Platelet Inhibition with 60 mg Ticagrelor twice daily plus 100 mg Aspirin once daily in patients after CABG

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Abstract

Objective: To optimize the antiplatelet therapy by observing the clinical outcomes in patients after coronary artery bypass grafting (CABG) treated with 60 mg ticagrelor twice daily plus 100 mg aspirin once daily for 1 year.

Methods: The observation group was composed of patients receiving 60 mg ticagrelor twice daily plus 100 mg aspirin once daily for antiplatelet therapy after CABG, whereas the control group comprised patients taking 90 mg ticagrelor twice daily plus 100 mg aspirin once daily after CABG.

Results: In the intention-to-treat (ITT) analysis of saphenous vein grafts (SVGs) patency, the difference was not statistically significant [RR=0.89, 95% confidence interval (CI): 0.29–2.71; P=0.84] between the two groups. The per-protocol (PP) analysis results of the 1-year SVGs patency rates were consistent with ITT analysis. There were no notable differences in the rates of bleeding, mild dyspnea or dyspnea leading to discontinuation of the study drug between the two groups (P=0.211).

Conclusions: In patients undergoing CABG, treatment with 60 mg ticagrelor twice daily plus 100 mg aspirin once daily can achieve satisfactory clinical outcomes. Besides, the rates of dyspnea in 60 mg ticagrelor treatment are significantly lower than that in 90 mg ticagrelor treatment. As a result, the 60 mg dose leads to a markedly lower discontinuation rate of the study drug and a better safety profile, which tends to provide a more attractive benefit-risk profile.

Background

Saphenous vein is the most frequently used graft in coronary artery bypass grafting (CABG)[1]. However, 20% vein grafts will be occluded in the first year after CABG, due to the destruction of intima, technical difficulty in harvesting or other factors[2–5]. Aspirin can improve the early graft patency and reduce the occurrence of cardiovascular events[6–9], which has been used as the fundamental drug for secondary prevention after CABG. Nonetheless, the relatively weak antiplatelet effect and resistance of aspirin in particular patients[10, 11] give rise to numerous cardiovascular events[12].The supplementation of P2Y12 receptor antagonist to aspirin has been proved to further reduce the risk of ischemic events in the first year among patients with acute coronary syndrome (ACS)[13–16]. Besides, aspirin combined with clopidogrel is the standard regimen to prevent cardiovascular events in ACS patients[17–19]. However, the clinical application of this regimen is limited because of its slow onset, individual variation, irreversible inhibition of platelet aggregation and other characteristics of clopidogrel[20]. Ticagrelor is a potent, reversible, and direct-acting P2Y12 receptor antagonist[21]. As reported in the PLATO[22]study, ACS patients receiving CABG show lower cardiogenic and all-cause mortality rates compared with those who receive aspirin plus clopidogrel treatment. In patients with stable coronary artery disease[23]and ACS[24, 25], the ticagrelor maintenance dose at 90 mg twice daily exerts stronger and longer-lasting inhibition on platelet P2Y12 than clopidogrel. Further, the PEGASUS-54[26]study suggests that in ischemic heart disease patients with previous myocardial infarction (MI), 100 mg aspirin combined with 60 mg or 90 mg

ticagrelorl can reduce the composite end point of cardiovascular death, MI or stroke after 3 years compared with aspirin alone treatment. Moreover, there is evidence that ticagrelor at 60 mg can reduce the risks of bleeding and dyspnea, and such dose performs better in the risk-benefit aspect. Li P[27]suggested that the low-dose ticagrelor had similar antiplatelet effect to standard-dose ticagrelor on the Chinese population, but the former had less side effects, such as bleeding and dyspnea. This study aimed to optimize the antiplatelet therapy by observing the clinical outcomes in patients after CABG treated with 60 mg ticagrelor twice daily plus 100 mg aspirin once daily for 1 year.

Materials And Methods

This was a retrospective case-control study. The observation group was composed of patients taking 60 mg ticagrelor twice daily plus 100 mg aspirin once daily for antiplatelet therapy after CABG, whereas the control group comprised patients receiving 90 mg ticagrelor twice daily plus 100 mg aspirin once daily after CABG. Propensity score matching (PSM) was used to balance the baseline characteristics of the two groups. Moreover, the protocol was approved by the independent ethics committee of Zhengzhou Cardiovascular Hospital, Henan, China. All patients provided the written informed consent for participation. Figure 1 shows the flowchart of the study.

Inclusion criteria: (1) patients aged over 18 years and under 80 years; those who prepared for CABG; and those who agreed to sign the informed consent.

Exclusion criteria: patients who received emergency revascularization or simultaneous additional cardiac surgery; those who took other anticoagulants after CABG; those with a risk of serious bleeding (such as intracranial hemorrhage history, coagulation dysfunction or gastrointestinal bleeding within one year); patients requiring other ADP receptor antagonists or IIb/IIIa receptor antagonists; those with intolerance or contraindications of aspirin or ADP receptor antagonists; those with severe heart failure (ejection fraction EF < 40%), severe liver dysfunction (transaminase content elevating over 3-fold), severe renal dysfunction requiring dialysis, and respiratory diseases (such as severe asthma and chronic obstructive pulmonary disease COPD); those with poor compliance, pregnant or lactating women; those who used CYP3A moderate to severe inhibitors.

The primary endpoint was patency rate of SVGs at 1 year after CABG (Fitzgibbon A), which was evaluated by multi-slice CT angiography or coronary angiography.

The secondary endpoint was patency rate of SVGs at 7 days after CABG and MACE (cardiovascular death, non fatal myocardial infarction or non fatal stroke, target vessel revascularization).

Safety and tolerability evaluation: the bleeding events were evaluated based on the criteria defined by TIMI: 1) major bleeding referred to fatal bleeding, intracranial bleeding and rapid decrease in hemoglobin > 50 g/L; 2) minor bleeding was bleeding observed without treatment, with the decrease in hemoglobin of 30–50 g/L; 3) minimal bleeding indicated that the decrease in hemoglobin was not obvious (< 30 g/L), or gingival bleeding and ecchymosis appeared under the skin.

In PSM analysis, the oral ticagrelor dose (60 mg or 90 mg) was taken as the treatment index. Additionally, age, gender, body mass index (BMI), hypertension, diabetes mellitus (DM), dyslipidemia, previous MI, percutaneous cardiovascular intervention (PCI), COPD, renal insufficiency, peripheral vascular disease, previous cerebrovascular disease, preoperative cardiac EF and coronary SYNTAX score were taken as the covariates. Among them, age, BMI, preoperative EF and SYNTAX score were the continuous variables, whereas the rest were classified variables. The caliper distance was 0.02, and the logistic regression formula was used to calculate the propensity score (PS). The PS value and PS weight were obtained and matched at a ratio of 1:1.

Statistical analysis

Categorical variables including demographics and comorbidities were summarized as frequencies and percentages and compared appropriately by χ^2 test or Fisher's exact test. Continuous data were presented as mean ± standard deviation (SD)and compared using the Student's t-test.

According to the intention-to-treat (ITT) principle, the preliminary analysis was conducted on a per-graft basis. The ITT population contained all recruitment. Patients who did not receive multi-slice CT angiography or coronary angiography evaluation were deemed to have occluded SVGs in ITT analysis. In addition, the per-protocol (PP) analysis was performed as a sensitivity analysis, which involved patients who received the arranged dose of the study drug without discontinuation or interruption for over 60 days or other major protocol infringement, and were evaluated for the primary outcome.

The generalized estimating equation model was utilized to evaluate the between-group differences in SVG patency and 95% CIs. A two-sided significance level of 0.05 was applied in universal comparisons. All analyses were performed using SPSS (IBM SPSS V.20, New York). Kaplan-Meier analysis of MACE, bleeding and dyspnea was provided.

Results

There were 105 patients in the 60 mg ticagrelor group and 672 in the 90 mg ticagrelor group. Using the PSM method, 95 pairs of patients were successfully matched. Data of the matched patients are presented in Table 1. Baseline characteristics of patients were well comparable between the two groups. A total of 721 SVGs were implanted in patients treated with 60 mg (n = 359) and 90 mg (n = 362) ticagrelor. Patients were enrolled from January 2017 to March 2018 and the follow-up was completed in August 2019.

Table 1
Baseline characteristics

Variable(n% or mean ± SD)	60 mg Ticagrelor (n = 95 patients)	90 mg Ticagrelor (n = 95 patients)	t/χ^2 Value	*P* Value
Age	64.1 ± 7.2	66.2 ± 6.3	0.835	0.409
Male	47(49.5)	45(47.4)	0.084	0.772
BMI	26.9 ± 3.5	26.3 ± 4.8	0.690	0.493
HTN	21(22.1)	23(24.2)	0.118	0.731
Diabetes mellitus	19(20)	17(17.9)	0.137	0.711
Dyslipidemia	24(25.3)	22(23.2)	0.115	0.735
Prior MI	18(18.9)	20(21.1)	0.132	0.717
Prior PCI	21(22.1)	20(21.1)	0.031	0.860
COPD	11(11.6)	10(10.5)	0.053	0.817
Chronic kidney disease	4(4.2)	5(5.3)	-	> 0.999*
Peripheral vascular disease	7(7.4)	6(6.3)	0.083	0.774
Cerebrovascular event	4(4.2)	5(5.3)	-	> 0.999*
LVEF	55.3 ± 7.1	56.2 ± 5.8	0.986	0.331
SYNTAX score#				
Low 0–22	7(7.4)	9(9.5)	0.273	0.601
Intermediate 23–32 [□(%)]	48(50.5)	47(49.5)	0.021	0.885
High ≥ 33 [□(%)]	40(42.1)	39(41.0)	0.022	0.883
*Fisher's exact test				
#Comprehensive angiographic evaluation of the coronary artery. As for SYNTAX score: 0–22 indicates low anatomical complexity, 23–32 stands for intermediate anatomical complexity, while ≥ 33 suggests high anatomical complexity[28].				

Completeness of Follow-up

Altogether 91.6% (87/95) patients in the 60 mg ticagrelor 60 mg group and 88.4% (84/95) in the 90 mg ticagrelor group completed the primary end point assessment at 1 year after CABG. Simultaneously, 83.1% (448/539) SVGs were assessed at 1 year after CABG, including 86.5% (231/267) from patients treated with 60 mg ticagrelor and 79.8% (217/272) from patients treated with 90 mg ticagrelor. In addition, 14.2% (38/267) and 20.2% (55/272) SVGs were ascribed as treatment failures. (Table 2).

Table 2
CABG procedural characteristics

Variable	60 mg Ticagrelor (n = 95 patients)	90 mg Ticagrelor (n = 95 patients)	χ^2 Value	*P* Value
Total grafts, No.	359	362		
Graft type, No.(%)				
Internal mammary artery	90(25.0)	87(24.1)	0.105	0.746
Radial artery	2(0.6)	3(0.8)	-	> 0.999*
Saphenous vein	267(74.4)	272(75.1)	0.056	0.813
Mean total graft/case	3.78	3.81		
Mean SVG/case	2.81	2.86		
*Fisher's exact test				

SVG Patency

The SVG assessment results were demonstrated based on the FitzGibbon grade. In the ITT analysis of SVG patency, the primary outcome of 1-year patency rates (FitzGibbon grade A) were 77.9% (208/267) among patients treated with 60 mg ticagrelor and 73.2% (199/272) among those receiving 90 mg ticagrelor treatment. The difference was not statistically significant [risk ratio(RR) 0.89, 95% CI 0.29–2.71; P = 0.84]. Besides, the PP sensitivity analysis results of 1-year SVG patency rates were consistent with the ITT analysis (Table 2). In addition, difference in the 7-day SVG patency rates after CABG was not statistically significant (RR 1.26, 95%CI 0.49–3.26; P = 0.64) between the two groups. For patients treated with 60 mg ticagrelor, the proportion of patients with patent SVGs at 1 year was 74%, while that was 70% for patients receiving 90 mg ticagrelor. The difference between the two groups was not statistically significant (RR 0.80, 95%CI 0.23–2.74; P = 0.72). (Table 3)

Table 3
Analysis of SVGs

Analysis and outcome	60 mg Ticagrelor	90 mg Ticagrelor	RR (95% CI)	*P* Value[a]
Per-graft analysis	n = 267 grafts	n = 272 grafts		
Primary outcome				
1-year SVG patency (ITT)[b,c]	208(77.9)	199(73.2)	0.89 (0.29 to 2.708)	0.84
1-year SVG patency (PP)[b,d]	n = 231 grafts	n = 217 grafts		
	208(90.0)	199(91.7)	1.01 (0.37 to 2.75)	0.99
Secondary outcome				
7-day SVG patency (ITT)[b]	241(92.1)	257(94.5)	1.26 (0.49 to 3.26)	0.64
Per-Patient Analysis	(n = 95 patients)	(n = 95 patients)		
1-y SVG patency(ITT)[b]	74(77.9)	70(73.4)	0.80 (0.23 to 2.74)	0.72
Abbreviations: ITT, intention-to-treat; PP, per-protocol; RR, relative risk.				
[a] Calculated by a generalized equation model.				
[b] FitzGibbon grade A (stenosis < 50%).				
[c] The ITT analysis contained all recruitment.				
[d] The PP analysis contained patients who received the arranged dose of the study drug without discontinuation or interruption for over 60 days or other major protocol infringement, and were evaluated for the primary outcome.				

MACEs (major adverse cardiovascular events)

A total of 24 MACEs were observed during the 1-year follow-up after CABG, including 13 (13.7%) in the 60 mg ticagrelor group and 11 (11.6%) in the 90 mg ticagrelor group (Table 4). In 60 mg the ticagrelor group, 1 patient suffered from sudden cardiac death at 2 days after the CABG procedure. There was no statistically significant difference (HR 1.081, 95%CI 0.477–2.488; P = 0.851) in the incidence of MACEs (Fig. 2).

Bleeding and Dyspnea

The bleeding rate was numerically lower in the 60 mg ticagrelor group (22.1%) than that in the 90 mg ticagrelor group (28.4%), but the difference was not statistically significant (HR 0.715, 95%CI 0.404–1.267; P = 0.248). Most of these events were identified as minimal bleeding, In the 90 mg ticagrelor group, one patient experienced major bleeding. There was no major bleeding resulting in either death or discontinuation of the study drug during the follow-up period (Table 4 and Fig. 2).

The 1-year dyspnea rates were 16.8% in the 90 mg ticagrelor group and 7.3% in the 60 mg ticagrelor group, and the difference was statistically different (HR 0.363, 95%CI 0.158–0.839; P = 0.026). Besides, the dyspnea rates leading to the discontinuation of the study drug were 5.3% in the 90 mg ticagrelor group and 1.1% in the 60 mg ticagrelor group. However, there was no notable difference between the two groups in the rate of mild dyspnea or dyspnea leading to discontinuation of the study drug (P = 0.211) (Table 4 and Fig. 2).

Table 4
Major Adverse Cardiovascular Events, Bleeding Episodes, and Dyspnea

	60 mg Ticagrelor (n = 95 patients)	90 mg Ticagrelor (n = 95 patients)	Hazard Ratio (95%CI)	*P* Value
Major Adverse Cardiovascular Events	13(13.7)	11(11.6)	1.081 (0.477 to 2.448)	0.851
Cardiovascular death[No.(%)]	1(1.1)	0(0)		
Myocardial infarction[No.(%)]	8(8.4)	8(8.4)		
Stroke[No.(%)]	2(2.1)	1(1.1)		
Target vessel revascularization [No.(%)]	2(2.1)	2(2.1)		
Bleeding[No.(%)]	21(22.1)	27(28.4)	0.715 (0.404 to 1.267)	0.248
Minor bleeding[No.(%)]	5(5.3)	3(3.2)		
Minimal bleeding[No.(%)]	14(14.7)	23(24.2)		
Major bleeding[No.(%)]	0(0)	1(1.1)		
Bleeding leading to temporary interruption of treatment[No.(%)]	0(0)	1(1.1)		
Dyspnea[No.(%)]	7(7.4)	16(16.8)	0.364 (0.158 to 0.839)	0.026
Mild Dyspnea[No.(%)]	6(6.3)	11(11.6)	-	0.309*
Severe Dyspnea leading to treatment discontinuation[No.(%)]	1(1.1)	5(5.3)	-	0.211*
*Fisher's exact test				

Discussion

Potent antiplatelet therapy is required for patients undergoing CABG, so as to minimize the risk of ischemic events mainly originated from early graft occlusion. Numerous studies have explored the

effects of DAPT in this respect[3,29–35]. Aspirin has been found to exert insufficient platelet inhibition effect on some patients after CABG[36, 37], so an alternative treatment with rapid-onset antiplatelet effect may be beneficial[38, 39]. Indeed, patients who receive ticagrelor combined with aspirin are associated with a higher rate of bypass graft patency than those receiving aspirin alone[31]. Moreover, a post-randomization analysis of the PLATO trial shows that patients who are revascularized by CABG and treated with ticagrelor plus aspirin can obtain a survival benefit compared with those receiving clopidogrel plus aspirin treatment[16, 29]. The combined antiplatelet therapy consisting of ticagrelor and aspirin may provide specific benefits for patients undergoing CABG[29, 31, 40, 41].

Ticagrelor at a maintenance dose of 90 mg twice daily (bid) can offer more potent platelet P2Y12 inhibition than that of clopidogrel alone in patients with stable coronary artery disease [23] and ACS[24,25]. However, the mean P2Y12 reaction unit (PRU) is far below the previous threshold of bleeding risk among the Chinese patients after ticagrelor treatment at 90 mg bid[42]. Furthermore, previous studies have shown that the Asian subjects are more exposed to ticagrelor and AR-C124910XX than the Caucasian subjects[43,44]. Teng[45] compared the pharmacokinetics of ticagrelor at 100 mg bid in the Caucasian healthy subjects and that at 90 mg bid in the Chinese healthy subjects. As a result, the Cmax and area under the curve (AUC) of ticagrelor and AR-C124910XX in the Chinese subjects were about 40% higher than those in the Caucasian subjects. Patients treated with ticagrelor at 60 mg bid or 90 mg bid attained the comparable mean platelet P2Y12 inhibition[46]. Additionally, two recent studies on low-dose ticagrelor in the Asian populations have observed the similar results[47,48]. In this study, no statistically difference in the 1-year graft patency, the rate of MACEs or major bleeding was observed between 60 mg and 90 mg ticagrelor treatment groups, suggesting that 60 mg ticagrelor obtained satisfactory clinical outcomes.

In the course of ticagrelor treatment, adverse events such as bleeding, dyspnea and serum uric acid levels increase, and cardiac arrhythmia occurs frequently, which lead to a high rate of drug discontinuation[16, 49]. An optimal dosing regimen can efficiently improve the clinical effect of platelet inhibition with the minimum side-effects[50]. Typically, the incidence of ticagrelor-related adverse events is dose-dependent[21, 51, 52]. Remarkably, in PEGASUS-TIMI 54[26]and a substudy[53], ticagrelor at 60 mg bid acquires a comparable level of antiplatelet potency to that at 90 mg bid. However, the rates of bleeding and dyspnea leading to treatment discontinuation are numerically lower at the 60 mg dose than at the 90mg dose, implying a better safety profile of the 60 mg dose. In this study, 1 major bleeding event was observed in the 90 mg ticagrelor group, whereas the minimal bleeding rate was numerically lower in the 60 mg ticagrelor group than in the 90 mg ticagrelor group. The 60 mg ticagrelor group showed a decreasing trend of bleeding rate compared with the 90 mg ticagrelor group ($p = 0.248$).

Some patients will develop dyspnea after taking ticagrelor. Previous studies show that the incidence of dyspnea leading to treatment discontinuation is 0.9%[54], but a recent real-world study reports that the proportion is as high as 11.6%[55]. In this study, the dyspnea rates in the 60 mg and 90 mg ticagrelor groups were 7.4% and 16.8%, respectively. Besides, the rates of mild dyspnea and severe dyspnea leading

to treatment discontinuation were numerically lower in the 60 mg ticagrelor group than in the 90 mg ticagrelor group; nevertheless, the difference in total dyspnea frequency between the two groups was statistically significant.

Limitations

This was a single-center retrospective cohort study. PSM can balance the baseline data between the two groups to a certain extent, but it can not replace the effect of randomized controlled trial (RCT). In addition, the small sample size and short follow-up time may affect the results. More large, multicenter RCTs should be conducted to further evaluate the clinical outcomes in patients undergoing CABG receiving 60 mg ticagrelor twice daily plus 100 mg aspirin once daily as the platelet inhibition therapy.

Conclusions

Compared with 90 mg ticagrelor twice daily plus 100 mg aspirin once daily treatment, satisfactory 1-year SVGs patency is achieved in patients undergoing CABG treated with 60 mg ticagrelor wice daily plus 100 mg aspirin once daily. In addition, the dyspnea rate after 60 mg ticagrelor treatment is significantly lower than that after the 90 mg dose. Further, the 60 mg dose results in a markedly lower discontinuation rate of the study drug and a better safety profile, which tends to provide a more attractive benefit-risk profile.

Declarations

Authors contribution Yanpeng Pan and Dongdong Yuan designed experiments; Hongwei Chen and Yanpeng Pan carried out experiments; Guiqing Liu analyzed experimental results. Qian Wang analyzed sequencing data and developed analysis tools. Yanpeng Pan wrote the manuscript.

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Compliance with Ethical Standards.

Conflict of Interest The authors declare that they have no conflict of interest.

The data that support the findings of this study are available on request from the corresponding author.The data are not publicly available due to ethical restrictions.

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Figures

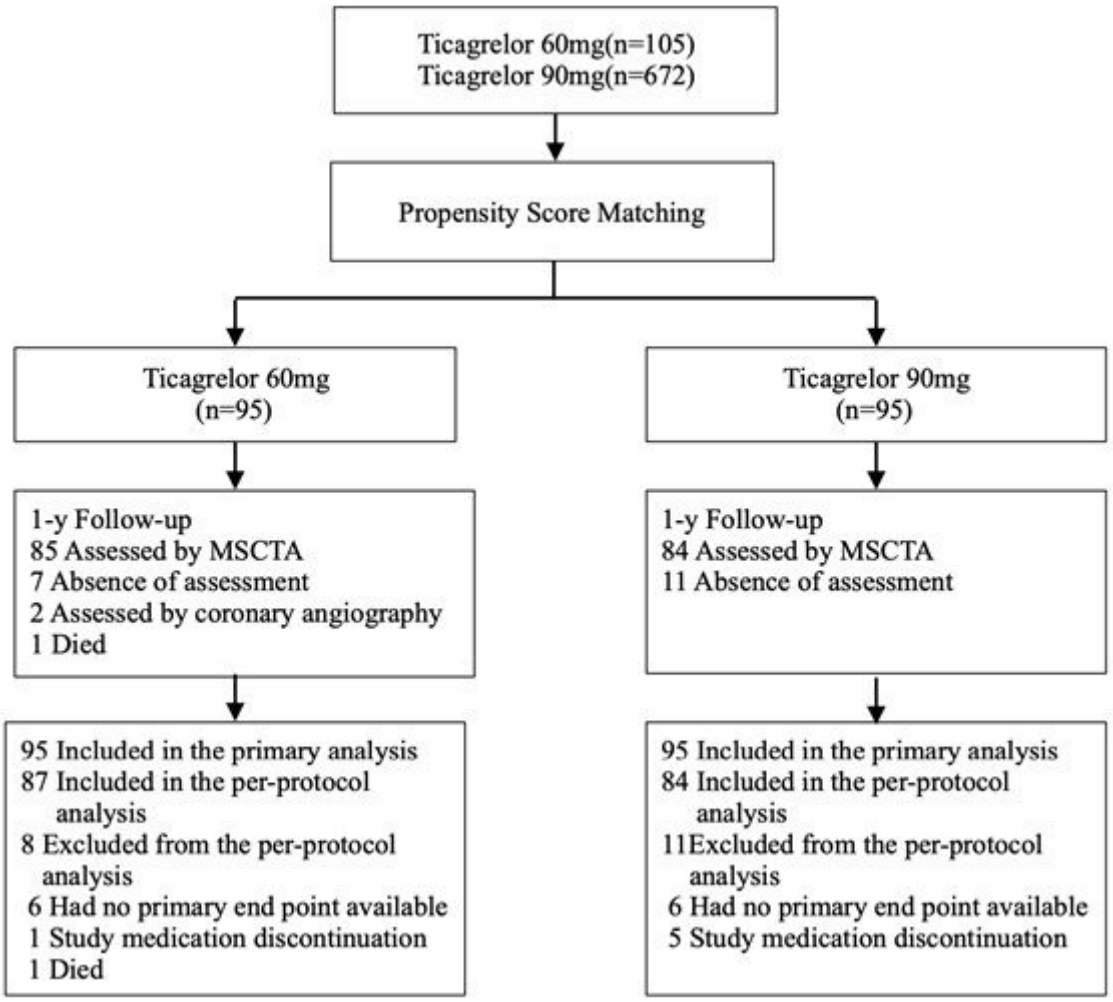

Figure 1

Flowchart of the Patients receiving 60 mg and 90 mg Ticagrelor treatment after CABG

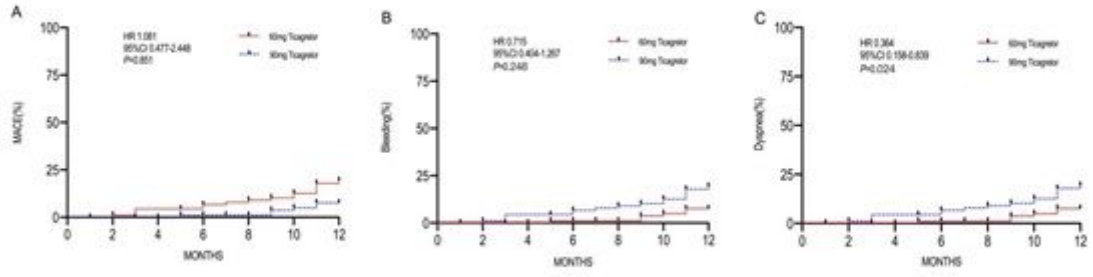

Figure 2

(A) Cumulative Kaplan–Meier curves for MACEs. (B) Cumulative Kaplan–Meier curves for bleeding. (C) Cumulative Kaplan–Meier curves for dyspnea.