Multicentre, randomised, double-blind, parallel controlled trial to investigate timing of platelet inhibition after coronary artery bypass grafting: TOP-CABG trial study

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ABSTRACT

INTRODUCTION

Data show that up to 20% of saphenous vein grafts (SVG) occlude within 1 year after coronary artery bypass grafting (CABG), which is associated with adverse outcomes such as angina pectoris, myocardial infarction and long-term mortality.1-4 Although occlusion of SVG is regarded as a complex process, platelet activation and thrombosis likely contribute to early process of SVG stenosis or occlusion.

Antiplatelet therapy with aspirin is recommended after CABG, 5-6 but even if aspirin were given, the SVG patency remains poor: during the first year after surgery, approximately 15%-20% SVG occluded.7 Reflecting this graft failure, angina recurs in up to 20% of patients during the first year after surgery.2,8

Recent studies showed that dual antiplatelet therapy (DAPT), referred to as the combination of aspirin and P2Y12 receptor antagonist (clopidogrel or ticagrelor), could potentially improve graft patency after CABG.9-12 However, DAPT significantly increases the risk of bleeding as compared with aspirin monotherapy, resulting in increase in risk of mortality and reoperation.6-12,13 Addressing this clinical scenario requires therapeutic strategies of lowering the risk of bleeding while preserving infarction benefit.

The de-escalated DAPT (De-DAPT) is an effective antiplatelet regimen for acute coronary syndrome treatment, which switches aspirin+strong P2Y12 inhibitors (ticagrelor or prasugrel 10mg) to monoclonal antibodies or aspirin+weak P2Y12 inhibitors (clopidogrel or prasugrel 5mg) 1to 3 months after the onset of acute coronary syndrome or PCI.14-17 Several randomised controlled trials show that, compared with DAPT, De-DAPT significantly reduces the risk of bleeding without increasing the incidence of major adverse cardiovascular events (MACCE).15-17 However, studies on the efficacy and safety of De-DAPT for patients undergoing CABG are still lacking.

The Timing of Platelet Inhibition after Coronary Artery Bypass Grafting (TOP-CABG
Figure 1  Flowchart. Ticagrelor (90mg twice daily) + aspirin (100mg once daily) for 1 year. Ticagrelor (90mg twice daily) + aspirin (100mg once daily) during first 3 months after CABG, then switching to aspirin (100mg once daily) + ticagrelor placebo (twice daily) for 9 months. CABG, coronary artery bypasses grafting surgery; CCTA, coronary CT angiography; DAPT, dual antiplatelet therapy; De-DAPT, de-escalated dual antiplatelet therapy.

Study settings
According to our protocol, a candidate centre has to own at least an annual volume of 500. According to a survey, there were 724 hospitals provide cardiac surgery, of which 115 leading hospitals, crossing 13 provinces reach the standard. Finally, 15 centres agreed to participate the TOP-CABG trial, all of which are large local centres with an annual cardiovascular surgery volume over 500 cases. The study has been approved in these 15 centres by whose ethics committee. At least two expert surgeons perform surgeries in each centre. Before entering the trial, the facilities, resources and faculties of the candidate centres will be fully evaluated.

Inclusion/exclusion criteria
Inclusion criteria
1. Patients more than 18 years and less than 80 years old.
2. Patients undergo planned CABG for the first time with ≥1 SVGs.
3. Patients with written informed consent.

Exclusion criteria
1. Concomitant valve (excluding aortic bioprosthesis), aorta, or rhythm surgery during the index operation.
2. Patients undergo emergent/urgent CABG.
3. Patients with single-vessel coronary artery disease.
4. Patients with cardiogenic shock and haemodynamic instability.
5. Patients with sick sinus syndrome or second or third atrioventricular block.
6. Patients with contraindications for coronary CCTA or coronary angiography (eg, contrast agents allergy).
7. Use of other antiplatelet drugs than aspirin (clopidogrel, prasugrel, etc) and unable to discontinue this medication after CABG.
8. Patients who take oral anticoagulants before CABG and have to use anticoagulants after surgery.
9. Contraindication for the use of ticagrelor or aspirin (eg, history of bleeding diathesis within 3 months prior presentation, severe gastrointestinal bleeding within 1 year prior presentation, peptic ulcer without gastrointestinal bleeding in past 3 years or history of intracranial haemorrhage, allergy, severe gastrointestinal reaction caused by aspirin).
10. Placement of a drug-eluting stent in a coronary or cerebral artery within 6 months of CABG or placement of a bare-metal stent in a coronary or cerebral artery within 1 month of CABG.
11. Thrombocytopenia before CABG (<100 × 10^9/L).
12. Patients with severe renal function impairment requiring dialysis or active liver disease, including patients with unexplained persistent elevated transaminase or any transaminase more than three times of the upper limit.
14. Patients who must use methotrexate and ibuprofen.
15. Patients with active malignant tumours with increase in bleeding risk.
16. Pregnant patients, patients who have given birth within the past 90 days, or who are breastfeeding.
17. Premenopausal women who do not take adequate contraception. Adequate contraception refers to the adoption of at least two reliable methods of contraception, one of which must be a barrier method of contraception.
18. CABG performed by surgeons with a total volume of less than 50 cases.

**Study drug and concomitant medication**

**Study drug**
Ticagrelor and the matching placebo (Nanjing Chia-Tai Tianqing pharmaceutical company) are packed in blisters by pharmaceutical company under supervision of statisticians who perform randomisation, according to good manufacturing practice of medical products (GMP) guidelines. The study drug is started as early as possible after CABG (preferably within 24 hours), but only when postoperative chest tube drainage does not exceed 30 mL/hour in the previous 2 hours.

Production, packaging, identification and storage of ticagrelor and placebo shall be implemented according to the requirements of GMP guidelines. The distribution of drugs to participating centres shall be carried out according to the requirements of the research process. The coordination centre tracks and manages all the investigational drugs in the whole study process, including storage, transportation, distribution, recovery and destruction. At the outpatient clinic, the research staff of the participating centres will give the study drug to patients according to the Standard Operating Procedures. The participating centres are responsible for recycling unused research drugs, delivering them to the designated drug factory where the drugs will be destroyed.

**Concomitant medication**
According to the protocols of TOP-CABG, aspirin will be continued perioperatively and administered postoperatively as soon as possible. For the patients who take antiplatelet drugs other than aspirin before CABG, it is required to stop ticagrelor for at least 3 days, clopidogrel for 5 days and prasugrel for 7 days preoperatively. The sponsor/investigator has an insurance, which is in accordance with the legal requirements in China. This insurance provides cover for damage to research subjects through injury or death caused by the study.

**Study endpoints**
1. Primary efficacy endpoint: 100% occlusion of SVG within 1 year after CABG. SVGs will be assessed by coronary CT angiography or coronary angiography and interpreted by an independent core-lab blinded to treatment allocation.
2. Primary safety endpoint: bleeding episodes as defined by the Bleeding Academic Research Consortium classification ≥2 within 1 year after CABG.

**Secondary endpoints**
1. SVG failure (a composite of SVG occlusion, SVG revascularisation, myocardial infarction in myocardial territory supplied by an SVG or sudden death) within 1 year after surgery.
2. Significant (≥70%) venous or arterial graft stenosis and any (venous or arterial) graft occlusion at 1 year after CABG.
3. MACCE episodes within 1 year after CABG (composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke or revascularisation), as defined by the American College of Cardiology and American Heart Association and judged by an independent clinical endpoint committee blinded to treatment allocation.

**Outcome assessment**
In this study, segments of Y-grafts and jump (sequential) grafts are regarded as separate grafts. A graft is adjudicated patent if contrast fills the graft conduit and the circuit beyond the anastomosis. Graft of 100% stenosis is considered as occlusion. An independent clinical event committee performs evaluation of SVGs, which is blinded for the patient’s randomisation. Images are analysed by two independent blinded experienced radiologists of clinical event committee. If there is no consensus between both radiologists, a third radiologist will be invited to analyse the images. The decision of the third radiologist is final. A blinded clinical endpoint committee adjudicates all clinical safety endpoints.

**Sample size**
Primary efficacy endpoint: patency in De-DAPT group is non-inferior to DAPT group
We assumed that the 1-year SVG occlusion rate would be 10% with De-DAPT and DAPT and non-inferiority margin would be 3.0%. Sample size calculations were performed with one-sided $\alpha$ level of 0.025 and power of 90%, in this study. Based on these assumptions, 2102 SVG would be required in each group for the comparison of De-DAPT versus DAPT. A total of 2000 patients would be required to provide a total of 4204 SVG, assuming that each patient would receive an average of 2.1 SVG. Considering that 10% of patients would not have available primary outcome, we estimated that 2300 patients needed to be included.

Primary safety endpoint: risk of bleeding in De-DAPT group is lower than that in DAPT group
We assumed that the 1-year bleeding rate would be 9% with De-DAPT and 15% with DAPT. Sample size calculations were performed with a two-sided $\alpha$ level of 0.05 and 90% power. Based on these assumptions, 1230 patients would be required for the comparison of De-DAPT versus DAPT. Considering that 10% of patients would not have available primary outcome, we estimated that 1367 patients needed to be included.

Therefore, a total of 2300 patients would be required in this study to meet both the hypotheses on primary efficacy...
and primary safety endpoint. The two primary endpoints in our study were treated as coprimary endpoints, it would not induce the multiplicity issue.

**Subgroups**

Prespecified subgroups will be performed are age (<70 vs ≥70 years), gender, SYNTAX scores (≤22 vs 23–32 vs ≥33), Society of Thoracic Surgeons risk scores for isolated CABG (<5% vs ≥5%), coronary stenosis (stenosis <70% vs ≥70%), diabetes mellitus, smoking, left ventricular ejection fraction (≥50% vs 30%–49% vs <30%), glomerular filtration rate (GFR, <60 mL/min vs ≥60 mL/min), volume of surgeon (50–100 vs 101–500 vs >500) indication for CABG (chronic coronary syndrome vs acute coronary syndrome), fractional flow reserve, number of SVGs (≤3 vs ≥3), pump-use (on-pump vs off-pump), optimal medical therapy (≤2 types of medications vs >2 types of medications) and time of first study drug dose (<12 hours after CABG vs ≥12 hours and <24 hours vs ≥24 hours).

**Scheme for statistical analysis**

The primary analysis will follow intention-to-treat (ITT) principle. The ITT analysis included all randomised patients. For patients with missed CCTA or angiographic data, the patient’s SVG would be considered as occluded in the ITT analysis. The modified full analysis set included all randomised patients who took at least one dose of study medication. For patients with failed bleeding events follow-up, the patient will be considered as patient with bleeding events. The per-protocol population included patients who take planned dose of study drugs without interruption for more than 60 days or other major protocol violation and own CCTA and bleeding event data. The per-protocol analysis is performed as a sensitivity analysis. The analysis will be conducted on a per-graft basis for efficacy endpoint and on a patient basis for safety endpoint. The generalised estimating equation is expressed as mean with SD, and categorical variables are described as frequencies and percentages. A two-sided value of p<0.05 is considered to be statistically significant.

**Data collection and process**

We develop a set of customised electronic data collection and management system based on the requirements of the current study, for the screening, recruiting, randomising and following patients. The coordination board will manage the data from participating centres through this system, to ensure the correctness, integrity and timeliness of the data collection process. The data are transmitted in an encrypted manner, and all data will be stored securely. A unique username and password are required to enter the system. Any modification to the data requires the user to enter his/her username and password as an electronic signature. Based on their roles in this study, researchers have different levels of data access and management rights. The independent Data Monitoring Committee will review the data every 6 months regularly. Early termination of clinical trials is a major decision for clinical studies. Data Monitoring Committee must be very careful in deciding whether to give recommendations for early termination of clinical trials. In addition to considering safety data, other possible relevant factors must be fully taken into account in the interpretation of the results. These factors include, but are not limited to: serious quality problems in the execution of the trial, such as poor data quality, randomisation errors, non-compliance of the study design, etc. All outcome data will be collected for participants who discontinue or deviate from intervention protocols.

Face-to-face or webinar training for study protocol, data collection and communicating important protocol modifications will be conducted at each participating centre. All data elements will be collected by trained clinical research staff including research nurses or residents. Practically, each centre has to follow the TOP-CABG’s standardised case report form (SCRF) that contains demographic, preoperative risk factors, operative information, postoperative treatment course and surgical outcomes to collect its data. The information about surgeons and centres will be also collected. SCRFs are then submitted electronically through the data collection and management system to the TOP-CABG’s data processing centre and entered into the database. Moreover, two reviewers from the data processing centre should reabstract a random sample of 5%–10% of medical records through on-site auditing at a 6-month interval. Information in a SCRF will be compared with the reabstracted information.

**Duration of the trial**

The research period, lasting 3 years, is composed of two parts: recruitment period (2 years, November 2022 to November 2024) and follow-up period (3 years, December 2022 to December 2024).

**Ethics approval**

The Ethics Committee in Fuwai hospital approved this study (2022–1774). The results of the trial will be submitted for publication in a peer-reviewed journal.

**Patient and public involvement**

Patients and public will not get involved in the development of the research question, study design or any other part of this protocol.

**DISCUSSION**

How to balance the benefit and risk of the DAPT strategy is quite important for improving surgical outcomes.
There is still a lack of evidence for this issue in the literature. Recently, two large meta-analyses demonstrated that DAPT can improve the patency rate of SVG after CABG.\(^1\)\(^2\) Especially, after including an important evidence not supporting DAPT (POpopular),\(^9\) the meta-analysis conducted by Sandner and colleagues still demonstrated that DAPT with ticagrelor plus aspirin, compared with aspirin alone, was associated with a significant reduction in the risk of SVG failure.\(^1\) However, the authors also reported a significantly increased risk of clinically important bleeding when DAPT was used.\(^1\)

The purpose of TOP-CABG study is to explore the timing of DAPT use after elective CABG. This study is a prospective, multicentre, randomised, double-blind, parallel controlled trial. Compared with most of the previous trials,\(^9\)\(^10\)\(^20\) the design of this study has the following advantages: (1) most of the previous trials were non-blind designs. The current study adopts a blind and placebo randomised controlled design to further ensure the robustness of the research results; (2) the current study with a sample size of 2300 patients is among the largest trials in this field. The expansion of sample size further reduced the risk of sampling bias; (3) most previous studies did not consider the impact of surgeons on the results. In the current study, candidate surgeons are required to have a surgical volume \(\geq 50\) cases.

The ‘de-escalation’ strategy used for patients receiving percutaneous coronary intervention is not a unified strategy; the time point of ‘de-escalation’ varies from one to 3 months.\(^1\)\(^5\)\(^13\)\(^17\) In the current study, we decided to de-escalate DAPT to aspirin 3 months after CABG. The reasons are as follows: (1) previous studies have shown that the activated platelet function returned to the baseline level 3 months after CABG;\(^2\) (2) previous studies have shown that the SVG stenosis mainly occurred within 3 months after surgeries, and the stenosis rate decreased significantly thereafter;\(^22\) (3) similarly, previous studies have shown that MACCE events mainly occurred within 3 months postoperatively.\(^23\)

This study has been registered in clinical trial website. The results will provide important evidence for anti-platelet strategies after CABG.

**Limitations**

The study has several limitations. We did not exclude patients with atrial fibrillation. But these patients only constitute a small proportion of the coronary artery disease cohort. The prevalence of atrial fibrillation among patients with coronary artery disease is estimated from 0.2% to 5%.\(^24\)\(^27\)

Although CCTA performed at high heart rate and heart rate variability poses a challenge to develop images of high quality and satisfactory diagnostic accuracy, strategies have been prepared for these patients in this design: 1. The patient’s heart rate needs to be controlled with medication or other means. Typical heart rate targets are less than 60 bpm for beta-blocker agents and less than 65 bpm for ivabradine administration.

2. At least, half of the participant centres are equipped with dual source CT scanners. This equipment resource can be shared within the participant centres.

3. Patients from whom high-quality images cannot be achieved may need to undergo alternative imaging studies, such as invasive coronary angiograms. But we expect that patients within this category will be quite small.

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**Contributors**

QC, XY, KC and S-SH developed protocol. YW and LZ developed statistic plan. QC, XY, YW, YZ and LZ wrote the manuscript. XY and S-SH supervised the project.

**Funding**

This study is supported by the National Clinical Research Centre for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences (NCRC2022001). The collection, analysis and publication of research data will be completely independent of the research fund source.

**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Supplemental material**

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