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ORIGINAL RESEARCH

Sex-Specific Differences in Clinical Outcomes After Percutaneous Coronary Intervention: Insights from the TAILOR-PCI Trial

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BACKGROUND: TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes due to decreased Clopidogrel Response After Percutaneous Coronary Intervention) studied genotype-guided selection of antiplatelet therapy after percutaneous coronary intervention versus conventional therapy with clopidogrel. The presence of *CYP2C19* loss-of-function alleles in patients treated with clopidogrel may be associated with increased risk for ischemic events. We report a prespecified sex-specific analysis of genotyping and associated cardiovascular outcomes from this study.

METHODS AND RESULTS: Associations between sex and major adverse cardiac events (MACE: cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia) and Bleeding Academic Research Consortium (BARC) bleeding at 12 months were analyzed using Cox proportional-hazards models. Among 5276 randomized patients, loss-of-function carriers were observed in ≈36% of both sexes, and >80% of carriers were heterozygotes. At 12 months, after adjustment for baseline differences, risks of MACE (HR , 1.28 [0.97 to 1.68]; P=0.088) and BARC bleeding (hazard ratio [HR], 1.36 [0.91 to 2.05]; P=0.14) were comparable among women and men. There were no significant interactions between sex and treatment strategy for MACE interaction P value (P_{int}=0.59) or BARC bleeding (P_{int}=0.47) nor for sex and genotype (MACE P_{int}=0.15, and BARC bleeding P_{int}=0.60).

CONCLUSIONS: *CYP2C19* loss-of-function alleles were present in ≈1 in 3 women and men. Women had similar adjusted risks of MACE and bleeding as men following percutaneous coronary intervention. Genotype-guided therapy did not significantly reduce the risk of MACE or bleeding relative to conventional therapy for both sexes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01742117.

Key Words: genotype ■ sex differences ■ TAILOR-PCI

Women undergoing percutaneous coronary interventions (PCI) in the setting of acute coronary syndromes (ACS) or ST-segment–elevation myocardial infarction are often older than men, and have more baseline comorbidities.[1,2] Women have lower rates of coronary revascularization, and are prescribed evidence-based medicines less frequently after ACS hospitalization.[3–5] Prior studies of sex-based differences in major adverse cardiovascular events (MACE) have demonstrated conflicting findings.[6–12] While unadjusted

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CLINICAL PERSPECTIVE

What Is New?

- Although *CYP2C19* loss-of-function alleles are present in ≈1 in 3 women and men, genotype-guided selection of antiplatelet therapy after percutaneous coronary intervention did not significantly reduce the risk of ischemic events or bleeding compared with conventional therapy with clopidogrel for both sexes.

What Are the Clinical Implications?

- Based on the TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes due to decreased Clopidogrel Response After Percutaneous Coronary Intervention) study, a genotype-guided strategy for the selection antiplatelet therapy after percutaneous coronary intervention is not routinely recommended.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
CT	conventional therapy
GG	genotype-guided
LOF	loss of function
MACE	major adverse cardiac events
TAILOR-PCI	Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention

rates of MACE and mortality have been higher among women in several studies, these associations were no longer significant after adjusting for differences in baseline comorbidity in most studies.[6–9] Female sex has been identified as an independent risk factor for major bleeding both in the short term (30 days) and longer term (1 year and beyond) follow-up.[12] It is unknown whether *CYP2C19* genotype modifies sex-specific differences for bleeding or ischemic events. These relationships were explored in a prespecified analysis of the TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention) randomized clinical trial.

METHODS

The authors declare that all supporting data are available within the article (and its online supplementary files).

Summary of TAILOR-PCI

TAILOR-PCI was an international, multicenter, open-label randomized trial. The methodology of TAILOR-PCI (including study design, inclusion and exclusion criteria, patients, and clinical outcomes) has been published.[13,14] In brief, 5302 patients undergoing PCI for ACS or stable coronary artery disease were randomized to the genotype-guided (GG) group and underwent point-of-care testing, or the conventional therapy (CT) group. *CYP2C19* loss-of-function (LOF) carriers (*CYP2C19*2* and **3*) were prescribed ticagrelor and noncarriers received clopidogrel. Point-of-care genotyping was performed using Spartan Rx (Spartan Bioscience, Canada). Patients randomized to the CT group were prescribed clopidogrel. All subjects underwent laboratory-based genotyping using TaqMan (Applied Biosystems) after 12 months. All patients received dual antiplatelet therapy, with the P2Y12 inhibitor and aspirin for 12 months after PCI. Randomization was stratified for age, sex, site, and clinical presentation. The primary end point was a composite of MACE comprising cardiovascular mortality, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia at 12 months. A secondary end point was major or minor bleeding at 12 months. The primary analysis focused on patients with *CYP2C19* LOF alleles and a secondary analysis included all randomized patients; a prespecified sensitivity analysis allowed for multiple events per patient. The research ethics board at each center approved the study, and all participants provided written informed consent. Notably, the sex of study participants was ascertained by self-report.

The TAILOR-PCI study provides a large contemporary PCI-treated cohort in which to examine sex-specific differences in presentation, management, and clinical outcomes. The main objectives of this analysis were to (1) study sex-based differences in clinical outcomes in a large ACS population undergoing PCI using all randomized patients; (2) characterize the prevalence of LOF carriers in this cohort by sex, and learn how this impacts the occurrence of MACE and bleeding events; and (3) evaluate for important interactions between sex and treatment strategy, sex and genotype, and sex and optimal medical treatment (see definition of optimal medical treatment below).

Outcomes

The primary end point for this analysis was a composite of MACE as defined for the main trial, at 12 months after PCI. Secondary outcomes for this analysis were the individual components of the primary end point, all-cause mortality, and the safety end points of Bleeding Academic Research Consortium (BARC) bleeding types 2, 3, and 5, and types 3 and 5.

Statistical Analysis

Continuous and ordinal variables were tested with the Wilcoxon rank sum test. Categorical variables were tested using the χ^2 test. Summary statistics were based on those without missing data. Frequencies of *2/*3 allele LOF carriers were compared by sex with the Armitage trend test. Carrier status was categorized as noncarrier, heterozygous, and homozygous carrier. Cox proportional hazards regression models were used to estimate the adjusted hazard ratios for the effect of sex on time to first event for study end points. A likelihood ratio test was used to test the effect of sex. As in the primary analysis for the trial, age group and clinical presentation were selected a priori as covariates, with site of enrollment included as a random effect; treatment arm, however, was not included. Additionally, the following covariates were also selected post hoc because they were distributed significantly differently between men and women: country of enrollment, diabetes, hypertension, current smoker, kidney disease (estimated glomerular filtration rate <60), number of stents placed (square-root transformed) and peri-PCI loading antiplatelet medication. For some outcomes with few events, Firth's correction for monotone likelihood was used to enable estimation of hazard ratios. Variables with substantial missing data (>10%) were excluded from being covariates. Missing data for eligible covariates (≤10% missing) had single values imputed based on the sample means specific to strata defined by age group, sex, and country (diabetes, n=19; hypertension, n=19; number of stents, n=20; low estimated glomerular filtration rate, n=461) to allow modeling on the entire data set, and avoid loss of power because of missing covariates. Kaplan–Meier methods were used to estimate unadjusted event rates in the first 12 months with the log-rank test used for group differences.

Interaction Analyses

The following interaction effects on study end points were analyzed: sex and genotype, sex and treatment (GG versus CT), and sex and optimal medical treatment. All models included the main effects for any interaction terms. An optimally treated patient was defined as a patient who received a specific P2Y12 receptor inhibitor according to their genotype (clopidogrel/noncarrier and ticagrelor/LOF carrier); a LOF carrier who received clopidogrel would be considered not optimally treated. Cox proportional hazards models were used with covariates as described above. To investigate the interaction between genotype and sex, patients were categorized into 6 groups: clopidogrel/male/noncarrier; clopidogrel/male/LOF; clopidogrel/female/noncarrier; clopidogrel/female/LOF; ticagrelor/male; and ticagrelor/female.

Although a P value of <0.05 was considered statistically significant, multiple comparisons were made, without correction for multiple comparisons. All analyses were undertaken using SAS version 9.4 (Cary, NC).

RESULTS

Baseline Characteristics

Of 5302 patients randomized in TAILOR-PCI, 5276 patients were eligible for analysis[13]; 1293 patients (24.5%) were women, and 3983 patients (75.4%) were men (Figure 1). Women were older than men, with lower body weight, but similar body mass index (Table 1). Approximately 6% of patients were LOF carriers for both sexes, with >80% of patients with LOF being heterozygotes (Figure 2). Women had a higher prevalence of diabetes, hypertension, and kidney disease than men, and lower rates of current smoking, prior myocardial infarction, and prior coronary revascularization. Approximately 50% of subjects presented with an acute myocardial infarction, and 40% had multivessel disease at angiography; most patients received 1 stent during PCI, and one third of subjects had radial vascular access.

Clinical Outcomes

At 12 months, women had a greater risk of experiencing the primary end point than men (6.5% versus 4.3%; hazard ratio [HR], 1.52 [95% CI, 1.16–1.98]; P=0.002) (Table 2, Figure 3). Women also had a greater risk of 12-month BARC 2-3-5 bleeding events (3.2% versus 1.9%; HR, 1.69 [95% CI, 1.14–2.49]; P=0.008) and BARC 3–5 bleeding (2.0% versus 1.2%; HR, 1.73 [95% CI, 1.06–2.81]; P=0.027) compared with men. The most common sites of bleeding were gastrointestinal bleeding and hematoma formation.

After adjustment for baseline differences, risks of the primary end point (HR, 1.28 [95% CI, 0.97–1.68]; P=0.09) and BARC 2-3-5 bleeding (HR, 1.36 [95% CI, 0.91–2.05]; P=0.14) or BARC 3-5 bleeding (P=0.30) were similar between men and women (Table 2). These results were also similar when assessing for multiple events per patient and in the LOF cohort specifically.

Interactions and Exploratory Analyses

Several analyses for potential interactions were undertaken. When compared with CT, GG therapy was associated with nonsignificant reductions in the primary end point for both men and women (male: 3.9% versus 4.8%, P=0.18, and female: 6.1% versus 6.8%, P=0.57). A significant interaction between sex and randomized treatment strategy was not identified for the primary ischemic end point interaction P value (P_{int}=0.59) or for BARC 2-3-5 bleeding events (P_{int}=0.47, Figure 4A,

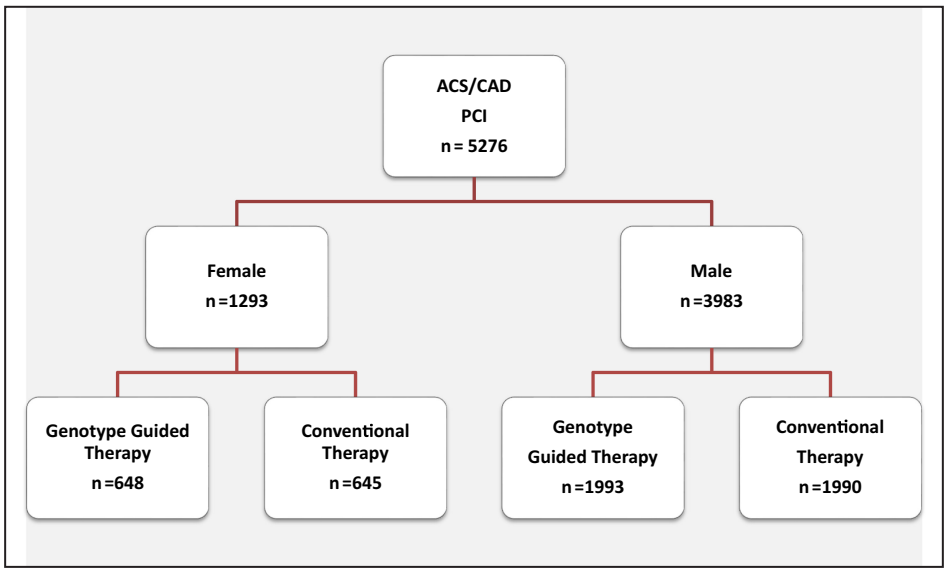

Figure 1. Study cohort.
A total of 5302 patients were randomized; however, only 5276 patients were eligible for analysis. ACS indicates acute coronary syndrome; CAD, stable coronary artery disease; and PCI, percutaneous coronary intervention.

Figure S1, Table S1). This finding was similar for MACE and bleeding end points when examining the LOF cohort alone (Figure 4B, the primary analysis for TAILOR-PCI). However, compared with CT, assignment to GG resulted in numerically lower rates of cardiovascular mortality among women, but not men (male: GG 0.6% versus CT 0.7%, P=0.82; female: GG 0% versus CT 1.4%, P=0.08, P_{int}=0.034). Specifically, there were 3 cardiovascular deaths (1.4%) among women with LOF assigned to CT (2 were because of myocardial infarction, and 1 of unknown cause) and no cardiovascular deaths (0%) among women with LOF assigned to GG (unadjusted log-rank P=0.08).

When studying the relationship between sex and *CYP2C19* genotype among 5044 participants with evaluable data (Figure 5, Figure S2), although we observed significantly higher unadjusted rates of MACE and BARC bleeding among noncarrier women receiving clopidogrel when compared with noncarrier men (MACE: 7.2% versus 4.0%, log rank P<0.001; adjusted HR, 1.56 [95% CI, 1.11–2.20]; and BARC 2-3-5 bleeding: 3.3% versus 1.7%, log rank P=0.006; adjusted HR, 1.60 [95% CI, 0.95–2.69]), these event rates were not statistically different among women and men for LOF carriers, regardless of whether they received clopidogrel or ticagrelor. Furthermore, the interaction of sex with genotype was not significant (primary end point P_{int}=0.15; BARC 2-3-5 bleeding P_{int}=0.60). Among LOF carriers receiving ticagrelor, 2 women (n=197, 1.0%) compared with no men (n=638, 0%, unadjusted log rank P=0.01) experienced stent thrombosis. The unadjusted rates of stent thrombosis among those subjects receiving clopidogrel (LOF carrier or noncarrier) were not significantly different among men and women, and the interaction between sex and genotype was not significant for this variable (P_{int}=0.08).

We explored the interaction of sex with whether the patient received optimal P2Y12 inhibitor therapy according to genotype (Figures S3 and S4). Among subjects considered optimally treated, women had a greater risk of MACE compared with men (6.8% versus 4.0%, unadjusted log rank P<0.001; adjusted HR, 1.48 [95% CI, 1.08–2.03]). For patients considered not optimally treated, the risk of the primary end point was not significantly different between sexes (female 5.7% versus male 5.8%, unadjusted log rank P=0.95; P_{int}=0.067). While greater unadjusted rates of BARC 2-3-5 bleeding were observed among optimally treated women compared with men (3.4% versus 2.0%, unadjusted log rank P=0.011; adjusted HR, 1.41 [95% CI, 0.90–2.21), the interaction of sex with treatment status was not significant (P_{int}=0.53).

DISCUSSION

In this study of sex-based differences in the TAILOR-PCI trial, there were no important sex differences in the prevalence of *CYP2C19* LOF carriers (≈1 in 3 subjects), and >80% of subjects were heterozygotes for LOF genotypes. Women had significantly higher rates

Table 1. Baseline and Procedural Characteristics

	Female n=1293	Male n=3983	*P* value
Age, y, median (IQR)	67 (59–74)	61 (54–69)	<0.001
Weight, kg, median (IQR)	70.3 (60–84.8)	85.1 (74–99.7)	<0.001
Body mass index, kg/m^2, median (IQR)	27.7 (24.2–32.5)	28 (25.1–31.8)	0.18
Randomization strategy			0.96
Genotype-guided therapy	648 (25)	1993 (75)	
Conventional therapy	645 (24)	1990 (76)	
Race			<0.001
White	815 (63.3)	2541 (64)	
East Asian	292 (22.7)	895 (22.5)	
South Asian	55 (4.3)	181 (4.6)	
Black	49 (3.8)	75 (1.9)	
Hispanic or Latin ethnicity	38 (3)	110 (2.8)	
Other*	39 (2.9)	165 (4.2)	
Country of enrollment			0.02
United States	693 (53.6)	2024 (50.8)	
Canada	243 (18.8)	914 (22.9)	
South Korea	332 (25.7)	972 (24.4)	
Mexico	25 (1.9)	73 (1.8)	
Loss of function *CYP2C19* genotype			0.72
Loss-of-function carrier	444 (35.8)	1405 (36.6)	
Loss-of-function noncarrier	797 (64.2)	2434 (63.4)	
Cardiac risk factors			
Diabetes	426 (33.1)	1002 (25.2)	<0.001
Hypertension	917 (71.2)	2386 (60.1)	<0.001
Dyslipidemia	680 (52.8)	2067 (52.1)	0.65
Current smoker	235 (18.2)	1050 (26.4)	<0.001
Family history of CAD	516 (40.1)	1484 (37.4)	0.09
Comorbidities			
Prior myocardial infarction	141 (10.9)	617 (15.5)	<0.001
Prior PCI	242 (18.8)	982 (24.7)	<0.001
Prior coronary bypass surgery	61 (4.7)	323 (8.1)	<0.001
Prior heart failure	124 (9.6)	320 (8.1)	0.08
Peripheral artery disease	34 (2.6)	102 (2.6)	0.89
Stroke/TIA	40 (3.1)	108 (2.7)	0.47
CAD presentation			0.32
Stable CAD	214 (16.6)	758 (19.0)	
Acute coronary syndrome			
Unstable angina	449 (34.7)	1173 (29.5)	
Non-STEMI	374 (28.9)	1160 (29.1)	
STEMI	256 (19.8)	892 (22.4)	
Pre-PCI LVEF, %, median (IQR)	60 (54–66)	58 (51–65)	<0.001
Laboratory investigations			
Kidney disease, eGFR <60 mL/min	220 (18.5)	319 (8.8)	<0.001
Creatinine, mg/dL, median (IQR)	0.8 (0.7–0.9)	1.0 (0.8–1.1)	<0.001
Baseline hemoglobin, g/dL, median (IQR)	13 (12–13.8)	14.5 (13.5–15.6)	<0.001
Procedural characteristics			
Multivessel disease	521 (40.5)	1698 (42.8)	0.14
PCI lesion location			
Left anterior descending	665 (51.6)	2046 (51.6)	0.97
Right coronary	465 (36.1)	1401 (35.3)	0.60
Left circumflex	324 (25.2)	1086 (27.4)	0.12
Left main	27 (2.1)	100 (2.5)	0.39
Number of stents placed, median (IQR)	1 (1–2)	1 (1–2)	0.002
Vascular access site			0.30
Radial	442 (34.3)	1310 (33.0)	
Femoral	839 (65.1)	2647 (66.7)	
Other*	7 (0.5)	12 (0.3)	
Intraprocedural anticoagulant use			
Unfractionated heparin	1108 (86)	3409 (85.9)	0.90
Bivalirudin	145 (11.3)	524 (13.2)	0.07
Low-molecular-weight heparin	65 (5)	213 (5.4)	0.66
Loading antiplatelet therapy at time of PCI			0.03
Clopidogrel	912 (70.9)	2666 (67.2)	
Ticagrelor	263 (20.4)	944 (23.8)	
Prasugrel	25 (1.9)	102 (2.6)	
Ticlopidine	0 (0)	2 (0.1)	
Other*	6 (0.5)	7 (0.2)	
None	81 (6.3)	247 (6.2)	

Unless otherwise specified, values are n (%). CAD indicates coronary artery disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; and TIA, transient ischemic attack.

*Other includes 16 Native American or Alaskan American subjects (7 females, and 9 males) and rest of subjects include those with unclassified race/ethnicity 32 females, and 156 males.

of 12-month MACE and BARC bleeding; however, after adjusting for differences in presenting characteristics, female sex was no longer a predictor of adverse ischemic events or bleeding. Based on the prespecified statistical assumptions made for TAILOR-PCI, genotype-guided therapy did not emerge as a dominant strategy for women compared with conventional

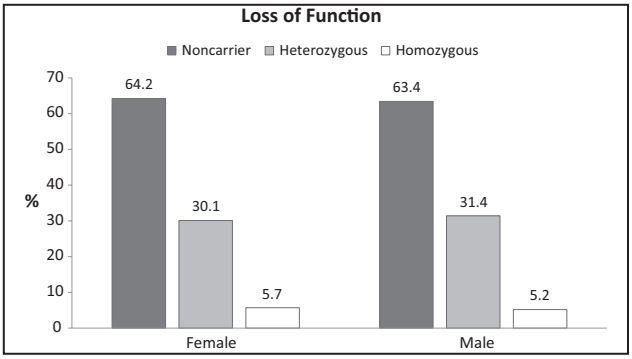

Figure 2. Genotype status.
Genotype status among 5276 randomized patients: female patients n=1293, and male patients n=3983.

therapy. However, among women with LOF alleles, those assigned to GG may have lower cardiovascular mortality compared with those receiving CT. While female noncarriers prescribed clopidogrel had higher rates of MACE and BARC 2-3-5 bleeding compared with men, there were no significant sex-by-genotype interactions identified for these end points. A related finding was that women considered optimally treated with either ticagrelor or clopidogrel according to their genotype may be at higher risk of MACE events than optimally treated men, given the trend for a significant interaction for this analysis. As observed in several prior comparative studies,[1,2] women were older and had a higher prevalence of certain cardiovascular risk factors such as diabetes, hypertension, and kidney disease, lower rates of smoking, and prior revascularization, and similar body mass index, extent of coronary artery disease, and procedural characteristics compared with men.

Although female sex is not an independent criterion in the Academic Research Consortium's definition of a patient with high bleeding risk, female sex is often associated with several defining criteria, such as older age, chronic kidney disease, and anemia, resulting in a higher prevalence of high bleeding risk status among women compared with men.[15,16] Our study confirms that that adjustment for baseline differences corrects the excess bleeding signal we observed for female participants in TAILOR-PCI. Compared with men, prior studies have demonstrated that women have high platelet reactivity, both at baseline, and while taking clopidogrel therapy.[17–20] This high platelet reactivity was associated with significantly lower rates of bleeding among women.[18,19] We observed numerically higher adjusted rates of BARC bleeding among women, but these findings did not reach statistical significance, possibly because we were underpowered to uncover these relationships, and low bleeding rates overall.

While the TAILOR-PCI study demonstrated that a GG strategy resulted in a 34% (HR, 0.66) relative reduction in ischemic events compared with conventional clopidogrel therapy without point-of-care genotyping among LOF carriers, this reduction did not achieve conventional statistical significance; however, consistent with this finding, the direction of reduction was similar in women (HR, 0.54) as compared with men (HR, 0.71).[13] We also did not identify significant interactions of sex with randomized treatment strategy for MACE (P_{int}=0.59) or BARC 2-3-5 bleeding (P_{int}=0.47) in the cohort of all randomized subjects. Furthermore, these findings did not change when examining the relationships in the LOF

Table 2. Clinical Outcomes 12 Months After Percutaneous Coronary Intervention

	Female n=1293	Male n=3983	Hazard ratio (95% CI)	Log-rank *P* value	Adjusted hazard ratio (95% CI)	Adjusted *P* value*
Primary end point						
Cardiovascular mortality, MI, stroke, severe recurrent ischemia, stent thrombosis	81 (6.5)	167 (4.3)	1.52 (1.16–1.98)	0.002	1.28 (0.97–1.68)	0.09
Secondary ischemic end points						
Cardiovascular mortality	15 (1.2)	26 (0.7)	1.78 (0.94–3.36)	0.07	1.01 (0.52–1.98)	0.97
Myocardial infarction	26 (2.1)	53 (1.4)	1.52 (0.95–2.43)	0.08	1.23 (0.75–2.00)	0.42
Stroke	8 (0.6)	14 (0.4)	1.77 (0.74–4.21)	0.19	1.20 (0.49–2.97)	0.69
Severe recurrent ischemia	38 (3.1)	82 (2.2)	1.44 (0.98–2.12)	0.06	1.36 (0.92–2.03)	0.13
Stent thrombosis	11 (0.9)	22 (0.6)	1.55 (0.75–3.19)	0.23	1.12 (0.53–2.39)	0.76
All-cause mortality	18 (1.4)	34 (0.9)	1.64 (0.92–2.90)	0.09	0.93 (0.51–1.70)	0.82
Safety end points						
BARC bleeding 2,3,5	39 (3.2)	72 (1.9)	1.69 (1.14–2.49)	0.008	1.36 (0.91–2.05)	0.14
BARC Bleeding 3,5	25 (2.0)	45 (1.2)	1.73 (1.06–2.81)	0.03	1.31 (0.79–2.19)	0.30

Unless otherwise specified, values are n (%). Percentages are Kaplan–Meier estimates. BARC indicates Bleeding Academic Research Consortium; and MI, myocardial infarction.

*Adjusted *P* values (likelihood ratio test) adjusted by age, clinical presentation, country of enrollment, diabetes, hypertension, current smoking, kidney disease (estimated glomerular filtration rate<60 mL/min), number of stents, and use of a thienopyridine loading dose.

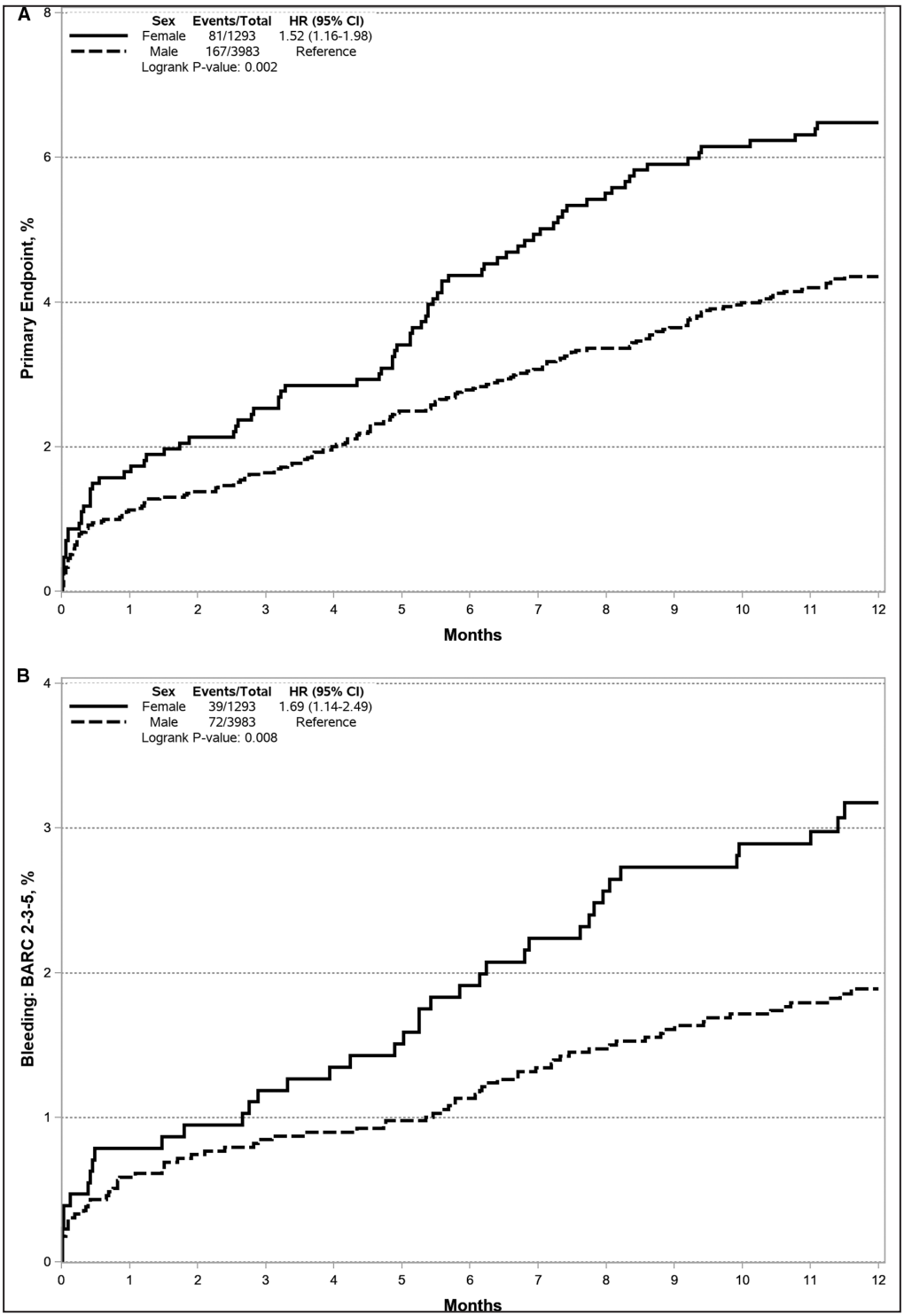

Figure 3. Event rates among all randomized patients according to sex.
Kaplan–Meier estimated event rates (unadjusted) in female and male subjects for the primary end point of time to cardiovascular mortality, myocardial infarction, stroke, stent thrombosis, or severe recurrent ischemia (A) and the safety end point time to Bleeding Academic Research Consortium 2, 3, 5 bleeding (B); n=5276 randomized patients: female patients n=1293, male patients n=3983. HR indicates hazard ratio.

cohort alone. Given the multiple comparisons undertaken, it is difficult to know whether the significant interaction identified—a lower risk of cardiovascular mortality with GG therapy in LOF carrier women but not men—is spurious; the extremely low adjusted HR of 0.07, with a broad CI of 0.00 to 2.18, makes this observation seem

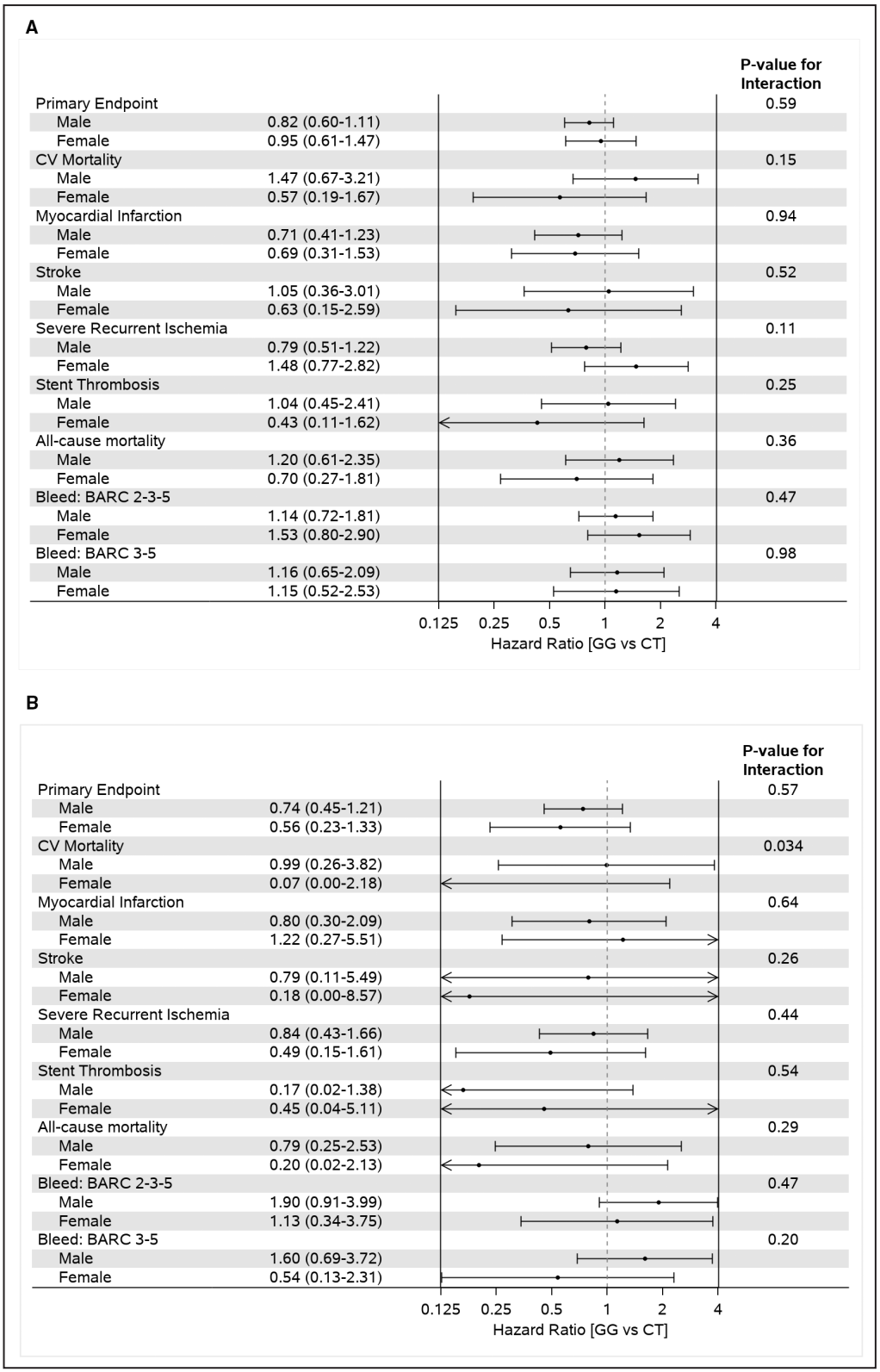

Figure 4. Analysis of interaction between sex and treatment strategy.
Interaction analysis between sex and randomized treatment strategy. **A**, All randomized patients (n=5, 276). (**B**) LOF cohort (n=1849 patients). BARC indicates Bleeding Academic Research Consortium; CT, conventional therapy; CV, cardiovascular; GG, genotype-guided therapy; and LOF, loss of function. Adjusted hazard ratios and 95% CIs are shown.

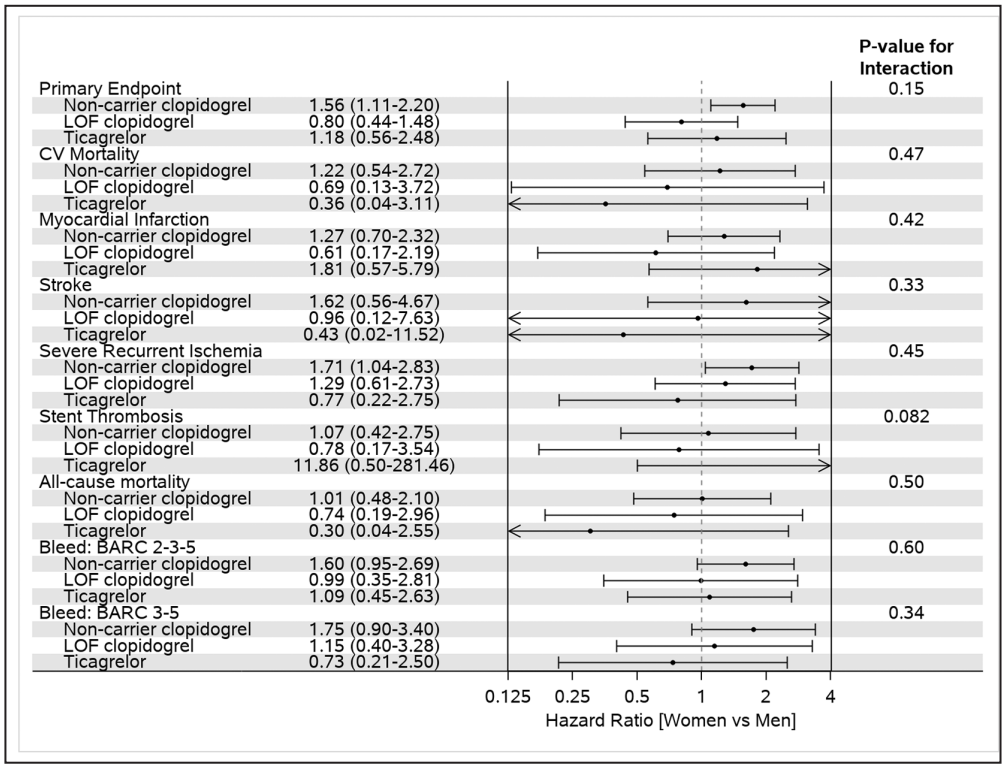

Figure 5. Analysis of interaction between sex and genotype.
n=5044 patients. BARC indicates Bleeding Academic Research Consortium; CV, cardiovascular; and LOF, loss of carrier. Adjusted hazard ratios and 95% CIs are shown.

less plausible. On the other hand, this observation may have some biological plausibility based on the published literature to date. A prior single center observational report of 1260 of patients undergoing *CYP2C19* genetic testing at the time of PCI (62% with ACS, and 31% female) demonstrated a 2-3-fold higher risk of MACE, but not bleeding, among LOF carriers receiving clopidogrel, compared with prasugrel or ticagrelor; this effect was observed among both men and women.[21] The POPular-GENETICS study (CYP2C19 Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients – Patient Outcome After Primary PCI) demonstrated the noninferiority of using a GG approach to de-escalate antiplatelet therapy to clopidogrel from more potent P2Y12 inhibitors such as ticagrelor or prasugrel in patients with ST-segment–elevation myocardial infarction.[22] In addition, this study demonstrated lower rates of PLATO (The Prospective, Randomized, Platelet Inhibition and Patient Outcomes) trial major or minor bleeding and BARC 2-3-5 bleeding using a GG strategy among patients with ST-segment–elevation myocardial infarction as compared with prescribing ticagrelor/prasugrel for all.[22] The results of the prespecified sex-based subgroup analysis of the POPular GENETICS trial were consistent with those in the overall cohort. In a GG therapy group, more patients would be expected to be appropriately assigned to clopidogrel based on genotyping with the attendant benefits of lower bleeding rates as opposed to the comparator group (using ticagrelor or prasugrel for all regardless of genotype). Both studies demonstrated higher clinical event rates among women compared with men; however, subgroup analyses did not identify significant interactions of sex with randomized treatment strategy. A meta-analysis of 15 949 patients (98% had ACS, 29% female) from 7 randomized trials, including TAILOR-PCI, found that ticagrelor or prasugrel therapy compared with clopidogrel resulted in a 30% relative risk reduction in ischemic events in *CYP2C19* LOF carriers, but not in noncarriers (P_{int}=0.013), suggesting that the main mechanism of benefit for more potent antiplatelet therapy such as ticagrelor and prasugrel may be in overcoming risk of MACE in LOF carriers.[23]

Prior studies of sex-based differences among patients presenting with chronic or ACS demonstrated conflicting findings.[4–12,24] Similar to our study, prior comparisons consistently show worse cardiovascular risk profile among women, and have also established disparity for women with less use of coronary revascularization, evidence-based therapies, and timely access to care.[25] Like other studies,[6,9–11] we found that unadjusted rates of MACE and bleeding events were higher among women compared with men; however, these associations were no longer significant after

adjusting for differences in baseline comorbidity. In 1 study of patients with ST-segment–elevation myocardial infarction, female sex remained an independent predictor of short-and long-term bleeding after adjustment for confounders.[12] Bleeding rates were low overall in the TAILOR-PCI study, making it difficult to identify potential relationships with sex, or even genotype. Even when treated optimally according to genotype, women may be at greater risk for MACE compared with optimally treated men. The optimally treated group is mainly composed of noncarrier/clopidogrel subjects. Our study demonstrates that hyporesponsiveness to clopidogrel because of LOF carrier status occurs with equal frequency between sexes. Clopidogrel pharmacodynamics are similar between men and women, with similar plasma concentrations of the active metabolite.[26] Several nongenetic factors could contribute to more hyporesponsiveness to P2Y12 inhibition in women than men. For example, high on-treatment platelet reactivity among women may be contributing to our observation of elevated MACE rates among noncarrier women receiving clopidogrel.[17] The elevated MACE rates could also be driven by sex differences in epigenetic factors such as poor adherence, decreased gastrointestinal absorption of therapy, differences in non-*CYP2C19* hepatic enzyme activity, glomerular filtration rate, volume of distribution, and drug interactions, as some examples.[27] Indeed, genotype-based antiplatelet therapy selection may be only 1 of several factors that need to be considered to mitigate sex-based differences in ACS quality of care and outcomes.

Limitations

Given the exploratory nature of our analysis, these results should be considered hypothesis generating. Given that the overall trial did not detect a statistically significant difference for the primary end point, the demonstration of any subgroup differences in events should be viewed cautiously. Consistent with other cardiovascular trials, women comprised only one fourth of the study population. Furthermore, the overall rates of ischemia and bleeding were very low in this modern cohort of patients undergoing PCI. Thus, TAILOR-PCI was similarly underpowered to detect sex-based differences in study end points. A larger sample size or higher event rates may have overcome some of these limitations. Given the low frequency of stent thrombosis events in TAILOR-PCI (10 events, in total), there is considerable uncertainty around the finding of excess stent thrombosis among women treated with ticagrelor compared with men (2 versus 0 events). Given that platelet function testing was not performed in TAILOR PCI, we are unable to formally assess the independent effect of residual on-treatment platelet reactivity on clinical outcomes in our study cohort.

CONCLUSIONS

In this sex-based analysis of the TAILOR-PCI study, we did not identify sex-based differences in the inheritance of *CYP2C19* LOF genotypes that were present in one third of all study subjects. Although women are at higher risk for ischemic or bleeding outcomes, sex was not an independent predictor of these outcomes. In this study, GG therapy did not significantly reduce the risk of MACE or bleeding relative to CT and the effect of GG therapy was not different in women compared with men.

APPENDIX

TAILOR PCI Site Principal Investigators

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Supplemental Material

Table S1
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Clinical outcomes 12 months after percutaneous coronary intervention, stratified by randomized strategy and sex

	Conventional Therapy*	Genotype-Guided Therapy*	Log-Rank *P* value	Adjusted Hazard ratio (95% CI)	*P* value for interaction
Primary endpoint					.59
Male	92/1990 (4.8)	75/1993 (3.9)	.18	0.82 (0.60-1.11)	
Female	43/645 (6.8)	38/648 (6.1)	.57	0.95 (0.61-1.47)	
CV mortality					.15
Men	11/1990 (0.6)	15/1993 (0.8)	.43	1.47 (0.67-3.21)	
Women	10/645 (1.6)	5/648 (0.8)	.20	0.57 (0.19-1.67)	
Myocardial infarction					.94
Men	31/1990 (1.6)	22/1993 (1.1)	.21	0.71 (0.41-1.23)	
Women	16/645 (2.6)	10/648 (1.6)	.23	0.69 (0.31-1.53)	
Stroke					.52
Men	7/1990 (0.4)	7/1993 (0.4)	>.99	1.05 (0.37-3.00)	
Women	5/645 (0.8)	3/648 (0.5)	.48	0.59 (0.14-2.48)	
Severe recurrent ischemia					.11
Men	46/1990 (2.4)	36/1993 (1.9)	.26	0.79 (0.51-1.22)	
Women	16/645 (2.6)	22/648 (3.6)	.32	1.48 (0.77-2.82)	
Stent thrombosis					.25
Men	11/1990 (0.6)	11/1993 (0.6)	>.99	1.04 (0.45-2.41)	
Women	8/645 (1.3)	3/648 (0.5)	.13	0.43 (0.11-1.62)	
All-cause mortality					.36
Men	16/1990 (0.8)	18/1993 (0.9)	.73	1.20 (0.61-2.35)	
Women	11/645 (1.7)	7/648 (1.1)	.34	0.70 (0.27-1.81)	
BARC 2,3,5 bleeding					.47
Men	34/1990 (1.8)	38/1993 (2.0)	.63	1.14 (0.72-1.81)	
Women	16/645 (2.6)	23/648 (3.7)	.26	1.53 (0.80-2.90)	
BARC 3,5 bleeding					.98
Men	21/1990 (1.1)	24/1993 (1.3)	.66	1.16 (0.65-2.09)	
Women	12/645 (2.0)	13/648 (2.1)	.85	1.15 (0.52-2.53)	

*Numbers presented are actual frequencies and percentages; Primary endpoint is a composite of cardiovascular mortality, myocardial infarction, stroke, severe recurrent ischemia, or stent thrombosis; CV Cardiovascular, BARC Bleeding Academic Research Consortium

Figure S1 Kaplan-Meier estimated event rates (unadjusted) in female and male subjects for the primary endpoint of time to cardiovascular-related death, myocardial infarction, stroke, stent thrombosis, or severe recurrent ischemia (Figure S1A) and the safety endpoint time to BARC 2,3,5 bleeding (Figure S1B) stratified according to randomized treatment strategy; N=5, 276 patients**.**

Figure S2 Kaplan-Meier estimated event rates (unadjusted) in female and male subjects for the primary endpoint of time to cardiovascular-related death, myocardial infarction, stroke, stent thrombosis, or severe recurrent ischemia (Figure S2A) and the safety endpoint time to BARC 2,3,5 bleeding (Figure S2B) stratified according to genotype and antiplatelet therapy received; N= 5, 044 patients.

Figure S3 Analysis of interaction of sex with assignment to optimal therapy based on genotype. N= 5,044 patients; CV cardiovascular, BARC Bleeding Academic Research Consortium; Adjusted hazard ratios and 95% confidence intervals are shown.

Figure S4 Kaplan-Meier estimated event rates (unadjusted) in female and male subjects for the primary endpoint of time to cardiovascular-related death, myocardial infarction, stroke, stent thrombosis, or severe recurrent ischemia (Figure S4A) and the safety endpoint time to BARC 2,3,5 bleeding (Figure S4B) stratified according to whether optimal antiplatelet therapy was received; N= 5,044 patients.

Figure S1A.

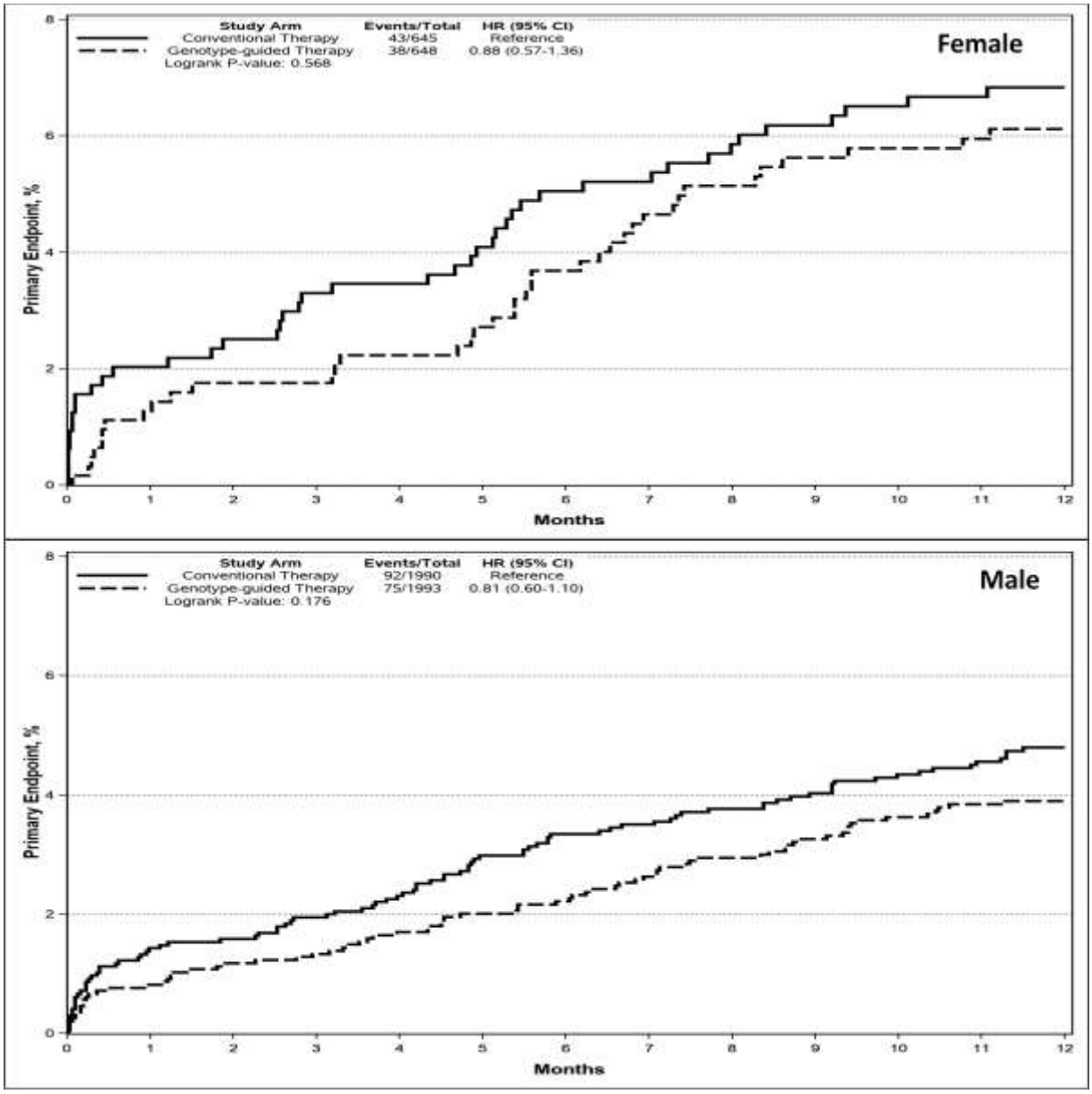

Study Arm
Conventional Therapy
Genotype-guided Therapy
Logrank P-value: 0.568
Events/Total
43/645
38/648
HR (95% CI)
Reference
0.88 (0.57-1.36)
Female
Primary Endpoint, %
Months
Study Arm
Conventional Therapy
Genotype-guided Therapy
Logrank P-value: 0.176
Events/Total
92/1990
75/1993
HR (95% CI)
Reference
0.81 (0.60-1.10)
Male
Primary Endpoint, %
Months

Figure S1B.

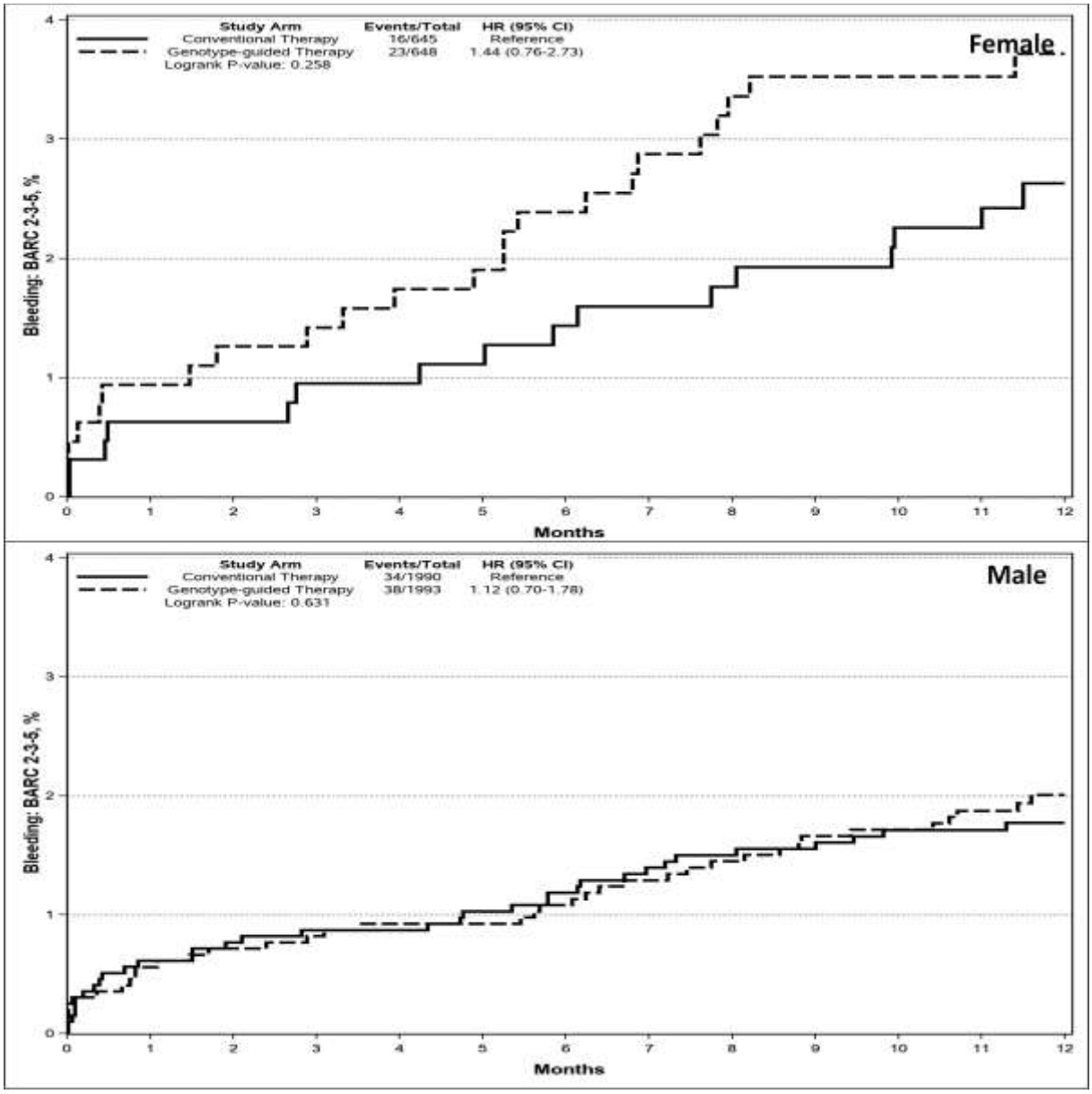

Study Arm
Conventional Therapy
Genotype-guided Therapy
Logrank P-value: 0.258
Events/Total
16/645
23/648
HR (95% CI)
Reference
1.44 (0.76-2.73)
Female
Bleeding: BARC 2-3-5, %
Months
Study Arm
Conventional Therapy
Genotype-guided Therapy
Logrank P-value: 0.631
Events/Total
34/1990
38/1993
HR (95% CI)
Reference
1.12 (0.70-1.78)
Male
Bleeding: BARC 2-3-5, %
Months

Figure S2A.

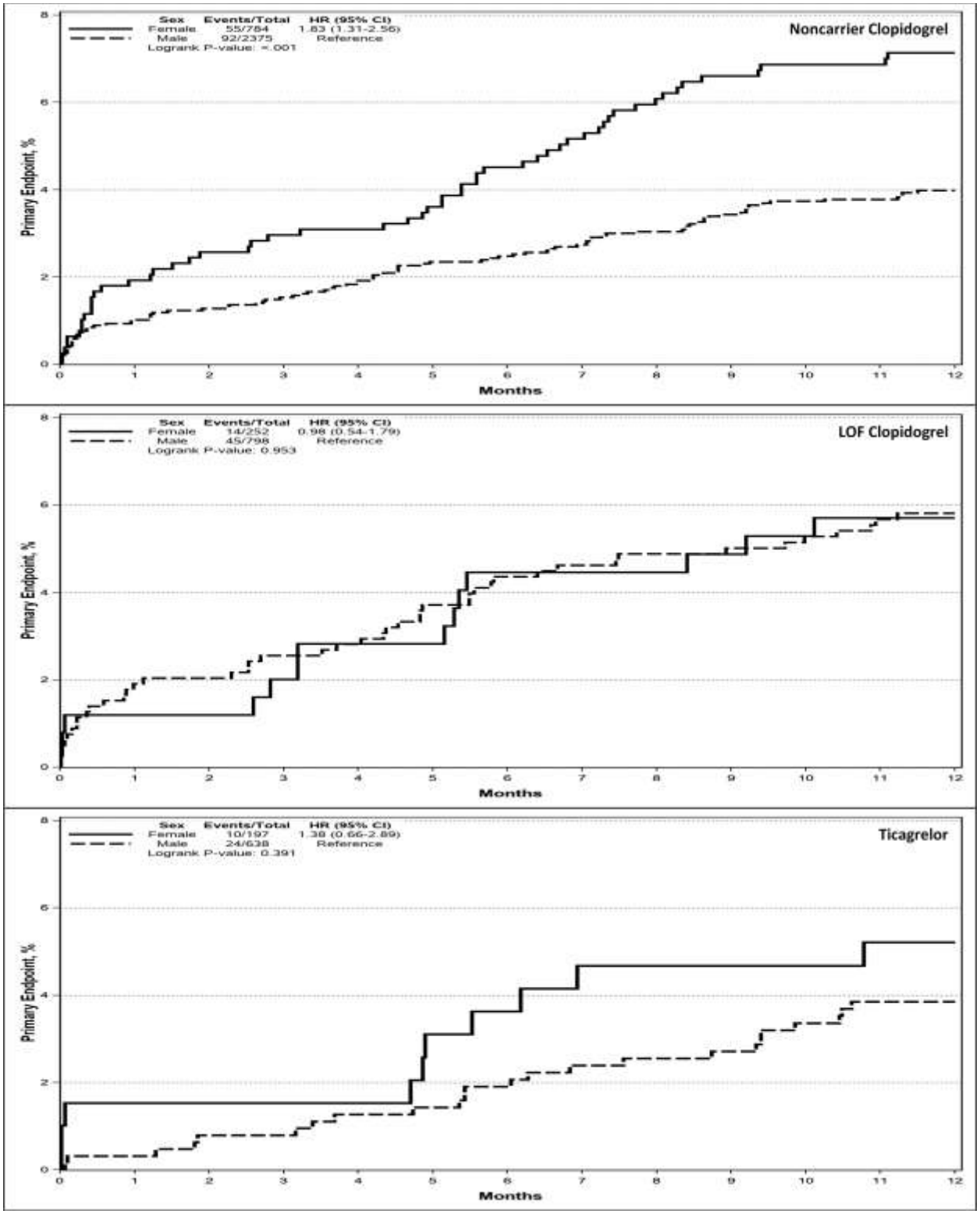

Noncarrier Clopidogrel
Sex Events/Total HR (95% CI)
Female 55/784 1.83 (1.31-2.56)
Male 92/2375 Reference
Logrank P-value: <.001
Primary Endpoint, %
Months
LOF Clopidogrel
Sex Events/Total HR (95% CI)
Female 14/252 0.98 (0.54-1.79)
Male 45/798 Reference
Logrank P-value: 0.953
Primary Endpoint, %
Months
Ticagrelor
Sex Events/Total HR (95% CI)
Female 10/197 1.38 (0.66-2.89)
Male 24/638 Reference
Logrank P-value: 0.391
Primary Endpoint, %
Months

Figure S2B.

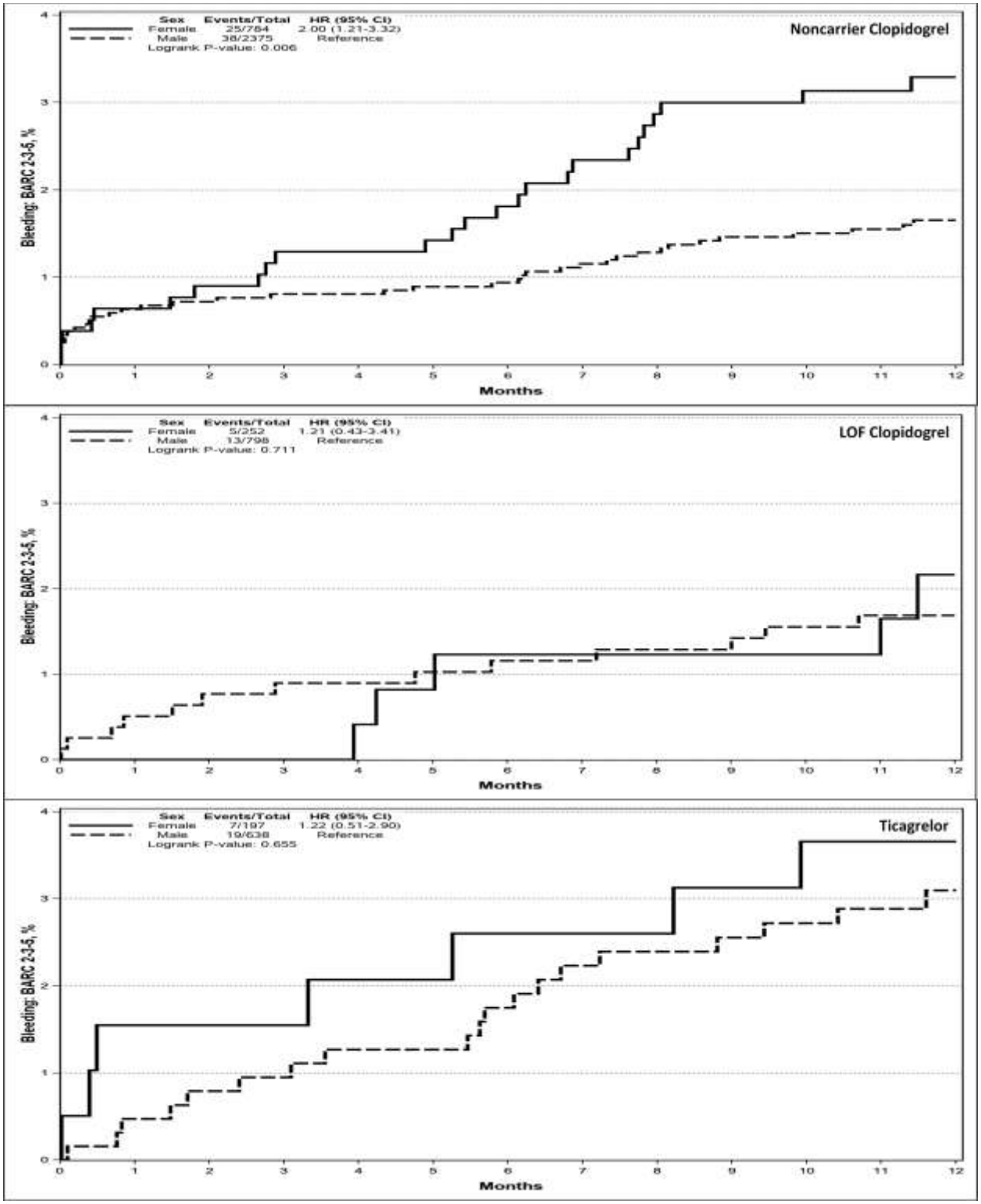

Noncarrier Clopidogrel
Sex Events/Total HR (95% CI)
Female 25/764 2.00 (1.21-3.32)
Male 38/2375 Reference
Logrank P-value: 0.006
Bleeding: BARC 2-3-5, %
Months
LOF Clopidogrel
Sex Events/Total HR (95% CI)
Female 5/252 1.21 (0.43-3.41)
Male 13/798 Reference
Logrank P-value: 0.711
Bleeding: BARC 2-3-5, %
Months
Ticagrelor
Sex Events/Total HR (95% CI)
Female 7/197 1.22 (0.51-2.90)
Male 19/638 Reference
Logrank P-value: 0.655
Bleeding: BARC 2-3-5, %
Months

Figure S3.

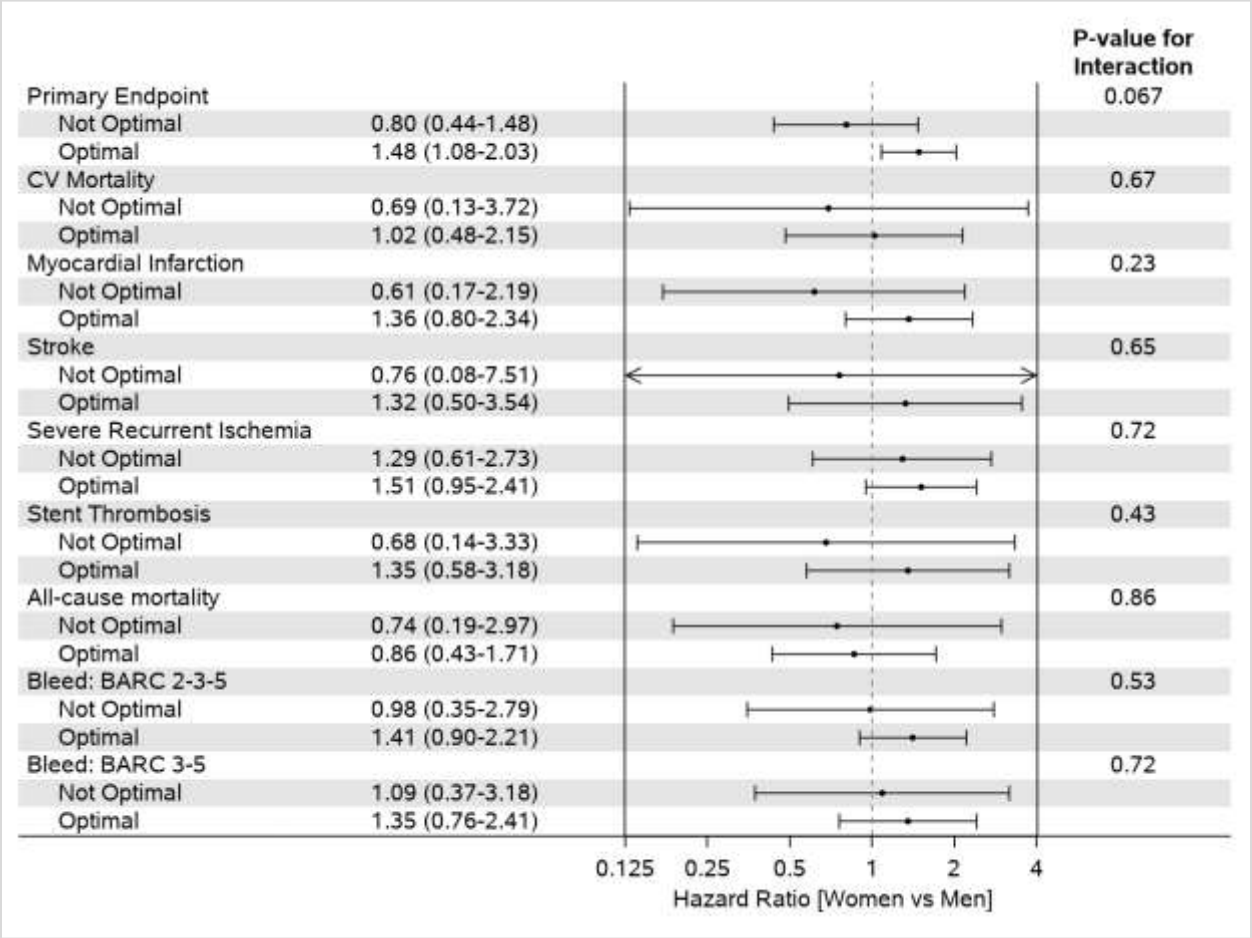

P-value for Interaction
Primary Endpoint
0.067
Not Optimal
0.80 (0.44-1.48)
Optimal
1.48 (1.08-2.03)
CV Mortality
0.67
Not Optimal
0.69 (0.13-3.72)
Optimal
1.02 (0.48-2.15)
Myocardial Infarction
0.23
Not Optimal
0.61 (0.17-2.19)
Optimal
1.36 (0.80-2.34)
Stroke
0.65
Not Optimal
0.76 (0.08-7.51)
Optimal
1.32 (0.50-3.54)
Severe Recurrent Ischemia
0.72
Not Optimal
1.29 (0.61-2.73)
Optimal
1.51 (0.95-2.41)
Stent Thrombosis
0.43
Not Optimal
0.68 (0.14-3.33)
Optimal
1.35 (0.58-3.18)
All-cause mortality
0.86
Not Optimal
0.74 (0.19-2.97)
Optimal
0.86 (0.43-1.71)
Bleed: BARC 2-3-5
0.53
Not Optimal
0.98 (0.35-2.79)
Optimal
1.41 (0.90-2.21)
Bleed: BARC 3-5
0.72
Not Optimal
1.09 (0.37-3.18)
Optimal
1.35 (0.76-2.41)
0.125
0.25
0.5
1
2
4
Hazard Ratio [Women vs Men]

Figure S4A.

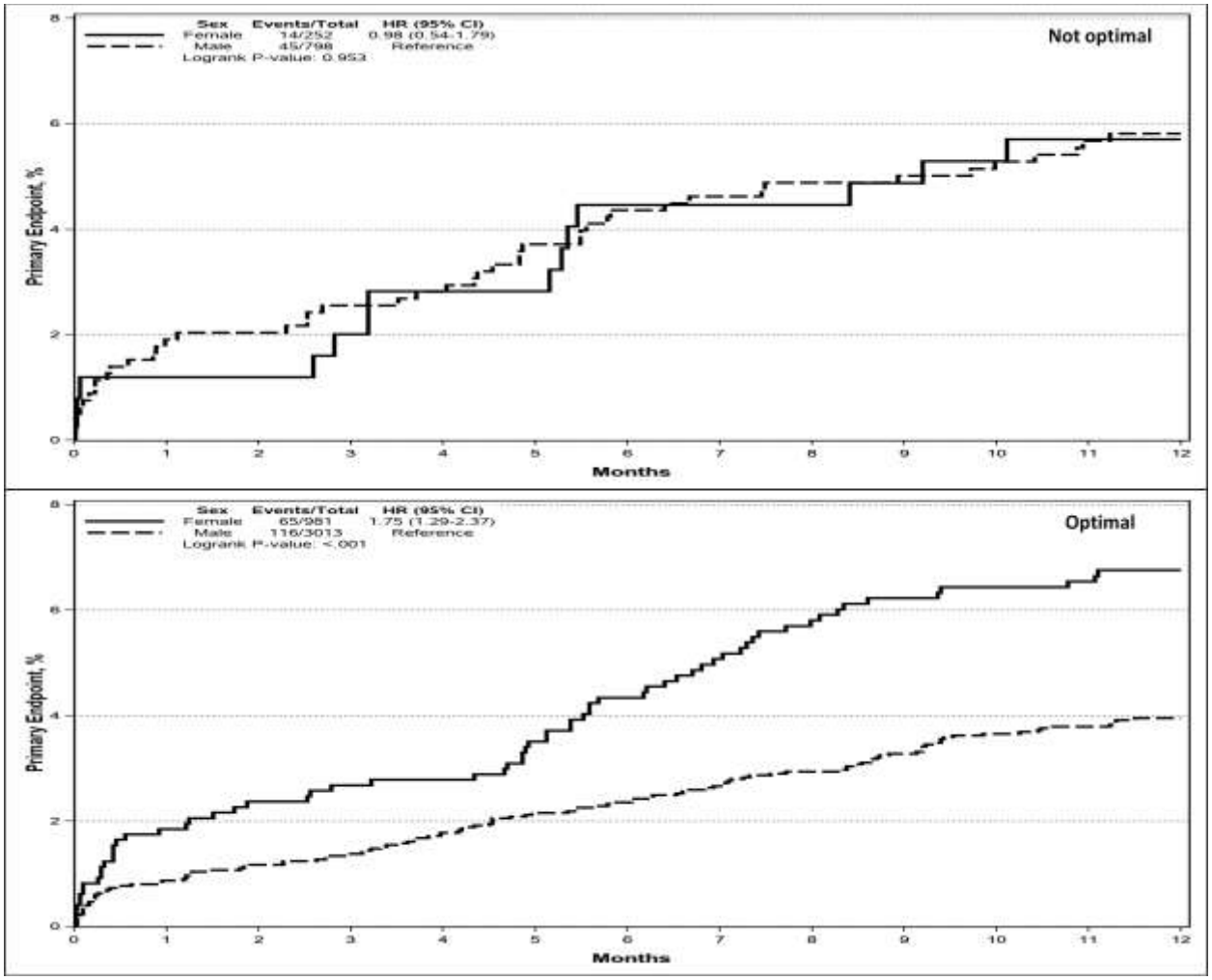
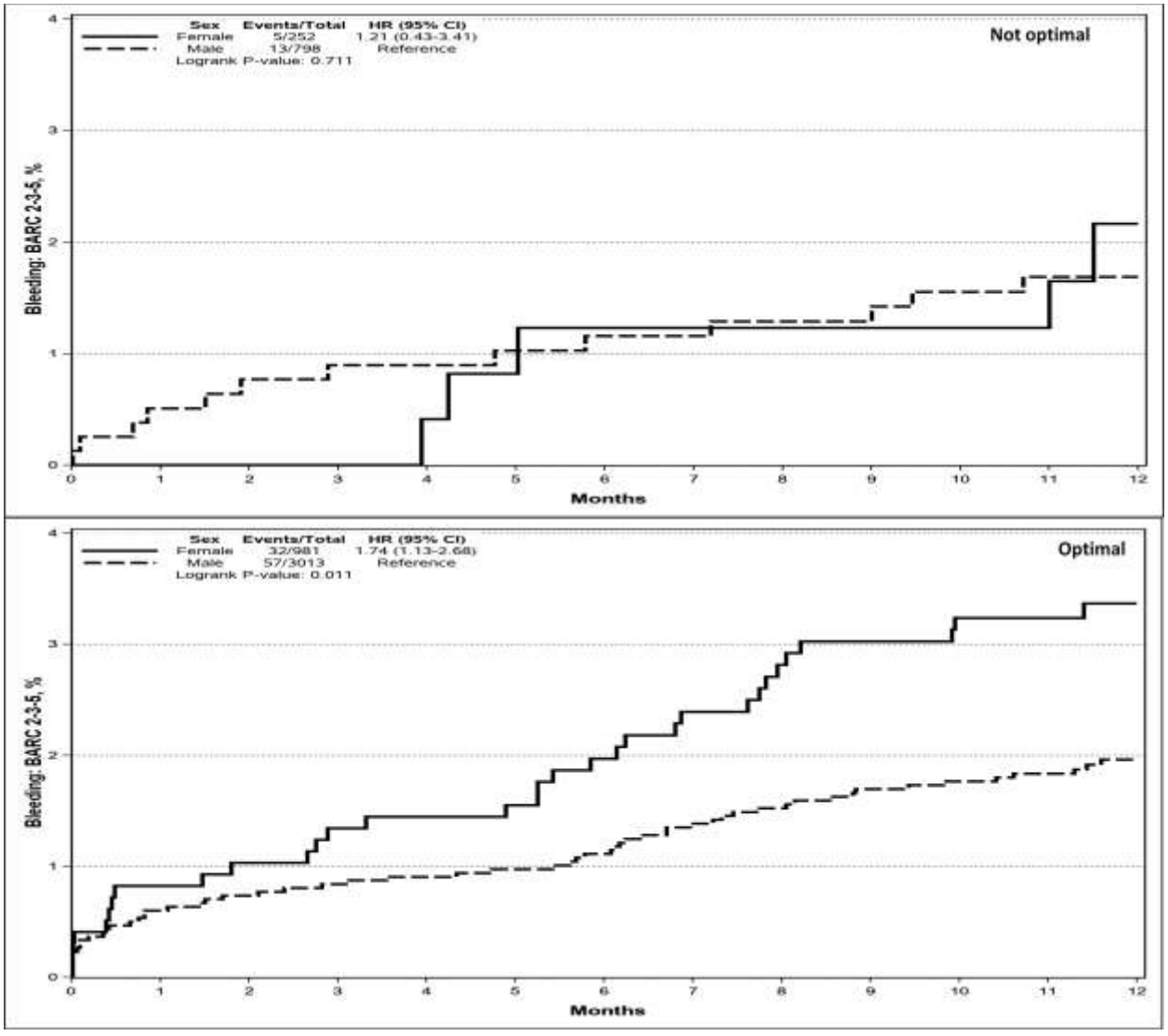

Sex Events/Total HR (95% CI)
Female 14/252 0.98 (0.54-1.79)
Male 45/798 Reference
Logrank P-value: 0.953
Not optimal
Primary Endpoint, %
Months
Sex Events/Total HR (95% CI)
Female 65/981 1.75 (1.29-2.37)
Male 116/3013 Reference
Logrank P-value: <.001
Optimal
Primary Endpoint, %
Months

Figure S4B.


Sex Events/Total HR (95% CI)
Female 5/252 1.21 (0.43-3.41)
Male 13/798 Reference
Logrank P-value: 0.711
Not optimal
Bleeding: BARC 2-3-5, %
Months
Sex Events/Total HR (95% CI)
Female 32/981 1.74 (1.13-2.68)
Male 57/3013 Reference
Logrank P-value: 0.011
Optimal
Bleeding: BARC 2-3-5, %
Months