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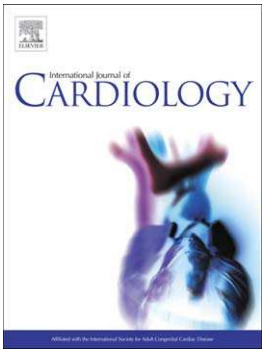

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GRACE risk score: sex-based validity of in-hospital mortality prediction in Canadian patients with acute coronary syndrome

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864-5465; Email: yana@smh.ca. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Disclosures

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Keywords: acute coronary syndrome, GRACE risk score, validation, risk stratification, sex differences

ABSTRACT

Background:

Although there are sex differences in management and outcome of acute coronary syndromes (ACS), sex is not a component of Global Registry of Acute Coronary Events (GRACE) risk score (RS) for in-hospital mortality prediction. We sought to determine the prognostic utility of GRACE RS in men and women, and whether its predictive accuracy would be augmented through sex-based modification of its components.

Methods:

Canadian men and women enrolled in GRACE and Canadian Registry of Acute Coronary Events were stratified as ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation ACS (NSTE-ACS). GRACE RS was calculated as per original model. Discrimination and calibration were evaluated using the c-statistic and Hosmer-Lemeshow goodness-of-fit test, respectively. Multivariable logistic regression was undertaken to assess potential interactions of sex with GRACE RS components.

Results:

For the overall cohort (n=14422), unadjusted in-hospital mortality rate was higher in women than men (4.5% vs. 3.0%, $p<0.001$). Overall, GRACE RS c-statistic and goodness-of-fit test p-value were 0.85 (95%CI 0.83-0.87) and 0.11, respectively. While the RS had excellent discrimination for all subgroups (c-statistics >0.80), discrimination was lower for women compared to men with STEMI [0.80 (0.75-0.84) vs. 0.86 (0.82-0.89), respectively, $p<0.05$]. The goodness-of-fit test showed good calibration for women ($p=0.86$), but suboptimal for men ($p=0.031$). No significant interaction was evident between sex and RS components (all $p>0.25$).

Conclusions:

The GRACE RS is a valid predictor of in-hospital mortality for both men and women with ACS. The lack of interaction between sex and RS components suggests that sex-based modification is not required.

Introduction

Women with acute coronary syndrome (ACS) tend to present with more atypical symptoms, which pose diagnostic challenges and often lead to delays to the correct diagnosis.[1, 2] More importantly, women have higher risk profiles at presentation and higher mortality rates compared to their male counterparts.[3, 4] It has been postulated that the worse outcomes in women may be partly due to their older age at presentation (generally 10 years older), and as such, women may have more comorbidities, carry a higher burden of coronary artery disease, and a greater propensity for decompensation at presentation.[1, 2] However, a sub-population of younger women presenting with ACS has also been shown to have worse prognosis than men.[5] Thus, it is also plausible that there are sex-related pathophysiology differences that impact ACS disease progression and outcomes.[6] The Global Registry of Acute Coronary Events (GRACE) was a large, prospective, international registry that led to the creation of a simple eight variable risk score (RS) to predict in-hospital mortality in ACS patients.[7, 8] Although the GRACE RS was developed over a decade ago, the most recent guidelines by international societies continue to recommend its use,[9, 10] suggesting that GRACE remains a relevant risk stratification tool.

Despite the well-recognized sex-related disparities in the management and outcome of ACS, sex is not a component of the GRACE RS. Further, there is a lack of data as to whether the predictive accuracy of the RS varies based on sex, highlighting the need for sex-specific validation of GRACE. Hence, we sought to determine whether the GRACE RS predicts in-hospital mortality equally well in men and women, and ascertain whether its predictive accuracy can be augmented through sex-based modification of its components.

Methods

Study population

The full details for the design of GRACE, expanded GRACE (GRACE^2), and Canadian Registry of Acute Coronary Events (CANRACE) have been published elsewhere.[8] Briefly, patients included in this study were those who participated in prospective, multicenter observational registries, and admitted with presumed ACS in 53 hospitals across Canada from June 1999 to December 2008.[7] GRACE started in 1999 and expanded to involve more hospitals in 2003 for GRACE^2. After completion of GRACE^2, Canadian hospitals continued recruitment of participants in CANRACE until 2008. Participants were eligible if they met the following inclusion criteria: ≥18 years of age; presumed diagnosis of ACS secondary to cardiac ischemia defined as at least one of the following features: abnormal serum biomarkers of myocardial necrosis, electrocardiographic changes consistent with ACS, or documented evidence of coronary artery disease (CAD). Participants were excluded if the ACS might have been precipitated by non-cardiovascular comorbidity, such as trauma. Research ethics approval was obtained from respective hospital ethics or institutional review boards. All study participants provided informed consent where required.

Study design

We stratified the patients with respect to sex and ACS subtype [ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation ACS (NSTE-ACS) including non-STEMI (NSTEMI) and unstable angina (UA)]. The GRACE RS was calculated for all patients according to the original model to predict in-hospital mortality, which comprised age, heart rate, systolic blood pressure, Killip class, cardiac arrest, creatinine, ST-deviation and elevated cardiac biomarkers.[8] Of note, in the original derivation of the GRACE risk model, sex was a significant predictor of in-hospital mortality in univariate analysis but not in multivariable analysis.[8]

The primary outcome was all-cause mortality during index hospitalization, which was identical to that of the original GRACE RS. We also examined in-hospital rates of myocardial (re)infarction (re-MI), heart failure, and cardiogenic shock.

Statistical analysis

We compared baseline characteristics between the patient groups using Mann-Whitney U and Pearson χ2 test for continuous and categorical data, respectively. The GRACE model performance for in-hospital mortality risk prediction in men and women was assessed based on discrimination and calibration.[11] Discrimination represents the model's ability to correctly classify patients into high versus low risk for developing the event of interest(i.e., in-hospital mortality for GRACE RS). To compare discrimination in men and women, the c-statistic was computed from the area under the receiver operator characteristic (ROC) curve. A model with a c-statistic of ≥0.75 is considered to have acceptable discriminatory ability.[11] The calibration of a model compares the agreement between the predicted and observed event rates. The Hosmer-Lemeshow goodness-of-fit test was employed to evaluate calibration. This test divides patients into deciles according to their RS and compares the predicted versus the observed rates of the outcome. A significant *p*-value indicates a lack-of-fit and suboptimal calibration.

In the original GRACE RS, sex was not included as a component. We performed individual multivariable logistic regressions to assess for potential interactions of sex with each of the GRACE RS predictor variables. A significant interaction between sex and a GRACE RS component would suggest that the prognostic significance of the component of interest is different between men and women. All statistical analyses were performed using SPSS version 22 (IBM). A 2-sided $p<0.05$ was considered statistically significant for all analyses.

GRACE and CANRACE were sponsored by an unrestricted grant from Sanofi-Aventis and Bristol-Myers Squibb. The industrial sponsors had no involvement in the current study conception or design; collection, analysis, and interpretation of data; writing, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Results

Table 1 provides a summary of baseline patient characteristics. In total, 14,422 Canadian patients with ACS were included in this study [9,603 (67.6%) men; 4,819 (33.4%) women]; 4,043 had STEMI and 10,379 had NSTE-ACS. Overall, women were older than men (median 73 versus 64 years), more likely to have diabetes, hypertension, heart failure, angina, peripheral vascular disease, and stroke. Women were less likely to have had prior cardiovascular interventions including percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, and tended to have higher Killip class on initial presentation. The median GRACE RS was significantly higher in women than men.

For inpatient management of ACS, women less frequently received an antiplatelet (aspirin or clopidogrel), a GP IIb/IIIa inhibitor, and heparin compared with men (Supplementary Table S1). Women with STEMI also received less fibrinolysis. Moreover, women were less likely to undergo coronary angiography, PCI, or CABG.

Figure 1 summarizes the in-hospital outcomes stratified by sex and ACS classification. In the overall cohort, the unadjusted in-hospital mortality rate was significantly higher in women than men (4.5% versus 3.0%, $p<0.001$). Women had significantly higher unadjusted rates of re-MI (5.0% versus. 3.8%, $p<0.001$), the composite endpoint of re-MI and mortality (9.0% versus 6.4%, $p<0.001$), heart failure (11.8% versus 9.2%, $p<0.001$), and major bleeding (2.5% versus 1.8%, $p<0.005$). These sex differences in unadjusted rates of in-hospital events were observed irrespective of ACS subgroup.

Although women had higher unadjusted in-hospital mortality rate than men, addition of sex to the original GRACE RS components in multivariable logistic regression failed to demonstrate

female sex as an independent predictor of in-hospital mortality [adjusted odds ratio 1.20, 95% confidence interval (CI) 0.97-1.49, *p*=0.09].

The GRACE RS showed good discrimination for the overall cohort, with c-statistic of 0.85 (95% CI 0.83-0.87) (Table 2). The GRACE RS also showed excellent discrimination for all subgroups, whereby all c-statistic >0.80 (Table 2). For the overall cohort, discrimination for women was significantly lower compared with men. When considering ACS subtype, the lower GRACE RS discrimination in women was observed for STEMI and not NSTE-ACS.

The GRACE RS showed adequate calibration in the overall cohort (Hosmer-Lemeshow goodness-of-fit *p*-value 0.11; Figure 2A). While the goodness-of-fit test showed good calibration for women (Hosmer-Lemeshow *p*-value=0.86, Figure 2B), calibration was suboptimal for men (Hosmer-Lemeshow *p*-value=0.031, Figure 2C). Comparison of predicted versus observed in-hospital mortality risk demonstrates that GRACE RS tended to overestimate the risk for men, while it predicted in-hospital mortality risk in women more accurately.

There was no significant interaction between sex and the GRACE RS components (all *p*-values ≥0.25, Supplementary Table S2), suggesting that the prognostic significance of each predictor variable was similar for men and women.

Discussion

We validated the original GRACE model for the risk stratification of both Canadian men and women presenting with ACS. The GRACE RS showed excellent model discrimination for in-hospital mortality, irrespective of sex or ACS subtype. Although discrimination was slightly better in men, the lack of interaction between sex and GRACE RS components suggests that the prognostic significance of each GRACE RS component was similar among men and women.

We found that women had significantly worse outcomes compared with men. The unadjusted relative in-hospital mortality risk was 50% greater in women compared to men, with the highest mortality rate in women with STEMI. The reasons for worse outcomes in women are likely multifactorial, owing to sex-differences in baseline characteristics and presenting clinical features known to modulate prognosis, as well as treatment gaps. As compared to men, our population of women was older, harbored more cardiovascular risk factors and comorbidities. Similarly, fewer women underwent coronary angiography, PCI, or CABG during index hospitalization. Taken together, our results corroborate with previous findings that high-risk women (harboring higher GRACE RS) likely received suboptimal treatment, which might have contributed to poorer outcomes.[5, 12-14]

Model indices are essential in the evaluation of risk stratification model performance. The c-statistics for men and women with STEMI or NSTE-ACS were all above 0.75,[11] a threshold generally considered to reflect good risk stratification. This suggests that GRACE RS is a useful tool to identify high-risk patients who may benefit from early aggressive management. However, our study did demonstrate that GRACE RS discrimination was slightly lower for women compared to men, particularly for STEMI.

The precise reason for the poorer discrimination in women with STEMI is difficult to discern. A previous study has confirmed the utility of GRACE RS in both STEMI and NSTE-ACS.[15] However, it was unclear whether components of the GRACE RS should be assigned sex-specific weights in the model to improve prediction of outcomes. Here, we showed that sex-specific interaction terms with RS components did not improve GRACE risk prediction, suggesting that sex-based modification of GRACE predictor variables would likely not increase accuracy of risk stratification. In keeping with this, women had significantly higher GRACE RS compared with men, indicating that the model appropriately accounted for the greater mortality risk at presentation. Moreover, given that treatment is not a component of GRACE RS, it is plausible that differential treatment may result in disparities in accuracy of in-hospital mortality prediction (particularly for STEMI patients), even for patients with similar GRACE RS.

In contrast to discriminatory power, the GRACE model calibration was adequate for women, but suboptimal for men. Thus, caution is required when interpreting the predicted probability of in-hospital mortality in men by GRACE RS. Several reasons may contribute to this finding. As aforementioned, this study and previous observational studies have concordantly demonstrated that both medical and interventional strategies are underutilized in women compared to men. Women with NSTE-ACS tend to be managed conservatively without undergoing invasive coronary angiography.[16-18] Similarly, not only do women present later during STEMI,[19] they are less frequently referred for coronary angiography.[20] Although overall ACS mortality rates have decreased in recent years, it is plausible that these dissimilarities led to a disproportionate smaller decline in mortality of women compared to men.[21, 22] In addition, the original GRACE RS was developed in a multi-national cohort with diverse geographic variations in risk factors, treatment patterns, and outcomes.[23] Previous studies have demonstrated

considerable geographic variation in ACS outcomes.[24, 25] As such, an overestimation of the mortality risk for Canadian men by GRACE might be partly attributed to better outcomes in Canadian men compared to men of other geographical regions. Furthermore, the Hosmer-Lemeshow goodness-of-fit test *p*-value is dependent on sample size, with tendency towards significance for larger sample sizes. In this cohort, the sample size of men was close to double that of women, resulting in greater power to detect minor differences in predicted versus observed event rates among men. Finally, the incidence of in-hospital mortality was generally low and thus, a statistical difference between predicted and actual mortality rates may be less clinically relevant. Indeed, the absolute difference of predicted versus observed mortality rate in men was predominantly small in the range of 0.14-0.40% for deciles 1-9. An exception to this is the small number of patients in decile 10, whereby the absolute difference was 2.53%. Overall, we postulate that the imprecision in predicted mortality rates may be clinically inconsequential for the majority of men with ACS.

Amongst the ACS risk stratification tools, the GRACE, TIMI, and PURSUIT models are the most widely validated and adopted in clinical practice. Of these, PURSUIT is the only one that incorporated sex as a predictor variable of mortality; however, its use is limited to NSTE-ACS patients.[26] Similar to GRACE, the TIMI RS for STEMI found sex as a significant predictor of 30-day mortality, but was not incorporated in the final model.[27] Subsequent studies also found that TIMI RS was appropriate for predicting risk irrespective of sex.[28, 29] Comparing the GRACE RS calibration to that of other risk models is complicated by the fact that most validation studies only used discrimination in evaluating the predictive accuracy.[30] An earlier study validating the in-hospital GRACE RS in Canadian ACS patients enrolled between late 1990s to early 2000s, showed both good calibration and discrimination.[31] Conversely, a subsequent study also indicated

suboptimal calibration but good discrimination in the overall cohort of Canadian patients.[32] Taken together, the slight imprecise prediction of in-hospital mortality probability in men may warrant future recalibration in face of evolving improvements in treatments and patient outcomes.

Study strengths and limitations

Our study is not without limitations. Although the study design aimed to enroll an unbiased patient population, selection bias might have remained. While consecutive enrolment of eligible patients was encouraged, this could not be verified across centers. Patients with very early death and complications from ACS might be underrepresented in the registry, creating a survivorship bias. The rate of revascularization interventions may not reflect current practice, as it has likely increased since completion of the registry. Although we have proposed several potential explanations for the inadequate calibration in men, the precise reason could not be identified. Similarly, the reason for the slightly better discrimination of GRACE RS in men compared with women also requires further investigation. Our study might not be adequately powered to test for interactions. While we evaluated sex-based predictive accuracy of in-hospital mortality, potential sex-differences in the accuracy of GRACE 6-month mortality model for long-term outcomes may exist. Of note, our primary objective was not to derive a new risk model for men and women, but to assess the validity of GRACE RS use in a sex-independent manner. Finally, future studies are required to confirm our findings in other patient populations.

Despite the limitations, our study has several strengths. This is the first study, to our knowledge, to systematically conduct a sex-based validation of the GRACE RS in predicting in-hospital mortality for the broad spectrum of ACS patients. Validation of the original GRACE model supports the continued relevance of the original predictor variables, despite evolution in diagnosis and

treatment patterns. The study population herein had broad inclusion and few exclusion selection criteria. Hence, the population likely closely reflects the diverse array of ACS encountered in everyday "real world" clinical practice. Taken together, our data support the routine use of GRACE RS in contemporary clinical practice to risk stratify ACS patients, irrespective of sex.

Conclusions

The GRACE RS remains an accurate and robust risk stratification tool for both men and women presenting with ACS, serving as a useful guidance for treatment decisions. Although presenting features are different between men and women, the prognostic significance of GRACE RS components did not differ according to sex in predicting in-hospital mortality. These findings suggest that sex-based modification of GRACE RS is likely not required.

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Table 1 Baseline characteristics of NSTE-ACS and STEMI patients stratified by sex.

	All patients (n=14422)	STEMI (n=4043)			NSTE-ACS (n=10379)		
		Male (n=2831)	Female (n=1212)	*P* value	Male (n=6772)	Female (n=3607)	*P* value
Age, years [a]	67 (57-77)	61 (53-72)	73 (60-81)	<0.001	65 (56-75)	72 (61-80)	<0.001
Cardiovascular risk factors, %							
Diabetes	27.4	20.9	25.5	0.0010	28.2	31.6	<0.001
Hypertension	60.1	45.5	61.7	<0.001	59.8	71.6	<0.001
Smoking	26.8	36.3	29.7	<0.001	26.3	19.1	<0.001
Dyslipidemia	53.4	45.2	42.3	0.086	58.5	54.1	<0.001
Prior cardiovascular comorbidities, %							
MI	32.7	25.0	22.2	0.056	36.8	34.7	0.033
Angina	43.6	26.5	27.5	0.43	49.2	52.0	0.008
HF	10.8	7.6	12.4	<0.001	9.8	14.4	<0.001
Stroke/TIA	9.2	6.1	9.1	0.0010	8.5	12.8	<0.001

PVD	8.8	7.0	7.7	0.42	9.8	8.7	0.065
Prior cardiovascular interventions, %							
PCI	17.4	11.1	8.9	0.030	21.3	18.1	<0.001
CABG	12.3	7.7	4.4	<0.001	16.9	10.1	<0.001
Clinical features at presentation							
Cardiac arrest, %	1.5	3.5	2.4	0.055	0.9	0.7	0.45
Systolic BP, mmHg [a]	143 (125-162)	140 (122-159)	140 (120-161)	0.41	144 (126-161)	146 (127-166)	<0.001
Diastolic BP, mmHg [a]	80 (69-91)	83 (71-95)	78 (66-90)	<0.001	80 (70-92)	77 (66-88)	<0.001
Heart rate, BPM [a]	78 (66-93)	77 (64-92)	80 (67-98)	<0.001	77 (65-92)	80 (68-95)	<0.001
Killip class, %							
I	83.6	84.4	75.6	<0.001	85.7	81.6	<0.001
II	10.7	9.9	13.7		9.8	12.1	
III/IV	5.7	5.7	10.7		4.5	6.3	
ST deviation, %	46.2	84.5	80.0	0.001	31.0	33.4	0.014

Abnormal cardiac biomarker at presentation, %	47.9	57.6	62.3	0.005	44.3	42.1	0.036
Creatinine, µmol/L [a]	93 (78-113)	96 (84-115)	86 (71-108)	<0.001	96 (83-116)	83 (70-106)	<0.001
GRACE risk score [a]	127 (103-157)	133 (114-160)	153 (128-180)	<0.001	118 (95-147)	128 (104-158)	<0.001

[a] Median (25th and 75th percentiles).

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; HF, heart failure; MI, myocardial infarction; NSTE-ACS, non ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST elevation myocardial infarction; TIA, transient ischemic attack.

Table 2 Comparison of GRACE risk score c-statistic and Hosmer-Lemeshow goodness-of-fit P value for ACS patients stratified by sex.

	Male (n=9603)	Female (n=4819)	*P* value
All patients (n=14422)			
c-statistic (95% CI)	0.86 (0.84-0.88)	0.82 (0.79-0.85)	0.034
Hosmer-Lemeshow goodness-of-fit *P* value	0.031	0.86	
STEMI (n=4043)			
c-statistic (95% CI)	0.86 (0.82-0.89)	0.80 (0.75-0.84)	0.042
NSTE-ACS (n=10379)			
c-statistic (95% CI)	0.85 (0.82-0.89)	0.82 (0.79-0.86)	0.20

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; NSTE-ACS, non-ST-elevation ACS; STEMI, ST-elevation myocardial infarction.

Figure 1 Unadjusted rates of in-hospital mortality and complications. Patients are stratified by sex and type of ACS, either ST-elevation myocardial infarction, or non-ST elevation ACS.

Figure 2 GRACE risk score calibration plot comparing between observed and predicted in-hospital mortality rates (%). Patients are divided into 10 deciles, with each point representing one decile. The x-axis shows the observed unadjusted in-hospital mortality rate. The y-axis shows the predicted in-hospital mortality rate by GRACE risk score. The dashed line shows absolute agreement between observed and predicted rates. (A) All ACS patients. (B) Women with ACS. (C) Men with ACS.

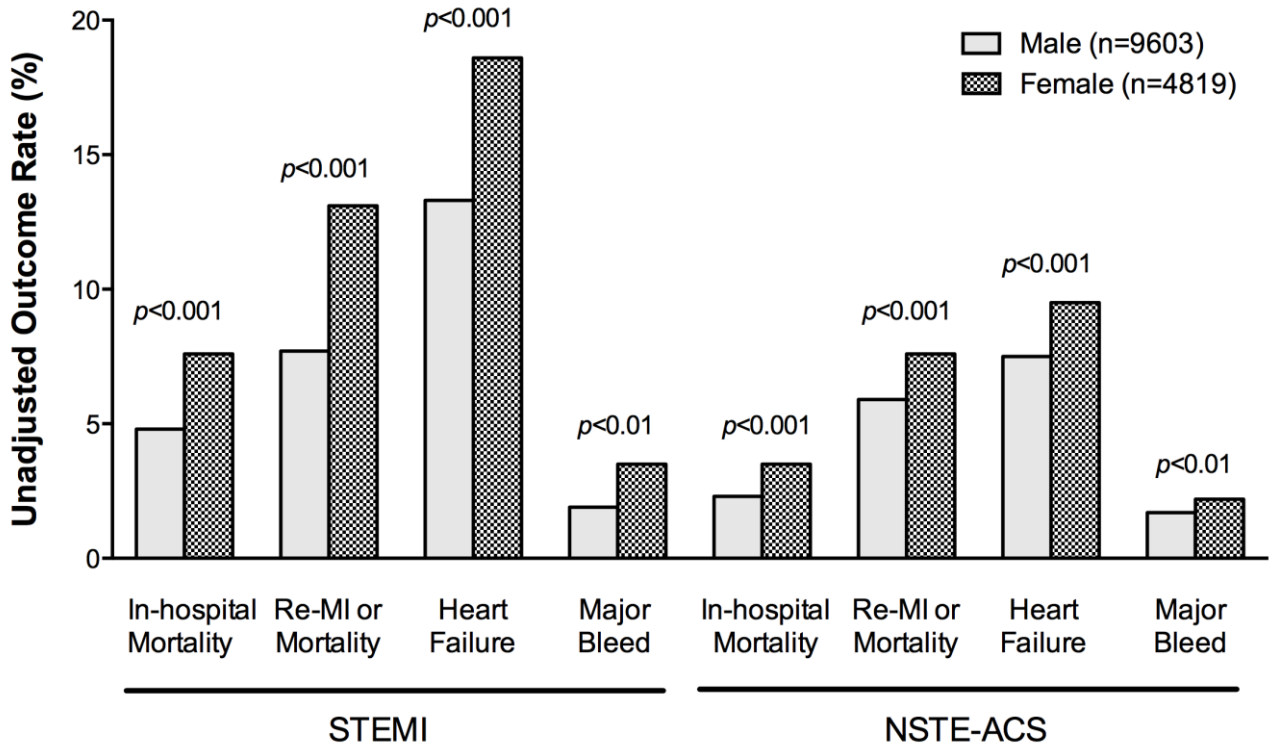

Fig. 1

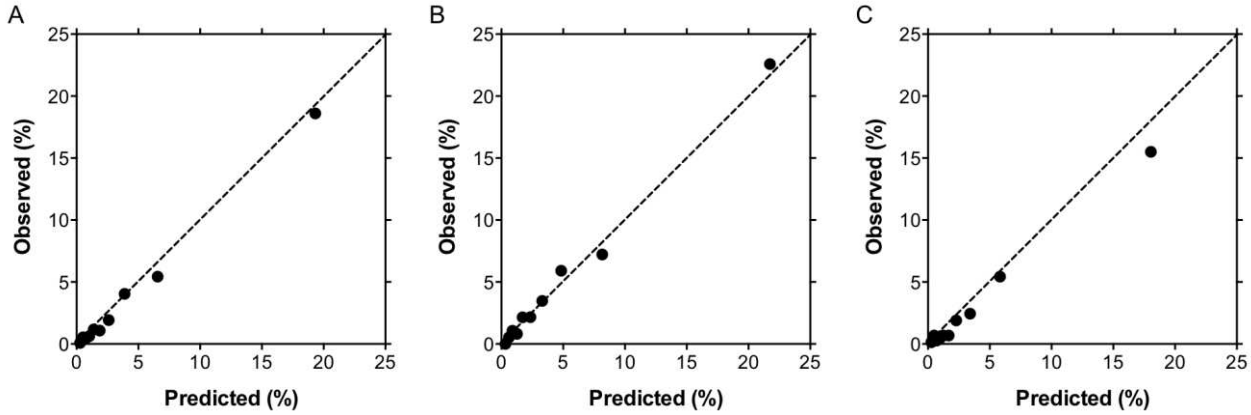

Fig. 2