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Sex differences among patients receiving ticagrelor monotherapy or aspirin after coronary bypass surgery: A prespecified subgroup analysis of the TiCAB trial☆

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ABSTRACT

Background: There is limited evidence on the association of sex with outcomes among patients undergoing coronary bypass surgery (CABG) and treated with ticagrelor monotherapy or aspirin.
Methods: This was a pre-specified sub-analysis of TiCAB, an investigator-initiated placebo-controlled randomized trial. Primary efficacy endpoint was the composite of cardiovascular death, myocardial infarction, stroke, or repeat revascularization 1 year after CABG. Safety endpoint was BARC type 2, 3 or 5 bleeding.
Results: A total of 280 (15.0%) women and 1579 (85.0%) men were included. Compared with men, women were older (66.1 ± 10.2 vs. 70.1 ± 9.3 years) with more acute presentation (17.0% vs 21.1%). The incidence of the primary endpoint was similar between women and men (9.2% vs. 8.9%, HR 1.08, 95%CI 0.71–1.66, $P = 0.71$). Cardiovascular death occurred more often in women (2.9% vs 1.0%, adjusted HR 2.87, 95%CI 1.23–6.70, $P = 0.02$). The incidence of bleeding was similar between the sexes (2.2% vs. 2.5%, HR 0.91, 95% CI 0.51–1.65, $P = 0.77$). Ticagrelor vs aspirin was associated with a similar risk of the primary endpoint in women (10.6% vs. 7.9%, HR 1.39, 95%CI 0.63–3.05, $P = 0.42$) and men (9.5% vs. 8.2%, HR 1.15, 95%CI 0.82–1.62, $P = 0.41$;$p_{interaction} = 0.69$), and a similar risk of bleeding in women (2.9% vs. 1.4%, HR 2.09, 95%CI 0.38–11.41, $P = 0.40$) and men (2.2% vs. 2.8%, HR 0.80, 95%CI 0.42–1.52, $P = 0.49$;$p_{interaction} = 0.35$).
Conclusions: Among women and men undergoing CABG, ticagrelor monotherapy was associated with a similar risk of the primary efficacy endpoint and bleeding compared with aspirin. The risk of cardiovascular death was increased in women irrespective of antiplatelet therapy.

1. Introduction

Antiplatelet therapy with aspirin represents the cornerstone of secondary prevention in patients with cardiovascular disease. Dual antiplatelet therapy (DAPT) consisting of aspirin and the potent oral P2Y12 inhibitor ticagrelor has shown increased efficacy in preventing ischemic events in patients with acute coronary syndromes [1] and in stable patients with high-risk coronary artery disease [2]. A recent meta-

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analysis of randomized clinical trials (RCTs) showed that ticagrelor DAPT is associated with a decreased risk of saphenous vein graft failure in patients undergoing coronary artery bypass grafting (CABG) [3]. However, the increased risk of bleeding associated with ticagrelor DAPT [3] has led to studies investigating the use of ticagrelor monotherapy both after percutaneous coronary intervention (PCI) [4,5] and CABG [6–8].

Women have longer bleeding times, higher baseline platelet reactivity, and stronger adenosine diphosphate-induced platelet aggregation compared with men [9]. The sex-specific variability in ischemic and bleeding outcomes with ticagrelor monotherapy has been investigated after PCI [10–12]. However, little is known about sex-specific outcomes of ticagrelor monotherapy in patients undergoing CABG. In this pre-specified sub-analysis of the Ticagrelor in Coronary Artery Bypass (TiCAB) trial we examined the sex-specific efficacy and safety of ticagrelor monotherapy compared with aspirin for secondary prevention after CABG.

2. Methods

2.1. Patients

The design and results of the TiCAB trial (NCT01755520) have been published previously [6,13]. In addition, several sub-analyses have provided further insights [14–17]. In brief, TiCAB was a multi-center, double-blinded, placebo-controlled RCT that enrolled patients with stable coronary artery disease or acute coronary syndrome undergoing CABG for three-vessel disease and/or left main stenosis, or two-vessel disease with impaired left ventricular function. Patients were randomly assigned to receive either aspirin 100 mg and placebo ticagrelor or placebo aspirin and ticagrelor 90 mg within the first 24 h after CABG. Maintenance doses consisted of aspirin 100 mg once daily or ticagrelor 90 mg twice daily. Under the initial TiCAB protocol 245 patients also received study medication on days −5 to −3 before CABG surgery [6,13]. Follow-up was performed by telephone 6 and 9 months after randomization and in person 3 months and 1 year after randomization. Compliance with randomized treatment was defined as regular intake of study medication for >80% of days between follow-up visits. The TiCAB study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and Institutional Review Boards of all participating sites approved the study. All participants gave written informed consent.

2.2. Outcomes

The primary outcome for this analysis was the TiCAB primary composite outcome of cardiovascular death, myocardial infarction, stroke, or repeat revascularization 1 year after CABG. Secondary efficacy outcomes were the individual components of the primary outcome, and all-cause death. The secondary safety outcome for this analysis was Bleeding Academic Research Consortium (BARC) [18] type 2, 3, or 5 bleeding 1 year after CABG. Definitions of events are provided in Supplementary Table 1. All clinical events were adjudicated by an independent external committee, the members of which were blinded to the randomized treatment assignment.

2.3. Statistical analysis

All analyses were performed on a modified intention-to-treat basis with inclusion of all patients who were randomly assigned to one of the two treatment groups, with the exception of those patients who withdrew consent before undergoing CABG or did not undergo CABG, and consequently, did not receive any study drug [6].

Categorical variables are reported as counts and percentages and compared among groups using chi-square test or Fisher's exact test. Continuous variables are reported as means and standard deviations and compared using Student's *t*-test or the non-parametric Wilcoxon rank sum test. Cumulative event rates were calculated using the Kaplan-Meier method. For composite endpoints time-to-first-event analysis was used. Outcomes were compared between groups by means of univariable Cox proportional hazards model after checking for fulfilment of the proportional hazard assumption. In addition, to estimate the interaction between the treatment arm and sex for the study endpoints and between the treatment arm and pre-specified subgroups in female or male populations, an interaction term was entered into the Cox proportional hazards models. The covariates entered into the multivariable models were selected by the use of the LASSO (Least Absolute Shrinkage and Selection Operator) regression method provided in the R-package "glmnet" (version 2.0–13) after entering the following relevant baseline characteristics as candidates: study medication, age, BMI, hypertension, diabetes, kidney function, acute coronary syndrome, NYHA class, prior myocardial infarction, severity of CAD, off-pump surgery, complete revascularization and multiple arterial grafting. A landmark analysis at 1-month (≤30 days) follow-up was performed for the endpoint cardiovascular death. All statistical analyses were performed with the use of R v3.5.1 software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients

A total of 1893 patients were randomized in TiCAB, of whom 1859 were included in the modified intention-to-treat analysis. Of analyzed patients, 280 (15.0%) were women (Supplementary Fig. 1). Baseline clinical and procedural characteristics are reported in Table 1. Compared with men, women were older (mean age, 66.1 ± 10.2 vs. 70.1 ± 9.3 years), and more likely to present with non-ST-elevation acute coronary syndrome (17.0% vs 21.1%). In contrast, women were less likely to be smokers. There were no significant differences with regard to prevalence of diabetes, history of myocardial infarction, or chronic kidney disease between the sexes. Women, compared with men, were less likely to receive ≥2 arterial grafts. In particular, women significantly less frequently received a right internal thoracic artery (RITA) graft compared with men (32.5% vs 45.0, $P < 0.001$), whereas there was no significant difference in the use of the radial artery (13.6% vs 17.4%, $P = 0.14$). In addition, women were less likely to be discharged on optimal medical therapy including beta-blockers (Table 1).

Among women and men, baseline clinical and procedural characteristics were balanced between the randomized treatment groups (Supplementary Table 2).

3.2. Outcomes by sex

Operative results within 30 days after CABG are summarized in Supplementary Table 3. Women, compared with men, had a higher incidence of operative cardiovascular death, and the association of female sex with cardiovascular death remained significant in the risk-adjusted model (2.5% vs. 0.8%, adjusted HR 3.07, 95% CI 1.22–7.69, $P = 0.02$). The incidence of myocardial infarction, stroke, and repeat revascularization was similar for women and men. The incidence of CABG-related bleeding (BARC type 4 bleeding) (6.8% vs. 5.1%, HR 1.35, 95% CI 0.82–2.23, $P = 0.23$) and BARC type 2–5 bleeding (5.4% vs. 3.7%, HR 1.48, 95% CI 0.84–2.61, $P = 0.17$) was also similar for women

Table 1
Baseline clinical and procedural characteristics by sex.

	Women (n = 280)	Men (n = 1579)	P Value
Age, mean (±SD), y	70.1 (±9.3)	66.1 (±10.2)	<0.0001
Body mass index, mean (±SD), kg/m^2	28.3 (±5.7)	28.7 (±4.9)	0.30
Cardiovascular risk factors, n (%)			
Diabetes mellitus	116 (41.4)	552 (35.0)	0.15
Smoking	108 (38.6)	931 (59.0)	<0.0001
Hypertension	254 (90.7)	1418 (89.8)	0.89
Dyslipidemia	218 (77.9)	1301 (82.4)	0.04
Clinical presentation, n (%)			<0.01
Stable angina	202 (72.1)	1086 (68.8)	
Unstable angina	19 (6.8)	224 (14.2)	
Non-ST-elevation ACS	59 (21.1)	269 (17.0)	
History, n (%)			
Myocardial infarction	64 (22.9)	358 (22.7)	0.73
PCI	43 (15.4)	332 (21.0)	0.08
Peripheral vascular disease	23 (8.2)	147 (9.3)	0.56
Transient ischemic attack	4 (1.4)	30 (1.9)	0.76
Stroke	9 (3.2)	65 (4.1)	0.48
Chronic obstructive pulmonary disease	23 (8.2)	125 (7.9)	0.87
Chronic kidney disease	15 (5.4)	116 (7.3)	0.23
Ejection fraction, mean (±SD), %	57.7 (±11.4)	56.3 (±12.4)	0.04
Left main disease, n (%)	113 (40.4)	639 (40.5)	0.64
Complete revascularization, n (%)	231 (82.5)	1319 (83.5)	0.67
Number of vein grafts per patient, n (%)	75 (26.8)	551 (34.9)	<0.01
0	110 (39.3)	608 (38.5)	
1	88 (31.4)	340 (21.5)	
2	6 (2.1)	72 (4.6)	
3	1 (0.4)	8 (0.5)	
4			
Number of arterial grafts, n (%)			<0.01
0	10 (3.6)	66 (4.2)	
1	156 (55.7)	629 (39.0)	
≥2	114 (40.7)	884 (56.0)	
Type of arterial grafts, n (%)			
LITA	267 (95.4)	1492 (94.5)	0.65
RITA	91 (32.5)	710 (45.0)	<0.001
Radial artery	38 (13.6)	274 (17.4)	0.14
Off-pump CABG, n (%)	6 (2.1)	59 (3.7)	0.18
Medication at discharge, n (%)			
Beta-blocker	235 (83.9)	1393 (88.2)	0.04
Angiotensin-converting-enzyme inhibitor	135 (48.2)	807 (51.1)	0.41
Angiotensin-receptor blocker	55 (19.6)	282 (17.9)	0.48
Statin	230 (82.1)	1358 (86.0)	0.09
Compliance with study medication at 12 months, n (%)	224 (83.9)	1330 (87.1)	0.16

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; LITA, left internal thoracic artery; PCI, percutaneous coronary intervention; RITA, right internal thoracic artery.

and men (Supplementary Table 3).

The primary composite outcome of cardiovascular death, myocardial infarction, stroke, or repeat revascularization 1 year after CABG occurred in 25 of 280 women and 134 of 1579 men (9.2% vs. 8.9%, HR 1.08, 95% CI 0.71–1.66, P = 0.71) (Table 2, Supplementary Fig. 2). Cardiovascular death occurred significantly more often in women than in men (2.9% vs 1.0%, adjusted HR 2.87, 95% CI 1.23–6.70, P = 0.02) (Table 2). In the landmark analysis starting at 30 days after CABG, female sex was no longer associated with an increased risk of cardiovascular death (0.4% vs. 0.2%, adjusted HR 1.91, 95% CI 0.12–30.17, P = 0.57) (Fig. 1). There were no statistically significant differences between the sexes in the non-fatal components of the composite outcome or all-cause death at 1 year (Table 2).

No significant differences between women and men were found in the incidence of BARC type 2, 3, or 5 bleeding (2.2% vs. 2.5%, HR 0.91, 95% CI 0.51–1.65, P = 0.77) (Table 2, Supplementary Fig. 3).

Use of the RITA (HR 0.28, 95% CI 0.13–0.61, P = 0.001) or the radial artery (HR 0.22, 95% CI 0.05–0.92, P = 0.04) as a second arterial graft was associated with a significantly lower risk of all-cause death at 1 year irrespective of sex. There was no association of type of second arterial graft used with the risk of bleeding.

Table 2
Outcomes by sex 1 year after coronary artery bypass grafting.

Outcome	Women, No. of events (%)	Men, No. of events (%)	HR (95% CI)	P value
Cardiovascular death, MI, stroke, or repeat revascularization	25 (9.2)	134 (8.9)	1.08 (0.71–1.66)	0.71
Cardiovascular death	8 (2.9)	16 (1.0)	2.87 (1.23–6.70)[a]	0.02[a]
MI	8 (3.1)	41 (2.7)	1.12 (0.52–2.39)	0.77
Stroke	9 (3.3)	44 (2.8)	1.18 (0.58–2.42)	0.65
Repeat revascularization	6 (2.4)	71 (4.8)	0.49 (0.21–1.13)	0.09
All-cause death	9 (3.3)	36 (2.4)	1.45 (0.70–3.00)	0.32
BARC type 2, 3, or 5 bleeding	6 (2.2)	38 (2.5)	0.91 (0.39–2.16)	0.80

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction. Percentages indicate cumulative incidence rates.
[a] Adjusted hazard ratio (HR) 2.87 (95% CI, 1.23 to 6.70), adjusted P value 0.015.

3.3. Outcomes by sex and randomized treatment

Ticagrelor and aspirin were associated with a similar risk of the primary composite outcome in women (10.6% vs. 7.9%, HR 1.39, 95% CI 0.63–3.05, P = 0.42) and in men (9.5% vs. 8.2%, HR 1.15, 95% CI 0.82–1.62, P = 0.41) without significant interaction between randomized treatment assignment and sex ($p_{interaction}$ = 0.69) (Fig. 2A). The risk of cardiovascular death was not significantly different in women receiving ticagrelor or aspirin (3.0% vs. 2.8%, HR 1.05, 95% CI 0.26–4.20, P = 0.95) and in men receiving ticagrelor or aspirin (0.9% vs. 1.2%, HR 0.77, 95% CI 0.29–2.07, P = 0.60). Similar results were found for the risk of the non-fatal components of the primary outcome, and all-cause death (Table 3).

Ticagrelor and aspirin were associated with a similar risk of BARC type 2, 3, or 5 bleeding in women (2.9% vs. 1.4%, HR 2.09, 95% CI 0.38–11.41, P = 0.40) and in men (2.2% vs. 2.8%, HR 0.80, 95% CI 0.42–1.52, P = 0.49) with no significant interaction between randomized treatment assignment and sex ($p_{interaction}$ = 0.35) (Fig. 2B).

4. Discussion

This pre-specified sub-analysis of the TiCAB trial examined the efficacy and safety of ticagrelor monotherapy compared with aspirin for secondary prevention after CABG in women and men. Ticagrelor monotherapy compared with aspirin was associated with a similar risk of the composite of cardiovascular death, myocardial infarction, stroke, or repeat revascularization, and a similar risk of BARC type 2, 3, or 5 bleeding in women and in men. Female sex was associated with an increased risk of cardiovascular death after CABG irrespective of antiplatelet therapy.

Increasing evidence shows that that there are key differences between women and men in outcomes of medical and invasive treatment of coronary artery disease [19]. In a recent study-level meta-analysis of 84 studies and 903,346 patients (224,340 women) investigating the impact of sex on outcomes following CABG, Robinson et al. found that female sex was associated with a higher risk of operative mortality (OR 1.77; 95% CI 1.64–1.92; P < 0.001) [20]. An individual patient data meta-analysis of four CABG trials including 13,193 patients (2714

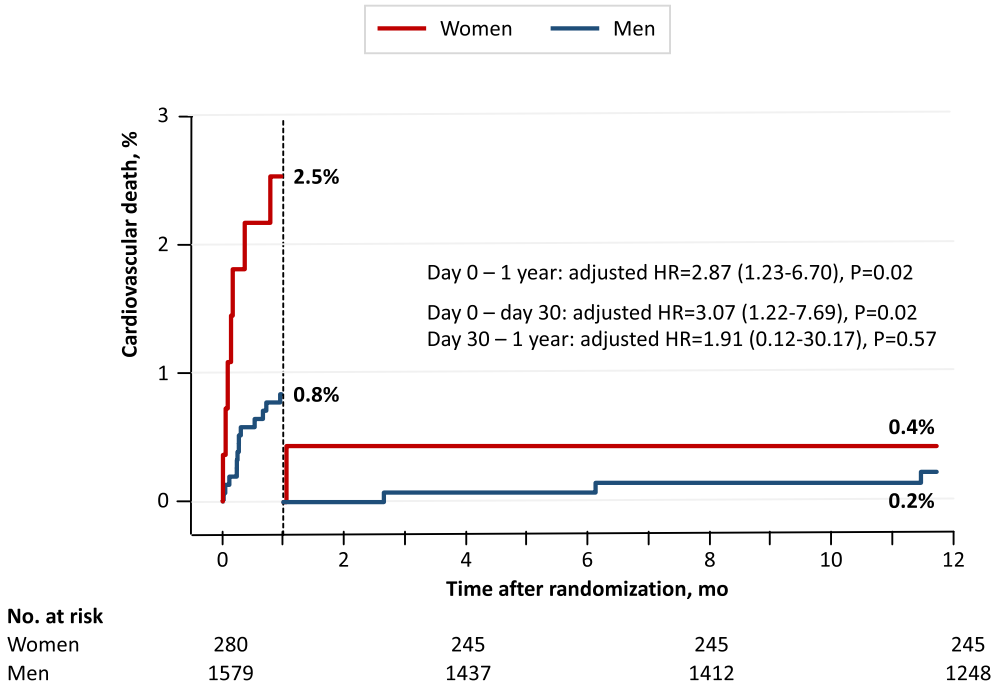


Fig. 1. Landmark analysis for cardiovascular death.

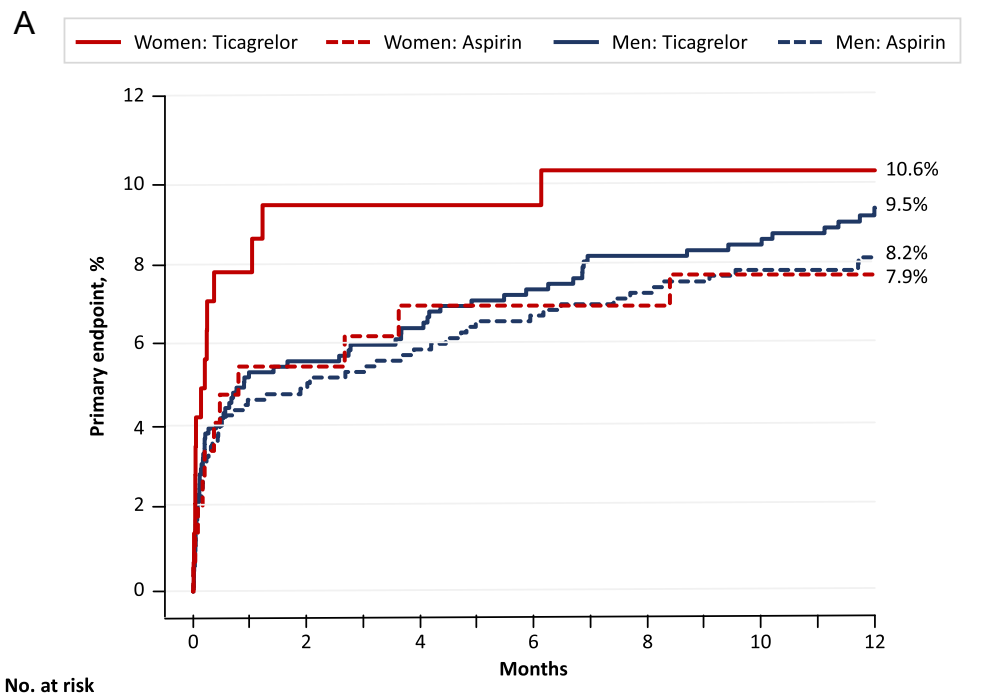
women) reported that women have a higher incidence of major adverse cardiac and cerebrovascular events 5 years after CABG compared to men (adjusted HR 1.12, 95% CI 1.04–1.21, $P = 0.004$), however, this difference in outcome was attenuated when the postoperative period was excluded in a landmark analysis [21]. Inequitable delivery of the CABG procedure itself has been proposed as a potential reason for worse outcomes in women. Jawitz et al. [22] in an analysis from the STS database including 1.2 million patients (25% women) showed that women were significantly less likely to receive a left internal thoracic artery graft to the left anterior descending coronary artery, considered the gold standard in CABG surgery, in addition to less frequently receiving multiple arterial grafting, and less completeness of revascularization. In the present study, women, compared with men, had a significantly higher risk of cardiovascular death after CABG even after adjustment for significant differences in clinical characteristics, operative technique, and completeness of revascularization. This was particularly evident in the first 30 days after CABG, after which the effect was clearly attenuated. The excess cardiovascular risk in women may be related to the difference in presentation pattern of ischemic heart disease that includes coronary microvascular dysfunction and associated impaired coronary flow reserve, representing a biological risk, and a phenotype less amenable to revascularization [23,24]. Women, compared with men, also have smaller caliber coronary arteries and conduits that are more prone to spasm, which may increase the technical complexity of the operation and risk of graft failure [25–27].

Ticagrelor exposure is higher and its elimination half-life slightly longer in women [28]. An increased bleeding risk in women compared with men has been reported after PCI and acute coronary syndrome [29]. While ticagrelor monotherapy and its differential effects on women and men have been investigated in RCTs after PCI [10–12], this is not the case after CABG. In a subgroup analysis by sex of the GLOBAL LEADERS trial ticagrelor monotherapy, compared with DAPT, was associated with a lower risk of bleeding in men (HR, 0.72; 95%CI, 0.53–0.98) but not in women (HR, 1.23; 95%CI, 0.80–1.89; P for interaction = 0.045) 1 year after PCI [10]. A subgroup analysis by sex of the TWILIGHT trial showed that withdrawing aspirin while continuing ticagrelor after 3 months of DAPT after PCI was associated with a reduction in bleeding and preserved ischemic benefits in women and men [11].

To date, the TiCAB trial is the only RCT investigating the effect of ticagrelor monotherapy on clinical events after CABG [6]. The results of the present study are consistent with the main trial, and did not show a benefit of ticagrelor over aspirin in the reduction of the primary composite efficacy outcome in women or in men. The findings further suggest that the risk of cardiovascular death in women is not associated with the type of antiplatelet therapy received. The trend towards a reduction in the risk of myocardial infarction with ticagrelor in men, that was not seen in women, may be related to the small sample size of women in the trial. In this sub-analysis of the TiCAB trial the incidence of BARC type 2, 3, or 5 bleeding after CABG was not significantly different in patients receiving ticagrelor compared to those receiving aspirin, and this finding was unrelated to sex. The lack of difference in clinically important bleeding between ticagrelor and aspirin in both women and men suggests that ticagrelor monotherapy can be used safely as an alternative to aspirin after CABG. Nevertheless, individual assessment of bleeding risk remains of utmost importance in women and men after CABG, as both ischemic and bleeding complications significantly influence outcomes and overall mortality risk [30].

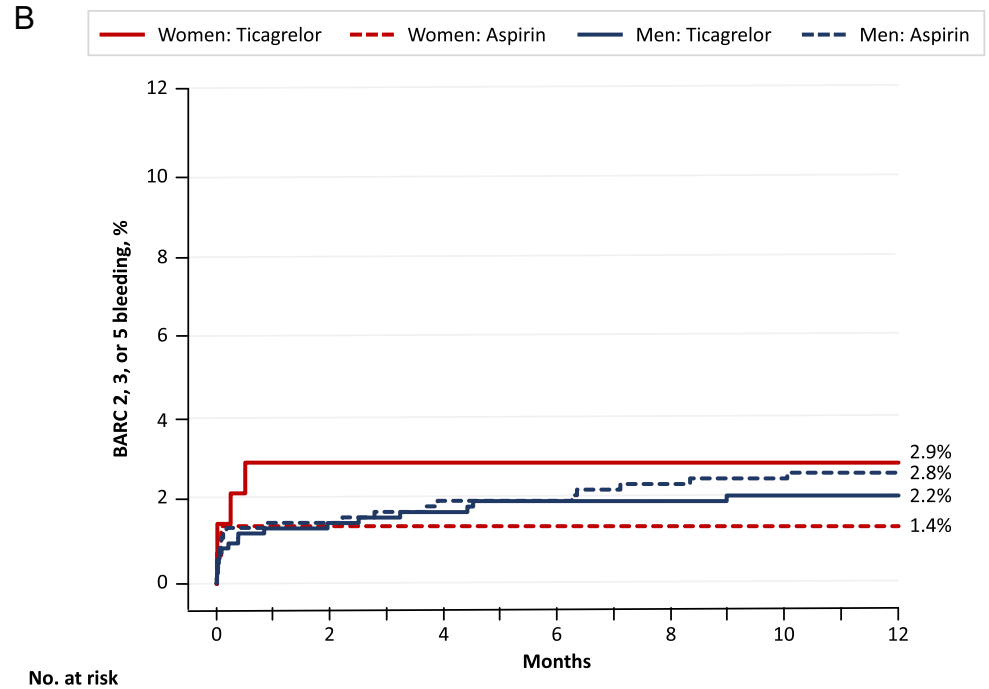
4.1. Limitations

This analysis incorporates the limitations of the original TiCAB trial which was prematurely halted and underpowered for clinical outcomes. The blinded interim analysis specified in the study protocol showed that the lower-than-expected event rates would require a substantially higher number of participants than originally expected based on the sample size calculations in the TiCAB study. The Data Safety and Monitoring Board (DSMB) consequently recommended to halt recruitment. Although this subgroup analysis was pre-specified, randomization in the TiCAB trial was not stratified by sex. The female subgroup comprises only 15% of the overall trial population. Smaller sample size inevitably results in lower precision and increase in the type II error rate. Therefore, in subgroup analyses, the group-specific *p*-values can be misleading and results remain hypothesis generating and require



No. at risk

Women: Ticagrelor	137	107	104	104	101	100	99
Women: Aspirin	143	125	122	121	120	118	118
Men: Ticagrelor	794	694	683	675	661	651	642
Men: Aspirin	785	694	678	670	662	647	643



No. at risk

Women: Ticagrelor	137	131	131	131	131	131	131
Women: Aspirin	143	141	141	141	141	141	141
Men: Ticagrelor	794	777	708	703	703	689	689
Men: Aspirin	785	769	697	696	686	684	672

Fig. 2. Kaplan-Meier event rates curves of (A) the composite primary endpoint of cardiovascular death, myocardial infarction, stroke, or repeat revascularization; and (B) Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding; by sex and randomized treatment assignment.

Table 3
Outcomes by sex and randomized treatment 1 year after coronary artery bypass grafting.

Outcome	Women (n = 280)				Men (n = 1579)			
	Ticagrelor No. of events (%)	Aspirin No. of events (%)	HR (95% CI)	*P* value	Ticagrelor No. of events (%)	Aspirin No. of events (%)	HR (95% CI)	*P* value
Cardiovascular death, MI, stroke, or repeat revascularization	14 (10.6)	11 (7.9)	1.39 (0.63–3.05)	0.42	72 (9.5)	62 (8.2)	1.15 (0.82–1.62)	0.41
Cardiovascular death	4 (3.0)	4 (2.8)	1.05 (0.26–4.20)	0.95	7 (0.9)	9 (1.2)	0.77 (0.29–2.07)	0.60
MI	4 (2.9)	4 (3.1)	1.09 (0.27–4.35)	0.91	15 (1.9)	26 (3.4)	0.57 (0.30–1.07)	0.08
Stroke	6 (4.5)	3 (2.1)	2.11 (0.53–8.45)	0.29	23 (3.0)	21 (2.7)	1.09 (0.60–1.96)	0.79
Repeat revascularization	4 (3.1)	2 (1.6)	2.22 (0.41–12.13)	0.36	39 (5.3)	32 (4.4)	1.21 (0.76–1.93))	0.42
All-cause death	5 (3.9)	4 (2.8)	1.32 (0.36–4.93)	0.68	17 (2.3)	19 (2.6)	0.89 (0.46–1.70)	0.71
BARC type 2, 3, or 5 bleeding	4 (2.9)	2 (1.4)	2.09 (0.38–11.41)	0.40	17 (2.2)	21 (2.8)	0.80 (0.42–1.52)	0.49

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction.
Percentages indicate cumulative incidence rates.

confirmation in future studies. Despite statistical adjustment for baseline confounders, unknown confounders warrant a careful interpretation of current findings. However, these data provide relevant insights from the largest contemporary CABG RCT comparing antiplatelet therapies.

5. Conclusions

Among women and men undergoing CABG, those receiving ticagrelor monotherapy had a similar risk of the composite efficacy endpoint of cardiovascular death, myocardial infarction, stroke, or repeat revascularization, and a similar risk of the safety endpoint BARC type 2, 3 or 5 bleeding compared with those receiving aspirin. The risk of cardiovascular death after CABG was increased in women compared with men irrespective of antiplatelet therapy. A greater representation of women in RCTs is paramount to adequately provide evidence for optimal antiplatelet therapy in women after CABG.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.10.166.

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