotarolimus-Eluting Stent in Uncertain DES Candidates; ISAR-SAFE = Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-Study; IVUS-XPL = Impact of Intravascular Ultrasound Guidance on the Outcomes of Xience Prime Stents in Long Lesions; MASTER DAPT = MAnagement of high-bleeding-risk pATients post bioresorbable polymer coated stent implantation with an Abbreviated versus prolonged DAPT regimen; OPTIMIZE = Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in Real-World Clinical Practice; PES = paclitaxel-eluting stent; SAPT = single antiplatelet therapy; SES = sirolimus-eluting stent; SMART CHOICE = Comparison between P2Y12 Antagonist MonotHerapy and Dual Antiplatelet Therapy in Patients UndergOing Implantation of Coronary Drug-Eluting Stents; SMART-DATE = Smart Angioplasty Research Team: Safety of 6-mo Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes; STOPDAPT-2 = Short and optimal duration of dual antiplatelet after everolimus-eluting cobalt-chromium stent: a randomized multicenter trial; RESET = REal Safety and Efficacy of 3-Month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; TICO = Ticagrelor monotherapy vs ticagrelor with aspirin in patients with acute coronary syndrome after percutaneous coronary intervention; TWILIGHT = Ticagrelor with aspirin or alone in high-risk patients after coronary intervention; ZES = zotarolimus-eluting stent.

both men and women after PCI, including among patients with ACS. Additionally, the risk of major bleeding was significantly lower with 1 and 3 months of DAPT compared with longer durations of DAPT in both men (12 months) and women (6 and 12 months), though there was no significant difference between 1 and 3 months of DAPT in either group. Similarly, shorter duration of DAPT in both men and women with ACS was associated with a lower risk of bleeding, although these estimates were statistically significant only among men. Furthermore, direct comparison of men and women among patients with shortened DAPT showed no difference in all-cause mortality, MACE, or myocardial infarction between the 2 sexes; however, women had a higher risk of bleeding despite shortened duration of DAPT.

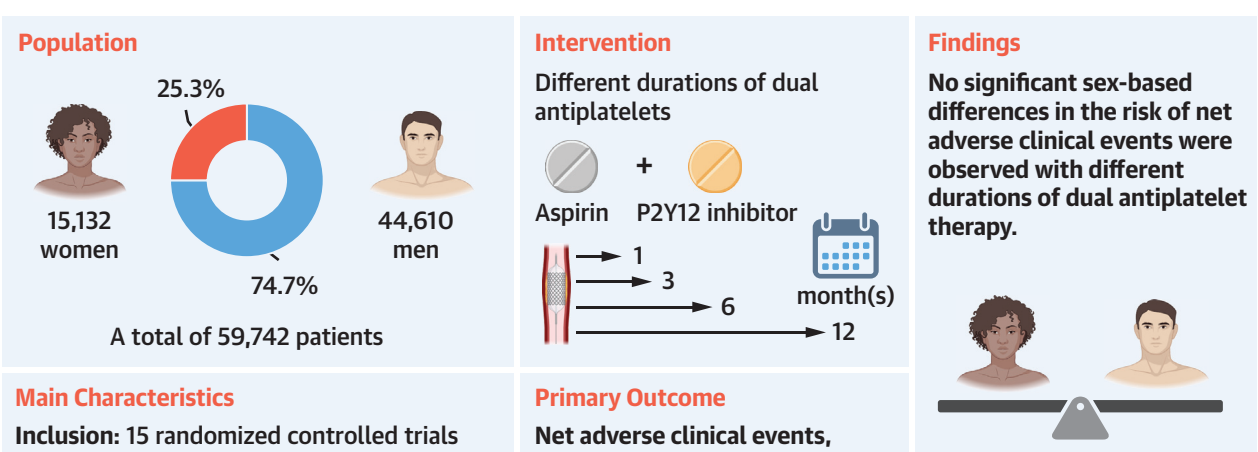
Ascertaining the optimal duration of DAPT is especially important in women for several reasons. Prior studies have demonstrated that women have a higher risk of ischemic events and worse outcomes after PCI.[4] Women undergoing PCI after ACS tend to be older and have a higher burden of comorbidities than men.[10,23] Women also have a higher risk of bleeding after PCI, as compared with men.[3] Differences in platelet reactivity and responsiveness to antiplatelet therapy have also been reported.[36] Whether the higher risk profile observed in women might lead to heterogeneity of treatment effects from varying DAPT durations remained unknown up to this point. Prior individual studies on sex differences in ischemic and bleeding outcomes with short-term vs long-term use of DAPT have been inconsistent. The PRODIGY trial, which compared 6 months vs 12 months of DAPT use after PCI, showed no significant difference in the 2-year ischemic and bleeding outcomes.[9] Similarly, a subgroup analysis of the TWILIGHT (Ticagrelor with aspirin or alone in high-risk patients after coronary intervention) trial evaluating the effects of monotherapy with ticagrelor after 3 months vs 12 months of ticagrelor-based DAPT showed that rates of ischemic and bleeding events were similar among men and women after adjustment for comorbidities.[23] On the other hand, the TICO trial demonstrated a higher risk of NACE and major bleeding among women even after multivariable adjustment [10] and a subgroup analysis of the GLOBAL

TABLE 2 Pooled Estimates of Frequentist Network Meta-Analysis for Each Outcome in Men and Women

Men	Net adverse clinical events (11 trials included)	1 mo			
		1.00 (0.82-1.23) $P = 0.986$	3 mo		
		0.97 (0.80-1.17) $P = 0.728$	0.96 (0.74-1.26) $P = 0.793$	6 mo	
		0.95 (0.87-1.03) $P = 0.179$	0.94 (0.79-1.13) $P = 0.539$	0.98 (0.80-1.19) $P = 0.829$	12 mo
	Major adverse cardiovascular events (9 trials included)	1 mo			
		1.10 (0.81-1.51) $P = 0.537$	3 mo		
		1.01 (0.78-1.31) $P = 0.913$	0.92 (0.64-1.32) $P = 0.651$	6 mo	
		1.07 (0.90-1.28) $P = 0.455$	0.97 (0.75-1.25) $P = 0.813$	1.05 (0.82-1.36) $P = 0.686$	12 mo
	Bleeding (7 trials included)	1 mo			
		1.04 (0.51-2.08) $P = 0.928$	3 mo		
		0.66 (0.32-1.35) $P = 0.258$	0.64 (0.24-1.74) $P = 0.384$	6 mo	
		0.56 (0.34-0.91) $P = 0.018$	0.54 (0.33-0.89) $P = 0.015$	0.84 (0.35-1.99) $P = 0.689$	12 mo
Women	Net adverse clinical events (11 trials included)	1 mo			
		1.21 (0.83-1.76) $P = 0.320$	3 mo		
		0.85 (0.61-1.17) $P = 0.318$	0.70 (0.45-1.10) $P = 0.124$	6 mo	
		0.95 (0.76-1.18) $P = 0.625$	0.78 (0.58-1.06) $P = 0.114$	1.12 (0.80-1.56) $P = 0.519$	12 mo
	Major adverse cardiovascular events (9 trials included)	1 mo			
		1.01 (0.63-1.60) $P = 0.977$	3 mo		
		0.76 (0.53-1.09) $P = 0.138$	0.76 (0.45-1.29) $P = 0.308$	6 mo	
		0.88 (0.69-1.12) $P = 0.305$	0.88 (0.59-1.31) $P = 0.515$	1.16 (0.81-1.64) $P = 0.421$	12 mo
	Bleeding (7 trials included)	1 mo			
		1.58 (0.98-2.55) $P = 0.059$	3 mo		
		0.78 (0.55-1.13) $P = 0.191$	0.50 (0.27-0.90) $P = 0.022$	6 mo	
		0.86 (0.74-0.99) $P = 0.0.49$	0.55 (0.35-0.86) $P = 0.008$	1.10 (0.74-1.63) $P = 0.635$	12 mo

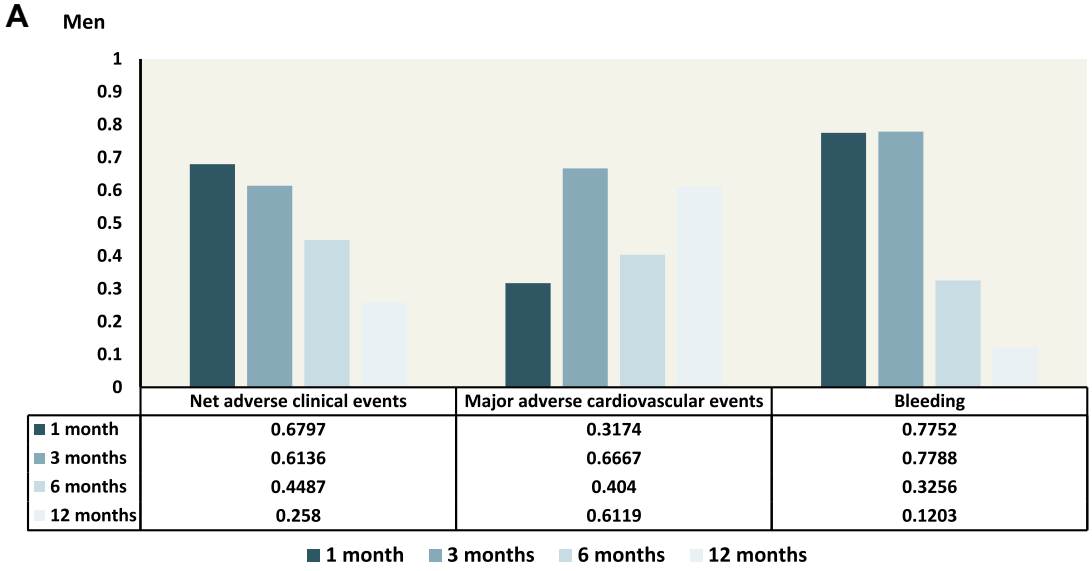
The duration of dual antiplatelet therapy in the rightmost column serves as the reference group for the respective column.

CENTRAL ILLUSTRATION Meta-Analysis: Sex Differences in Safety and Efficacy of Different Durations of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention

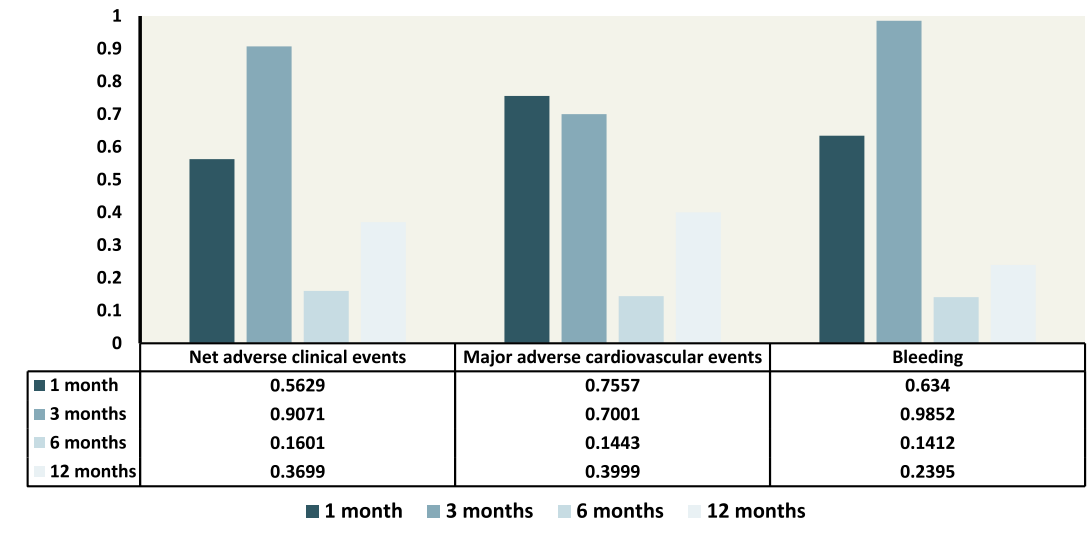


The central illustration summarizes the main findings of this study.

FIGURE 3 P-Scores of Each Duration of Dual Antiplatelet Therapy



	Net adverse clinical events	Major adverse cardiovascular events	Bleeding
1 month	0.6797	0.3174	0.7752
3 months	0.6136	0.6667	0.7788
6 months	0.4487	0.404	0.3256
12 months	0.258	0.6119	0.1203



	Net adverse clinical events	Major adverse cardiovascular events	Bleeding
1 month	0.5629	0.7557	0.634
3 months	0.9071	0.7001	0.9852
6 months	0.1601	0.1443	0.1412
12 months	0.3699	0.3999	0.2395

The bar graphs demonstrate the P-scores of 1 month, 3 months, 6 months, and 12 months of dual antiplatelet therapy after percutaneous coronary intervention in (A) men and (B) women. P-scores measure the extent of certainty that the specified duration of dual antiplatelet therapy is superior to other durations of dual antiplatelet therapy.

LEADERS (Global Leaders Strategy With the Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus 2-Month Dual Antiplatelet Therapy in Patients Undergoing PCI) trials revealed a higher risk of major bleeding among women after PCI.[21] In this large meta-analysis synthesizing all available trials to date, we found that a shorter duration of DAPT (3 months) lowers the risk of major bleeding in both men and women, without any significant cost in terms of ischemic events. These findings should provide reassurance to clinicians, in the absence of competing prothrombotic comorbidities, that shortening DAPT duration to 3 months can be done safely in appropriately selected patients irrespective of sex and does not reduce efficacy.

Current European and U.S. guidelines recommend 6 months of DAPT after PCI with second-generation drug-eluting stent (DES) among patients with stable

coronary artery disease and at least 12 months of DAPT for patients with ACS not at increased risk for bleeding.[37] This meta-analysis, one of the largest in evaluating sex-based differences in safety and efficacy of different durations of DAPT after PCI, suggests that a very short duration of DAPT (1 month) may be appropriate in both men and women after PCI for stable coronary artery disease as well as among patients with ACS. These findings may be especially relevant for individuals at higher bleeding risk. Given the higher risk of NACE with 1 month of DAPT (vs 3 months) among women who used ticagrelor as the single antiplatelet agent in our analyses, caution should be exercised before shortening to less than 3 months of DAPT.

STUDY LIMITATIONS. This meta-analysis has some limitations. First, various types of DES were used across the studies, some of which are no longer in wide use. However, there was no sex-specific bias in the selection of the DES used. As the newer generation DES is considered to be safer and have a lesser thrombogenic profile than the early generation DES, the net benefit for shorter duration of DAPT may even be greater in contemporary practice. Second, many of the trials included in this meta-analysis were open-label, potentially leading to performance bias. Third, a large proportion of the study population were of East Asian descent, which may limit the generalizability of our findings to other races and ethnicities. Fourth, there was clinical heterogeneity in baseline characteristics and definitions of clinical endpoints across trials, potentially introducing bias into our findings. In particular, the baseline bleeding risk of the participants included in the trials were variable, with 2 trials exclusively enrolling patients with high bleeding risk. Fifth, there were baseline differences between the male and female cohorts in the studies included, which likely impacted the observed clinical effectiveness and safety for different treatment approaches. Sixth, we had limited number of patients who were 65 and older, and as such, more evidence is needed regarding the older population. Seventh, different P2Y12 inhibitors were used across different trials, which could have affected the comparisons and its transitivity. 8, the use of RRs in meta-analysis require compatibility with study-level event rates, which can result in bias.[38] Finally, we had limited information on complete vs incomplete revascularization in each trial particularly in patients with ACS to determine whether MACE was due to the original culprit vessel or a nonculprit vessel.

CONCLUSIONS

This meta-analysis demonstrates that there were no significant sex-based differences in risk of NACE or MACE with different durations of DAPT after PCI, with lower risk of major bleeding with shorter durations of treatment (1-3 months) among both men and women. Taken together, these data suggest that shorter duration (1-3 months) of DAPT may be appropriate in both men and women after PCI and that sex alone should not determine DAPT duration.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Kelsey reports consulting for HeartFlow and Bayer. Dr Douglas reports grant support to the institution from HeartFlow. Dr Gupta is the cofounder of Heartbeat Health, Inc. Dr Frampton has received research support from the Patient-Centered Outcomes Research Institute (PCORI). Dr Nanna has received current research support from the American College of Cardiology Foundation, supported by the George F. and Ann Harris Bellows Foundation, the PCORI, the Yale Claude D. Pepper Older Americans Independence Center (P30AG021342), and the National Institute on Aging/National Institutes of Health from R03AG074067 (GEMSSTAR award), and consulting from Heartflow, Inc, and Merck. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Michael Nanna, Section of Cardiovascular Medicine, Department of Medicine, 333 Cedar Street, New Haven, Connecticut 06510, USA. E-mail: michael.nanna@yale.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this meta-analysis, no significant sex-based differences in the risk of NACE or MACE were observed with different durations of DAPT after PCI. A lower risk of major bleeding was observed with 1 and 3 months of DAPT in both sexes. Shorter duration (1-3 months) of DAPT may be appropriate in both men and women after PCI, and sex alone should not determine the duration of DAPT.

TRANSLATIONAL OUTLOOK: More data are needed to elucidate sex-based differences according to variable DAPT durations in specific patient groups, such as those with high-bleeding risk and acute coronary syndrome.

REFERENCES

1. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation*. 2022;145:e18–e114.

2. Palmerini T, Della Riva D, Benedetto U, et al. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *Eur Heart J*. 2017;38:1034–1043.

3. Yu J, Mehran R, Grinfeld L, et al. Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: three year results from the HORIZONS-AMI trial. *Cathet Cardiovasc Interv*. 2015;85:359–368.

4. Kosmidou I, Leon MB, Zhang Y, et al. Long-term outcomes in women and men following percutaneous coronary intervention. *J Am Coll Cardiol*. 2020;75:1631–1640.

5. Yu J, Baber U, Mastoris I, et al. Sex-based differences in cessation of dual-antiplatelet therapy following percutaneous coronary intervention with stents. *JACC Cardiovasc Interv*. 2016;9:1461–1469.

6. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025–1034.

7. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749.

8. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166.

9. Gargiulo G, Ariotti S, Santucci A, et al. Impact of sex on 2-year clinical outcomes in patients treated with 6-month or 24-month dual-antiplatelet therapy duration: a pre-specified analysis from the PRODIGY trial. *JACC Cardiovasc Interv*. 2016;9:1780–1789.

10. Lee B, Lee S-J, Kim B-K, et al. Sex differences in outcomes of ticagrelor therapy with or without aspirin after percutaneous coronary intervention in patients with acute coronary syndrome: a post hoc secondary analysis of the TICO randomized clinical trial. *Arterioscler Thromb Vasc Biol*. 2023;43:e218–e226.

11. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med*. 2021;385:1643–1655.

12. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321:2414–2427.

13. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA*. 2013;310:2510–2522.

14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.

15. Park DY, Wang P, An S, et al. Shortening the duration of dual antiplatelet therapy after percutaneous coronary intervention for acute coronary syndrome: a systematic review and meta-analysis. *Am Heart J*. 2022;251:101–114.

16. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Br Med J*. 2008;336:924–926.

17. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

18. Ahn E, Kang H. Concepts and emerging issues of network meta-analysis. *Korean J Anesthesiol*. 2021;74:371–382.

19. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15:58.

20. Balduzzi S, Rücker G, Nikolakopoulou A, et al. Netmeta: an R package for network meta-analysis using frequentist methods. *J Stat Software*. 2023;106:1–40.

21. Chichareon P, Modolo R, Kerkmeijer L, et al. Association of sex with outcomes in patients undergoing percutaneous coronary intervention: a subgroup analysis of the GLOBAL LEADERS randomized clinical trial. *JAMA Cardiol*. 2020;5:21–29.

22. Shin ES, Her AY, Kim B, et al. Sex-based outcomes of P2Y12 inhibitor monotherapy after three months of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention. *J Kor Med Sci*. 2023;38:e383.

23. Vogel B, Baber U, Cohen DJ, et al. Sex differences among patients with high risk receiving ticagrelor with or without aspirin after percutaneous coronary intervention: a subgroup analysis of the TWILIGHT randomized clinical trial. *JAMA Cardiol*. 2021;6:1032–1041.

24. De Luca G, Damen SA, Camaro C, et al. Final results of the randomised evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with a new-generation stent (REDUCE trial). *EuroIntervention*. 2019;15:e990–e998.

25. Franzone A, McFadden E, Leonardi S, et al. Ticagrelor alone versus dual antiplatelet therapy from 1 Month after drug-eluting coronary stenting. *J Am Coll Cardiol*. 2019;74:2223–2234.

26. Hahn JY, Song YB, Oh JH, et al. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet*. 2018;391:1274–1284.

27. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. 2019;321:2428–2437.

28. Han JK, Hwang D, Yang S, et al. Comparison of 3- to 6-month versus 12-month dual antiplatelet therapy after coronary intervention using the contemporary drug-eluting stents with ultrathin struts: the HOST-IDEA randomized clinical trial. *Circulation*. 2023;147:1358–1368.

29. Han Y, Xu B, Xu K, et al. Six versus 12 Months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 trial. *Circ Cardiovasc Interv*. 2016;9:e003145.

30. Hong S-J, Shin D-H, Kim J-S, et al. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation. *JACC Cardiovasc Interv*. 2016;9:1438–1446.

31. Kim B-K, Hong S-J, Cho Y-H, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome. *JAMA*. 2020;323:2407–2416.

32. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol*. 2012;60:1340–1348.

33. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042.

34. Schulz-Schupke S, Byrne RA, Ten Berg JM, et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J*. 2015;36:1252–1263.

35. Ge Z, Kan J, Gao X, et al. Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes (ULTIMATE-DAPT): a randomised, placebo-controlled, double-blind clinical trial. *Lancet*. 2024;403:1866–1878.

36. Patti G, De Caterina R, Abbate R, et al. Platelet function and long-term antiplatelet therapy in women: is there a gender-specificity? A 'state-of-the-art' paper. *Eur Heart J*. 2014;35:2213–2223b.

37. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134:e123–e155.

38. Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth Methods*. 2019;10:398–419.

KEY WORDS dual antiplatelet therapy, meta-analysis, percutaneous coronary intervention, randomized controlled trials, sex differences

APPENDIX For supplemental tables and figures, please see the online version of this paper.