Original Article

Effect of ticagrelor with or without aspirin on vein graft outcome 1 year after on-pump and off-pump coronary artery bypass grafting

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Background: In the present post hoc analysis of the DACAB trial, we evaluated the effects of ticagrelor with or without aspirin on 1-year vein graft outcomes after coronary artery bypass grafting (CABG) with and without cardiopulmonary bypass (CPB) (on-pump and off-pump).

Methods: The DACAB trial was a multicenter, randomized, open-label, parallel control study enrolling 500 patients with 1,460 vein grafts undergoing CABG. For current post-hoc study, all patients in the DACAB study were included in the analysis to compare the effects of different antiplatelet regimens under on/off pump. Patients were randomly assigned to 1 of 3 antiplatelet treatment regimens (ticagrelor plus aspirin, T + A; ticagrelor alone, T; or aspirin alone, A) within 24 hours after CABG, and were stratified into on-pump and off-pump subgroups. The primary outcome was 1-year vein graft patency rate.

Results: Totally 121 patients underwent on-pump CABG (39 with 121 vein grafts in T + A, 36 with 101 vein grafts in T, and 46 with 137 vein grafts in A) and 379 patients underwent off-pump CABG (129 with 336 vein grafts in T + A, 130 with 387 vein grafts in T, and 120 with 348 vein grafts in A). Compared with A, T + A showed a higher 1-year vein graft patency rate in both on-pump (adjusted OR for non-patency =0.62, 95% CI: 0.16–2.45) and off-pump (adjusted OR for non-patency =0.35, 95% CI: 0.20–0.62) subgroups, P interaction =0.647; whereas T did not in either on-pump (adjusted OR for non-patency = 0.92, 95% CI: 0.31–2.76) or off-pump (adjusted OR for non-patency =0.58, 95% CI: 0.34–1.00) subgroups, P interaction =0.430.

Conclusions: In the DACAB trial, for patients underwent either on-pump or off-pump CABG, ticagrelor plus aspirin showed consistent benefit for achieving 1-year vein graft patency, with particular benefit being seen in the off-pump.

Keywords: Aspirin; cardiopulmonary bypass (CPB); coronary artery bypass grafting (CABG); dual antiplatelet therapy; ticagrelor; vein graft

Submitted Mar 05, 2020. Accepted for publication Jul 15, 2020.
doi: 10.21037/jtd-20-1177
View this article at: http://dx.doi.org/10.21037/jtd-20-1177

Introduction

Various factors are suggested to affect the outcomes of coronary artery bypass grafting (CABG), among which, the effects of cardiopulmonary bypass (CPB) has been extensively discussed for years but still controversial (1-3). Studies suggested that the activation and consumption of clotting factors and platelets in CABG with CPB (on-pump CABG) were associated with systemic inflammatory response and poor hemostasis compared with CABG without CPB (off-pump CABG) (1). On the other hand, the clotting disorders and platelet dysfunction with on-pump CABG may increase graft (especially vein graft) patency compared with off-pump surgery (4,5). Therefore, although different guidelines recommend dual antiplatelet therapy (DAPT) after CABG to reduce major adverse cardiovascular events (MACEs) and preserve graft patency in patients with a history of acute coronary syndrome (ACS) (1,6,7), the recommendation levels for off-pump (Class I) and on-pump (Class IIb) are different by considering that the use of CPB during CABG may affect the choices of therapeutic regimen and effects of antiplatelet therapy. In addition, beneficial effects of DAPT on graft patency was suggested not well demonstrated (8). These evidences indicate that the benefits of DAPT are not well established in both on-pump and off-pump CABG.

Moreover, the recommended DAPT regimens after CABG are mostly based on findings on the use of clopidogrel plus aspirin. Ticagrelor, a reversible inhibitor of the P2Y12 receptor, in addition to aspirin, significantly reduced MACE in patients with ACS compared with clopidogrel (9). The CABG substudy from the PLATO trial showed that compared with clopidogrel, ticagrelor was associated with a substantial reduction in all-cause and cardiovascular mortality, without an excess risk of CABG-related bleeding (10). The Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB) trial showed that ticagrelor plus aspirin resulted in a significant improvement in vein graft patency 1 year after CABG compared with aspirin alone (11). Compared with the practice in US and Europe, a higher proportion of patients (approximately 76%) in this trial underwent off-pump CABG, revealing the local practice in China, further on in East Asia. Here we examined the effects of ticagrelor with or without aspirin on vein graft patency 1 year after on-pump or off-pump CABG.

We present the following article in accordance with the 2010 CONSORT reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1177).

Methods

Background

The DACAB trial was a multicenter, randomized, open-label, parallel control study of 500 patients with 1,460 vein grafts undergoing CABG in China. Details about the study design, patients, and results have been published previously (11). The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. The trial protocol and all amendments were reviewed and approved by the independent Institutional Review Board responsible for each participating site. Written informed consent was obtained from all individual participants included in the study.

Population

For current post-hoc study, all patients in the DACAB study were included in the analysis. Briefly, patients aged 18–80 years with indications for CABG using vein grafts were eligible for the trial. Major exclusion criteria included urgent revascularization or other concomitant cardiac surgery, a need for dual antiplatelet or vitamin K antagonist therapy after CABG, and serious bleeding risk. Detailed inclusion and exclusion criteria are listed in *Table S1*.

Patients were randomly (in blocks of 3) assigned in a 1:1:1 ratio to receive ticagrelor (Brilinta, AstraZeneca) 90 mg twice daily plus aspirin 100 mg (Bayaspirin, Bayer) once daily, T + A regimen; ticagrelor 90 mg twice daily, T regimen; or aspirin 100 mg once daily, A regimen. Both on-pump and off-pump CABG was allowed in the trial and was selected according to the surgeons' decisions. Only surgeons with the experience of more than 100 off-pump cases annually were invited to participate in the trial. The vein graft was openly harvested. The patients started their allocated regimen within 24 hours after the surgery, and the median duration of study treatment was 1 year.

Outcomes

Consistent with the DACAB trial, the primary outcome

of this post hoc analysis was the vein graft patency (stenosis<50%) rate 1 year after CABG. Vein grafts were assessed by multislice computed tomographic angiography or coronary angiography and interpreted by an independent Image Data Review Centre blinded to treatment allocation. Other cardiovascular outcomes includes: (I) the rate of MACE [defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (12)] 1 year after the surgery; and (II) the rate of relief from angina pectoris evaluated using a questionnaire based on the Canadian Cardiovascular Society grade 1 year after the surgery.

For safety outcomes, the adverse events (AEs) and serious AEs (SAEs) were recorded for 1 year. Bleeding events were classified as those in the DACAB trial. The definitions of these outcomes have been previously reported (11).

Statistical analysis

This post-hoc analysis was to compare vein graft patency 1 year after CABG between patients receiving T + A or T versus A in the on-pump and off-pump patients, respectively. The primary analysis was conducted on a per-graft basis according to the intention-to-treat (ITT) principle. The ITT population included all randomized patients. Missing data on graft outcome were handled as occlusion. One-year patency was also evaluated based on a per-patient basis. A per-patient analysis was performed in which patients were classified according to the graft with the worst degree of stenosis.

Differences in baseline characteristics between treatment groups after on-pump and off-pump CABG, as well as between on-pump and off-pump were compared using one-way analysis of variance or Kruskal-Wallis test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Generalized estimating equations logistic model and multivariable logistic model were applied to estimate odds ratio (OR) and 95% confidence interval (CI) in per-graft and per-patient analysis, respectively. Outcome was defined as non-patency or occlusion when calculating OR. Confounders adjusted in the multivariable model included age; sex; medical history of hypertension, diabetes, and hyperlipidemia; SYNTAX score; target vessel distribution; and statin use 1 year after CABG. The potential modifying effect of pump status on different antiplatelet strategies was formally tested by including a multiplicative interaction term between pump status and antiplatelet treatment. All statistical analyses were carried out using SAS 9.4 (SAS Institute, NY, USA). Two-sided P values <0.05 were considered statistically significant.

Results

Baseline characteristics

Among 500 patients with 1,460 vein grafts randomized in the trial, 121 patients with 359 vein grafts received on-pump CABG (39 patients with 121 vein grafts in T + A regimen, 36 with 101 vein grafts in T regimen, and 46 with 137 vein grafts in A regimen) and 379 patients with 1,101 vein grafts received off-pump CABG (129 patients with 336 vein grafts in T + A regimen, 130 with 387 vein grafts in T regimen, and 120 with 348 vein grafts in A regimen). The baseline characteristics were generally balanced among the three randomized antiplatelet treatment regimens in either on-pump or off-pump subgroups, except that of the history of stroke, SYNTAX score, and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) use among the three antiplatelet treatment regimens in the off-pump subgroup (*Table S2*). The comparisons on baseline demographics between on-pump and off-pump subgroups are detailed in *Table S3*.

One-year vein graft outcomes

The graft-level analysis showed that the 1-year patency rate of vein graft was 91.7% in T + A regimen compared with 83.2% in A regimen for the on-pump subgroup (adjusted OR for non-patency =0.62; 95% CI, 0.16–2.45), and 87.7% in T + A regimen compared with 73.9% in A regimen for the off-pump subgroup (adjusted OR for non-patency =0.35; 95% CI, 0.20–0.62). As the interaction P between on-pump and off-pump subgroups while comparing T + A versus A was 0.647, the result suggested that T + A was associated with a higher 1-year patency rate of vein grafts compared with A in both on- and off-pump subgroups, which was consistent with the findings of overall trial. On the contrary, no significant differences were observed in the 1-year patency rate of vein grafts between T and A neither in on-pump (adjusted OR for non-patency =0.92; 95% CI, 0.31–2.76) nor in off-pump (adjusted OR for non-patency =0.58; 95% CI, 0.34–1.00) subgroups (P interaction= 0.430). The comparison of 1-year non-occlusion outcome were consistent with the patency outcome, where T + A showed a higher non-occlusion rates compared with A in both off-pump (OR =0.38; 95% CI, 0.20–0.71) and on-pump (OR

Table 1 Vein graft patency rates among patients receiving ticagrelor + aspirin, ticagrelor alone, or aspirin alone at 1 year by on-pump CABG and off-pump CABG subgroups

Grouping categories	T + A		T		A		T + A *vs.* A		T *vs.* A	
	N	n (%)	N	n (%)	N	n (%)	*Adjusted OR for non-patency (95% CI)	Interaction P value	*Adjusted OR for non-patency (95% CI)	Interact P value
Per graft								0.647		0.430
Overall	487	432 (88.7)	488	404 (82.8)	485	371 (76.5)	0.41 (0.25–0.69)		0.68 (0.43–1.07)	
On-pump	121	111 (91.7)	101	85 (84.2)	137	114 (83.2)	0.62 (0.16–2.45)		0.92 (0.31–2.76)	
Off-pump	366	321 (87.7)	387	319 (82.4)	348	257 (73.9)	0.35 (0.20–0.62)		0.58 (0.34–1.00)	
Per patient								0.731		0.429
Overall	167	137 (82.0)	166	117 (70.5)	166	108 (65.1)	0.41 (0.25–0.68)		0.78 (0.49–1.24)	
On-pump	39	35 (89.7)	36	27 (75.0)	46	36 (78.3)	0.70 (0.16–3.17)		1.06 (0.29–3.85)	
Off-pump	128	102 (79.7)	130	90 (69.2)	120	72 (60.0)	0.43 (0.23–0.79)		0.73 (0.42–1.29)	

*, aspirin as reference. Adjusted for age, sex, medical history of hypertension, diabetes and hyperlipidemia, SYNTAX score, target vessel distribution, antiplatelet therapy and statin use. CABG, coronary artery bypass grafting; A, aspirin; CI, confidence interval; OR, odds ratio; T, ticagrelor.

=0.76; 95% CI, 0.18–3.12) groups with an interaction P=0.587, and no significant differences were found in the comparisons between T and A. Similar results were seen in the patient-level analysis. Detailed vein graft patency and non-occlusion status in graft- and patient-level analyses are summarized in *Tables 1* and *2*. Comparisons between on-pump and off-pump subgroups are shown in *Table S4*.

Cardiovascular and bleeding outcomes

Overall, the incidence of cardiovascular events, including the MACE and recurrent angina within 1 year after the surgery, were relatively low for all three regimens in both on- and off-pump subgroups. In statistical analysis, none of the rates of these events were significantly different among three regimens (*Table 3*). The bleeding events were similar for the three regimens in the on-pump subgroup; whereas in the off-pump subgroup, the non-CABG-related bleeding rate, particularly minimal bleeding, was significantly higher in T + A compared with A (difference in the rate, 28%; 95% CI, 18.2–37.9) (*Table 4*). Comparisons between the on- and off-pump subgroups regarding MACE, recurrent angina and bleeding events are shown in *Tables S5* and *S6*.

Other clinical AEs

Some other clinical AEs, including renal dysfunction (creatinine >200 μmol/L), liver dysfunction (ALT/AST >320/200 U/L), pulmonary infections, and delayed incision healing, are listed in *Tables S7* and *S8*.

Discussion

In this post-hoc analysis of the DACAB trial, we aimed to explore the effects of ticagrelor with or without aspirin on vein graft outcomes 1 year after CABG with or without CPB. The results showed a consistent level of benefits of T + A over A alone for both on-pump and off-pump subgroups in increasing vein graft patency. This observation was consistent with the findings of overall DACAB trial, indicating that DAPT with a 12-month T + A regimen may be recommendable for all patients undergoing CABG with vein graft, regardless of the use of CPB.

Life-long aspirin is recognized as the gold standard of care after CABG (13). However, whether additional antiplatelet therapy with a P2Y12 receptor antagonist is beneficial is still controversial (12,14,15). Therefore, recent guidelines suggest that dual antiplatelet treatment

Table 2 Vein graft non-occlusion rates among patients receiving ticagrelor + aspirin, ticagrelor alone, or aspirin alone at 1 year by on-pump CABG and off-pump CABG subgroups

Grouping categories	T + A		T		A		T + A *vs.* A		T *vs.* A	
	N	n (%)	N	n (%)	N	n (%)	*Adjusted OR for occlusion (95% CI)	Interaction P value	*Adjusted OR for occlusion (95% CI)	Interaction P value
Per graft								0.587		0.346
Overall	487	438 (89.9)	488	420 (86.1)	485	391 (80.6)	0.47 (0.27–0.81)		0.67 (0.41–1.12)	
On-pump	121	111 (91.7)	101	86 (85.2)	137	117 (85.4)	0.76 (0.18–3.12)		1.01 (0.32–3.23)	
Off-pump	366	327 (89.3)	387	334 (86.3)	348	274 (78.7)	0.38 (0.20-0.71)		0.57 (0.31–1.04)	
Per patient								0.643		0.197
Overall	167	141 (84.4)	166	127 (76.5)	166	119 (71.7)	0.47 (0.27–0.80)		0.78 (0.48–1.27)	
On-pump	39	35 (89.7)	36	27 (75.0)	46	38 (82.6)	0.81 (0.17–3.86)		1.40 (0.37–5.32)	
Off-pump	128	106 (82.8)	130	100 (76.9)	120	81 (67.5)	0.47 (0.25–0.89)		0.68 (0.38–1.23)	

*, aspirin as reference. Adjusted for age; sex; medical history of hypertension, diabetes, and hyperlipidemia; SYNTAX score; target vessel distribution; and statin use. CABG, coronary artery bypass grafting; A, aspirin; CI, confidence interval; OR, odds ratio; T, ticagrelor.

should be started after CABG in selected patients (1,6,16). Whether the use of CPB during CABG influences the effects of DAPT needs further investigation. Regarding the effect of on-pump and off-pump CABG on patient outcomes, several studies suggested better graft outcomes in patients undergoing on-pump CABG. Sousa Uva *et al.* showed a lower graft patency rate for off-pump CABG, but the difference disappeared after controlling the heparin dose (17). Kim *et al.* demonstrated that the 1-year vein graft patency rate after off-pump CABG was low; they suggested that a specific perioperative anticoagulant therapy could be advisable (18). Gundry *et al.* reported the re-intervention rates of 30% in the off-pump group and 16% in the on-pump group (19). On the contrary, some other studies showed similar outcomes for the two approaches (2,3). Such contradictory results might be due to the complex prothrombotic response elicited by CABG. Therefore, antithrombosis therapy could be a key to enhancing graft patency, particularly for the hypercoagulated status in off-pump CABG (20,21).

Indeed, a few studies compared the different antiplatelet regimens after on-pump and off-pump CABG. To our knowledge, this post-hoc study is the first clinical report that examined whether the beneficial effect of T + A based DAPT was consistent in patients with or without CPB. The results of this post-hoc study indicated that the T + A regimen was superior in achieving 1-year vein graft patency compared with A alone in both on-pump and off-pump subgroups. On the other hand, clinical outcome was not statistically affected by DAPT, which might due to the insufficient event rates in DACAB trial. As limited analysis, including CURE and PLATO subgroup analysis (22,23), has revealed the benefits of post-CABG DAPT, the potential risks, particularly intracranial bleeding and major gastrointestinal bleeding should be taken into consideration. Therefore, Costa *et al.* suggested that decision-maker should evaluate the individual patient's bleeding risk and consider the net clinical benefit from post-revascularization DAPT (24).

Regarding the higher early hypercoagulable state in off-pump than in on-pump CABG, studies suggested that the short-term (1-year) vein graft patency was also affected, resulting in a lower patency rate in off-pump CABG (18,21). However, more randomized trials indicated that the hypercoagulable state did not affect either very short-term (30 days) or short-term (1 year) graft patency; they also showed that on-pump and off-pump CABG achieved similar patency (25). In the very short-term, vein graft

Table 3 Cardiovascular events among patients receiving ticagrelor + aspirin, ticagrelor alone, or aspirin alone by on-pump CABG and off-pump CABG subgroups

Events	T + A		T		A		P value
	N	n (%)	N	n (%)	N	n (%)	
MACE in 1 year							
On-pump	39	1 (2.6)	36	1 (2.6)	46	3 (6.5)	0.625
Off-pump	129	2 (1.6)	130	3 (2.3)	120	6 (5.0)	0.292
CV death							
On-pump	39	0 (0.0)	36	0 (0.0)	46	1 (2.2)	
Off-pump	129	1 (0.8)	130	0 (0.0)	120	1 (0.8)	
Nonfatal MI							
On-pump	39	1 (2.6)	36	1 (2.8)	46	2 (4.4)	
Off-pump	129	1 (0.8)	130	1 (0.8)	120	1 (0.8)	
Nonfatal stroke							
On-pump	39	0 (0.0)	36	0 (0.0)	46	0 (0.0)	
Off-pump	129	0 (0.0)	130	2 (1.5)	120	4 (3.3)	
Recurrent angina in 1 year							
On-pump	39	1 (2.6)	36	0 (0.0)	46	2 (4.4)	0.776
Off-pump	129	9 (7.0)	130	11 (8.5)	120	10 (8.3)	0.888

CABG, coronary artery bypass grafting; A, aspirin; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; T, ticagrelor.

failure might be triggered not only by the hypercoagulable state, but more by surgical accuracy, graft and target vessel quality, which could be hardly compensated by sophisticated antiplatelet strategy. In the short term or long term, the effects of antiplatelet strategy may play a greater role. The present study obtained similar results that 1-year patency rates were consistent in on- and off-pump CABG, suggesting a limited effect from the early coagulant state in most patients receiving antiplatelet therapy after CABG. Nevertheless, such conclusions should be confirmed in further trials with patients randomly allocated to on-pump and off-pump groups.

Study limitations

This post-hoc analysis had several limitations. First, as a non-prespecified subgroup analysis, the use of CPB was not randomized, but decided by surgeons instead, making the study inadequately powered to detect a statistically significant difference. Similarly, the insufficiency of statistical power, due to the relatively low event rate, to analyze the risk of bleeding and adverse events should be taken into consideration when interpreting the results that no significant differences were observed on major bleeding and MACEs among different antiplatelet strategy groups. Second, the graft outcome, which was the primary outcome in the present study, might not lead to clinical events. Although studies suggested a relationship between occluded grafts and subsequent outcomes, many graft failures are actually clinically silent (26). Also, the vein graft failure was not found to directly result in subsequent death or myocardial infarction (27).

Conclusions

In the present post-hoc analysis, the benefits of ticagrelor plus aspirin for achieving 1-year vein graft patency are consistent in both on-pump and off-pump subgroups, with particular benefit being seen in the off-pump subgroup. The results suggested that patients with vein graft could benefit from 1-year ticagrelor plus aspirin-based dual antiplatelet therapy regardless of the use of CPB during CABG.

Table 4 Bleeding events among patients receiving ticagrelor + aspirin, ticagrelor alone, or aspirin alone by on-pump CABG and off-pump CABG subgroups

Events	T + A		T		A		Total		P value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
CABG-related									
On-pump	39	0 (0.0)	36	1 (2.8)	46	0 (0.0)	121	1 (0.8)	0.298
Off-pump	129	1 (0.8)	130	0 (0.0)	120	0 (0.0)	379	1 (0.3)	0.657
Non-CABG-related									
On-pump	39	3 (7.7)	36	2 (5.6)	46	4 (8.7)	121	9 (7.4)	0.912
Off-pump	129	48 (37.2)	130	18 (13.9)	120	11 (9.2)	379	77 (20.3)	<0.001
Major									
On-pump	39	0 (0.0)	36	0 (0.0)	46	0 (0.0)	121	0 (0.0)	–
Off-pump	129	2 (1.6)	130	1 (0.8)	120	0 (0.0)	379	3 (0.8)	0.656
Minor									
On-pump	39	0 (0.0)	36	0 (0.0)	46	1 (2.2)	121	1 (0.8)	1.000
Off-pump	129	2 (1.6)	130	0 (0.0)	120	1 (0.8)	379	3 (0.8)	0.425
Minimal									
On-pump	39	3 (7.7)	36	2 (5.6)	46	3 (6.5)	121	8 (6.6)	1.000
Off-pump	129	45 (34.9)	130	17 (13.1)	120	10 (8.3)	379	72 (19.0)	<0.001
*Overall major bleeding									
On-pump	39	0 (0.0)	36	1 (2.8)	46	0 (0.0)	121	1 (0.8)	0.298
Off-pump	129	3 (2.3)	130	1 (0.8)	120	0 (0.0)	379	4 (1.1)	0.276

*, overall major bleeding includes CABG-related bleeding and non-CABG-related major bleeding. CABG, coronary artery bypass grafting; A, aspirin; T, ticagrelor.

Acknowledgments

We thank Dr. Zheng Ke and MedSci for providing medical writing assistance. The statistical analysis was assisted by Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China. All were compensated for their contributions.

Funding: The study was sponsored by Ruijin Hospital, Shanghai, China, and funded by AstraZeneca.

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-1177

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-20-1177

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1177). YZ has served as a speaker for AstraZeneca, Johnson & Johnson, Novartis, and Sanofi, also as an investigator on clinical trials sponsored by AstraZeneca, Bayer, Novartis, and Sanofi. HL has served as a speaker for Pfizer. RW has served as a speaker for AstraZeneca and as an investigator on clinical trials sponsored by Bayer. XW has served as a speaker for AstraZeneca and Johnson & Johnson. LH has served as a speaker for Medtronic. QZ has served as a speaker for AstraZeneca, Johnson & Johnson, and Medtronic, and also been an investigator on clinical trials sponsored by AstraZeneca, Bayer, Novartis, and Sanofi. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. The trial protocol and all amendments were reviewed and approved by the independent Institutional Review Board responsible for each participating site. Written informed consent was obtained from all individual participants included in the study.

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Cite this article as: Zhu Y, Xue Q, Zhang M, Hu J, Liu H, Wang R, Wang X, Han L, Zhao Q. Effect of ticagrelor with or without aspirin on vein graft outcome 1 year after on-pump and off-pump coronary artery bypass grafting. J Thorac Dis 2020;12(9):4915-4923. doi: 10.21037/jtd-20-1177

Supplementary

Table S1 Inclusion and exclusion criteria

Inclusion criteria

1. Female and male patients aged 18–80 years
2. Patients are able to provide written informed consent
3. Informed consent prior to any study specific procedures
4. Indication for CABG surgery:

   ≥3 coronary vessels (partially) occlusion, or

   Left major coronary vessel stenosis, or

   Two coronary vessels (partially) occlusion and impaired left ventricular function

Exclusion criteria

1. Cardiogenic shock, hemodynamic instability
2. Need for urgent revascularization within 5 days from presentation
3. Single vessel disease
4. Two vessel disease with normal left ventricular function (>50%)
5. Need for concomitant other cardiac surgery (e.g., valve replacement)
6. Need for dual antiplatelet treatment for the patients undergoing CABG after acute coronary syndrome
7. Contraindication for aspirin and ticagrelor use (e.g., known allergy)
8. History of bleeding diathesis within 3 months prior presentation
9. History of significant GI bleed within 1 year prior to presentation
10. History of peptic ulcer without GI bleeding in past 3 years
11. History of intracranial hemorrhage
12. History of moderate to severe liver impairment
13. Patient requiring dialysis
14. Patient with an increased risk of bradycardia (e.g., patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope)
15. Need vitamin K antagonist therapy after CABG (e.g., persistent atrial fibrillation, mechanical heart valves)
16. Known, clinically important thrombocytopenia (i.e., $<100\times10^9$/L)
17. Known, clinically important anemia (i.e., <100 g/L)
18. Participation in another investigational drug or device study in the last 30 days
19. Pregnant or lactating female patients. Premenopausal women are required to use 2 methods of reliable contraception, one of which must barrier method
20. Concomitant oral or intravenous therapy with strong CYP3A4 inhibitors, CYP3A4 substrates with narrow therapeutic indices, or strong CYP3A4 inducers which cannot be stopped for the course of the study (strong inhibitors include ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and >1 liter/day of grapefruit juice. Substrates with a narrow therapeutic index include cyclosporine, and quinidine Strong inducers include rifampin, phenytoin, and carbamazepine)
21. Active cancer
22. Life expectancy <12 months
23. Indication for major surgery (e.g., cancer treatment, carotid surgery, cerebral surgery, major vascular surgery)

CABG, coronary artery bypass grafting.

Table S2 Baseline demographics and characteristics among patients receiving ticagrelor + aspirin, ticagrelor alone, or aspirin alone by on-pump CABG and off-pump CABG subgroups

Patient characteristics	On-pump				Off-pump			
	T + A (n=39)	T (n=36)	A (n=46)	P value	T + A (n=129)	T (n=130)	A (n=120)	P value
Age (SD), y	61.0 (9.2)	61.9 (8.5)	62.8 (9.2)	0.677*	64.2 (7.7)	63.7 (8.2)	64.5 (7.6)	0.753*
Male, n (%)	34 (87.2)	30 (83.3)	38 (82.6)	0.832*	100 (77.5)	104 (80.0)	103 (85.8)	0.232*
Clinical status, n (%)								
Stable angina	7 (18.0)	8 (22.2)	9 (19.6)	0.932**	48 (37.2)	55 (42.3)	41 (34.2)	0.363**
Unstable angina	30 (76.9)	25 (69.4)	35 (76.1)		78 (60.5)	74 (56.9)	74 (61.7)	
NSTEMI	2 (5.1)	3 (8.3)	2 (4.4)		3 (2.3)	1 (0.8)	5 (4.2)	
History of myocardial infarction, n (%)	11 (28.2)	12 (33.3)	9 (19.6)	0.357*	42 (32.6)	48 (36.9)	34 (28.3)	0.351*
Heart function (NYHA), n (%)								
III	19 (48.7)	17 (47.2)	20 (43.5)	0.950**	50 (38.8)	48 (36.9)	42 (35.0)	0.809**
IV	1 (2.6)	0 (0.0)	1 (2.2)		0 (0.0)	0 (0.0)	1 (0.83)	
Medical history, n (%)								
Hypertension	28 (71.8)	25 (69.4)	32 (69.6)	0.968*	99 (76.7)	97 (74.6)	88 (73.3)	0.821*
Hyperlipidemia (or LDL-C ≥1.8 mmol/L)	34 (87.2)	28 (77.8)	34 (73.9)	0.310*	87 (67.4)	96 (73.9)	85 (70.8)	0.526*
Diabetes mellitus (or HbA1c ≥6.5%)	17 (43.6)	15 (41.7)	19 (41.3)	0.975*	58 (45.0)	60 (46.2)	48 (40.0)	0.587*
Peripheral vascular disease	4 (10.3)	2 (5.6)	3 (6.5)	0.753**	22 (17.1)	25 (19.2)	26 (21.7)	0.654*
Stroke	3 (7.7)	4 (11.1)	4 (8.7)	0.855**	23 (17.8)	9 (6.9)	18 (15.0)	0.027*
Smoking	22 (56.4)	16 (44.4)	20 (43.5)	0.435*	63 (48.8)	58 (44.6)	67 (55.8)	0.203*
LVEF, median (Q1, Q3), %	59 (52.0, 63.0)	60.5 (56.0, 63.0)	61.5 (55.0, 64.0)	0.136*	63 (57.0, 68.0)	62 (58.0, 67.0)	64 (57.5, 68.0)	0.823*
SYNTAX score, n (%)				0.317*				0.030*
Low (0–22)	5 (12.8)	9 (25.0)	9 (19.6)		13 (10.1)	12 (9.2)	22 (18.3)	
Intermediate [23–32]	19 (48.7)	15 (41.7)	27 (58.7)		74 (57.4)	68 (52.3)	71 (59.2)	
High (≥33)	15 (38.5)	12 (33.3)	10 (21.7)		42 (32.6)	50 (38.5)	27 (22.5)	
EuroSCORE, n (%)				0.681*				0.097*
Low (0–2)	9 (23.1)	5 (13.9)	12 (26.1)		62 (48.1)	58 (44.6)	52 (43.3)	
Medium [3–5]	20 (51.3)	23 (63.9)	24 (52.2)		45 (34.9)	59 (45.4)	58 (48.3)	
High (≥6)	10 (25.6)	8 (22.2)	10 (21.7)		22 (17.1)	13 (10.0)	10 (8.3)	
Baseline medication, n (%)								
Aspirin	3 (10.0)	2 (6.9)	3 (8.8)	1.000**	35 (28.9)	35 (28.7)	31 (28.4)	0.997*
β-blocker	31 (79.5)	25 (69.4)	33 (71.7)	0.578*	122 (94.6)	124 (95.4)	116 (96.7)	0.725*
ACEI/ARB	18 (46.2)	12 (33.3)	21 (45.7)	0.441*	69 (53.5)	86 (66.2)	83 (69.2)	0.024*
Statins	34 (87.2)	30 (83.3)	40 (87.0)	0.864*	123 (95.4)	125 (96.2)	117 (97.5)	0.703**
Proton pump inhibitor	8 (20.5)	9 (25.0)	12 (26.1)	0.823*	96 (74.4)	99 (76.2)	93 (77.5)	0.849*
Total grafts, n	156	137	178		475	499	446	
Graft type, n (%)				0.440**				0.836**
IMA	35 (22.4)	33 (24.1)	38 (21.4)		106 (22.3)	111 (22.2)	95 (21.3)	
RA	0 (0.0)	3 (2.2)	3 (1.7)		3 (0.6)	1 (0.2)	3 (0.7)	
SVG	121 (77.6)	101 (73.7)	137 (77.0)		366 (77.1)	387 (77.6)	348 (78.0)	

*, P value was obtained from one-way analysis of variance for continuous variable or the Chi-square test for a categorical variable; **, P value was obtained from the Kruskal-Wallis test for continuous variable or the Fisher's exact test for categorical variable. CABG, coronary artery bypass grafting; A, aspirin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EuroSCORE, European system for cardiac operative risk evaluation; HbA1c, glycated hemoglobin; IMA, internal mammary artery; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST segment elevation myocardial infarction; NYHA, New York Heart Association; RA, radial artery; SD, standard deviation; SVG, saphenous vein graph; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; T, ticagrelor.

Table S3 Baseline demographics and characteristics between patients receiving on-pump and off-pump CABG

Characteristics	On-pump (n=121)	Off-pump (n=379)	Overall (n=500)	P value*
Age, mean (SD), y	62.0 (9.0)	64.1 (7.8)	63.6 (8.2)	0.010
Age stratified				
≤60 y	51 (42.2)	114 (30.1)	165 (33.0)	0.044
61–75 y	60 (49.6)	233 (61.5)	293 (58.6)	
>75 y	10 (8.3)	32 (8.4)	42 (8.4)	
Male gender, No. (%)	102 (84.3)	307 (81.0)	409 (81.8)	0.414
Clinical status, No. (%)				
Stable angina	24 (19.8)	144 (38.0)	168 (33.6)	<0.001
Unstable angina	90 (74.4)	226 (59.6)	316 (63.2)	
NSTEMI	7 (5.8)	9 (2.4)	16 (3.2)	
History of myocardial infarction, No. (%)	32 (26.5)	124 (32.7)	156 (31.2)	0.195
Time since onset of myocardial infarction				
<21 d	8 (6.6)	10 (2.6)	18 (3.6)	0.041**
21–90 d	3 (2.5)	11 (2.9)	14 (2.8)	
>90 d	21 (17.4)	103 (27.2)	124 (24.8)	
Angina (CCS), No. (%)				
III	89 (73.6)	208 (54.9)	297 (59.4)	<0.001
IV	6 (5.0)	10 (2.6)	16 (3.2)	
Heart function (NYHA), No. (%)				
III	56 (46.3)	140 (36.9)	196 (39.2)	0.033**
IV	2 (1.7)	1 (0.3)	3 (0.6)	
Medical history, No. (%)				
Hypertension	85 (70.3)	284 (74.9)	369 (73.8)	0.307
Hyperlipidemia (or LDL-C ≥1.8 mmol/L)	96 (79.3)	268 (70.7)	364 (72.8)	0.063
Diabetes mellitus (or HbA1c ≥6.5%)	51 (42.2)	166 (43.8)	217 (43.4)	0.750
Peripheral vascular disease	9 (7.4)	73 (19.3)	82 (16.4)	0.002
Cerebrovascular accident	11 (9.1)	50 (13.2)	61 (12.2)	0.230
Peptic ulcer disease	2 (1.7)	9 (2.4)	11 (2.2)	1.000**
Chronic kidney disease	2 (1.7)	7 (1.9)	9 (1.8)	1.000**
Smoking	58 (47.9)	188 (49.6)	246 (49.2)	0.749
COPD	5 (4.1)	34 (9.0)	39 (7.8)	0.084
LVEDD, median (Q1, Q3), mm	46.0 (44.0, 52.0)	50.0 (47.0, 53.0)	49.0 (46.0, 53.0)	0.003
LVEF, median (Q1, Q3), %	60.0 (55.0, 63.0)	63.0 (58.0, 68.0)	62.0 (57.0, 67.0)	<0.001
LVEF, N (%)				
30–50%	16 (13.2)	39 (10.3)	55 (11.0)	0.374
>50%	105 (86.8)	339 (89.7)	444 (89.0)	
SYNTAX score, No. (%)				
Low (0-22)	23 (19.0)	47 (12.4)	70 (14.0)	0.179
Intermediate [23–32]	61 (50.4)	213 (56.2)	274 (54.8)	
High (≥33)	37 (30.6)	119 (31.4)	156 (31.2)	
EuroSCORE, No. (%)				
Low (0-2)	26 (21.5)	172 (45.4)	198 (39.6)	<0.001
Medium [3–5]	67 (55.4)	162 (42.7)	229 (45.8)	
High (≥6)	28 (23.1)	45 (11.9)	73 (14.6)	
Medication use, baseline, No. (%)				
Aspirin	8 (8.6)	101 (28.7)	109 (24.5)	<0.001
β-blocker	89 (73.6)	362 (95.5)	451 (90.2)	<0.001
ACEI/ARB	51 (42.2)	238 (62.8)	289 (57.8)	<0.001
Statins	104 (86.0)	365 (96.3)	469 (93.8)	<0.001
Proton pump inhibitor	29 (24.0)	288 (76.0)	317 (63.4)	<0.001
Medication use, 7 days, No. (%)				
β-blocker	113 (93.4)	374 (98.7)	487 (97.4)	0.004**
ACEI/ARB	47 (38.8)	211 (55.7)	258 (51.6)	0.001
Statins	107 (88.4)	374 (98.7)	481 (96.2)	<0.001**
Proton pump inhibitor	118 (97.5)	347 (91.6)	465 (93.0)	0.025
Medication use, 1 year, No. (%)				
β-blocker	108 (89.3)	361 (95.3)	469 (93.8)	0.017
ACEI/ARB	34 (28.1)	206 (54.4)	240 (48.0)	<0.001
Statins	115 (95.0)	364 (96.0)	479 (95.8)	0.633
Proton pump inhibitor	0 (0.0)	9 (2.4)	9 (1.8)	0.122
Surgical procedure characteristics				
Total grafts, No.	471	1420	1891	
Graft type, No. (%)				0.196
IMA	106 (22.5)	312 (22.0)	418 (22.1)	
LAD	106 (100.0)	310 (99.4)	416 (99.5)	1.000
LCX	0 (0.0)	2 (0.6)	2 (0.5)	
RA	6 (1.3)	7 (0.5)	13 (0.7)	
LAD	0 (0.0)	2 (28.6)	2 (15.4)	0.462
LCX	6 (100.0)	5 (71.4)	11 (84.6)	
SVG	359 (76.2)	1101 (77.5)	1460 (77.2)	
LAD	95 (26.5)	320 (29.1)	415 (28.4)	0.476
LCX	143 (39.8)	402 (36.5)	545 (37.3)	
RCA	121 (33.7)	379 (34.4)	500 (34.3)	
Intervention				
T + A	39 (32.2)	129 (34.0)	168 (33.6)	0.412
T alone	36 (29.8)	130 (34.3)	166 (33.2)	
A alone	46 (38.0)	120 (31.7)	166 (33.2)	

*, P value was obtained from t test for continuous variable or Chi-square test for categorical variable; **, P value was obtained from Fisher's exact test. CABG, coronary artery bypass grafting; A, aspirin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; HbA1c, glycated hemoglobin; ITA, internal thoracic artery; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular internal dimensions at end diastole; LVEF, left ventricular ejection fraction; NSTEMI, non-ST segment elevation myocardial infarction; NYHA, New York Heart Association; RA, radial artery; RCA, right coronary artery; SD, standard deviation; SVG, saphenous vein graph; T, ticagrelor.

Table S4 Vein graft patency and non-occlusion rates at 1 year between patients receiving on-pump and off-pump CABG

Grouping categories	N	Patency			Non-occlusion		
		n (%)	*Adjusted OR for non-patency (95% CI)	P value	n (%)	*Adjusted OR for occlusion (95% CI)	P value
Per graft			0.63 (0.37–1.08)	0.092		0.73 (0.41–1.28)	0.265
On-pump	359	310 (86.4)			314 (87.5)		
Off-pump	1,101	897 (81.5)			935 (84.9)		
Per patient			0.51 (0.30–0.88)	0.016		0.62 (0.36–1.09)	0.097
On-pump	121	98 (81.0)			100 (82.7)		
Off-pump	378	264 (69.8)			287 (75.9)		

*, off-pump as reference. Adjusted for age, sex, medical history of hypertension, diabetes and hyperlipidemia, SYNTAX score, target vessel distribution, antiplatelet therapy and statin use. CABG, coronary artery bypass grafting; CI, confidence interval; OR, odds ratio.

Table S5 Cardiovascular events between patients receiving on-pump and off-pump CABG

Events	On-pump (N=121) (%)	Off-pump (N=379) (%)	P value
MACE in 1 year	5 (4.1)	11 (2.9)	0.553
CV death	1 (0.8)	2 (0.5)	
Nonfatal MI	4 (3.3)	3 (0.8)	
Nonfatal stroke	0 (0.0)	6 (1.6)	
Recurrent angina in 1 year	3 (2.5)	30 (7.9)	0.036

CABG, coronary artery bypass grafting; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.

Table S6 Patients with bleeding events between on-pump and off-pump CABG

Event categories	On-pump (N=121) (%)	Off-pump (N=379) (%)	P value
CABG-related	1 (0.8)	1 (0.3)	0.426
Non-CABG-related	9 (7.4)	77 (20.3)	0.001
Major	0 (0.0)	3 (0.8)	1.000
Minor	1 (0.8)	3 (0.8)	1.000
Minimal	8 (6.6)	72 (19.0)	0.001
*Overall major bleeding	1 (0.8)	4 (1.1)	1.000

*, overall major bleeding includes CABG-related bleeding and non-CABG-related major bleeding. CABG, coronary artery bypass grafting.

Table S7 Other adverse events by on-pump CABG and off-pump CABG subgroups

Categories	T + A		T		A		Total		*P value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Renal dysfunction (Cr >200 μmol/L)									
On-pump	39	3 (7.7)	36	0 (0.0)	46	2 (4.4)	121	5 (4.1)	0.273
Off-pump	129	9 (7.0)	130	9 (6.9)	120	4 (3.3)	379	22 (5.8)	0.375
Liver dysfunction (ALT/AST >320/200 U/L)									
On-pump	39	4 (10.3)	36	6 (16.7)	46	2 (4.4)	121	12 (9.9)	0.202
Off-pump	129	1 (0.8)	130	3 (2.3)	120	1 (0.8)	379	5 (1.3)	0.627
Pulmonary infectious									
On-pump	39	0 (0.0)	36	0 (0.0)	46	0 (0.0)	121	0 (0.0)	–
Off-pump	129	1 (0.8)	130	3 (2.3)	120	2 (1.7)	379	6 (1.6)	0.697
Delayed incision healing									
On-pump	39	2 (5.1)	36	1 (2.8)	46	1 (2.2)	121	4 (3.3)	0.829
Off-pump	129	7 (5.4)	130	5 (3.9)	120	9 (7.5)	379	21 (5.5)	0.450

*, P value was obtained from the Fisher's exact test. CABG, coronary artery bypass grafting.

Table S8 Other adverse events between patients receiving on-pump and off-pump CABG

Event categories	On-pump (N=121) (%)	Off-pump (N=379) (%)	P value
Renal dysfunction (Cr >200 μmol/L)	5 (4.1)	22 (5.8)	0.479
Liver dysfunction (ALT/AST >320/200 U/L)	12 (9.9)	5 (1.3)	<0.001*
Pulmonary infectious	0 (0.00)	6 (1.6)	0.344*
Delayed incision healing	4 (3.3)	21 (5.5)	0.326

*, P value was obtained from Fisher's exact test. CABG, coronary artery bypass grafting; SAE, serious adverse event.