BMJ Open

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 Dual antiplatelet therapy (DAPT), referred to as the combination of aspirin and P2Y12 receptor antagonist (clopidogrel or ticagrelor), potentially improves patency of saphenous vein grafts (SVG) after coronary artery bypass grafting (CABG), while it is further proposed that DAPT potentially increases bleeding risk. Compared with DAPT, de-escalated DAPT (De-DAPT) is an effective antiplatelet strategy for acute coronary syndrome treatment, which significantly reduces the risk of bleeding without increasing the incidence of major adverse cardiovascular events. However, insufficient evidence is available to determine the timing of DAPT after CABG.

Methods and analysis

Ethics and dissemination The Ethics Committee in Fuwai hospital approved this study (2022-1774). Fifteen centres agreed to participate in the TOP-CABG trial, and the study has been approved in these 15 centres by whose ethics committee. The results of the trial will be submitted for publication in a peer-reviewed journal.

Trial registration number NCT05380063.

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.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) 1 to 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
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.

Figure 1  Flowchart. Ticagrelor (90 mg twice daily) + aspirin (100 mg once daily) for 1 year. Ticagrelor (90 mg twice daily) + aspirin (100 mg once daily) during first 3 months after CABG, then switching to aspirin (100 mg 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.

METHODS

Study design and follow-up

TOP-CABG is a multicentre, randomised, double-blind, parallel controlled trial, which will be conducted in 17 centres. We plan to include 2300 patients receiving CABG with one or more SVGs. The first screening for inclusion and exclusion criteria is conducted before surgery. A second screening is conducted within 5 days postsurgery and only the patients who are tolerant to DAPT will be randomised. Informed consent is obtained before randomisation. Eligible patients with informed consent are randomised on postoperative day 5, by using by central randomisation system based on interactive web response, to De-DAPT referred to as ticagrelor (90 mg two times per day) + aspirin (100 mg/day) during first 3 months after CABG, then switching to aspirin (100 mg/day) + ticagrelor placebo (two times per day) for 9 months or to DAPT group with ticagrelor (90 mg two times per day) + aspirin (100 mg/day) for 1 year. Patients, treating physicians and investigators were blinded to allocation. Patients are evaluated at 1, 3, 6, 9 and 12 months after CABG. Evaluation in month 1, 3, 6, 9 and 12 is performed by telephone or through an outpatient hospital visit (patient preference), in month 12 through an outpatient hospital visit. In month 12 after CABG, patients are required to take coronary CT angiography (CCTA) to evaluate SVG. A flowchart depicting the study procedures is shown in figure 1.
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 50mL/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 (online supplement).

**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 α 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 α 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 used to estimate between-group differences in SVG occlusion and 95% CI. The independent covariates structure will be conducted to model the correlation of SVG occlusion in the same patient. Unstructured and exchangeable covariance structures will be used to check the stability of the model. The generalised linear model is used to calculate the incidence of bleeding events and the difference of 95% CI between groups. Kaplan-Meier curves will be used to depict the occurrence of MACCE episodes over time. Continuous variables with normal distribution were 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.\textsuperscript{11, 12} Especially, after including an important evidence not supporting DAPT (POPUlar),\textsuperscript{19} 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.\textsuperscript{11} However, the authors also reported a significantly increased risk of clinically important bleeding when DAPT was used.\textsuperscript{11}

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,\textsuperscript{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 ≥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.\textsuperscript{15–17} 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;\textsuperscript{21} (2) previous studies have shown that the SVG stenosis mainly occurred within 3 months after surgeries, and the stenosis rate decreased significantly thereafter;\textsuperscript{22} (3) similarly, previous studies have shown that MACCE events mainly occurred within 3 months postoperatively.\textsuperscript{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%.\textsuperscript{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.

REFERENCES


**Supplement**

**Definitions of study endpoints**

The study endpoints will be adjudicated by a blinded clinical endpoint committee. In this study, only events occurred during 0-day to 1 year after coronary artery bypass grafting (CABG) or 0-day to the day conducting coronary computed tomography angiography (CCTA) will be registered as endpoints and be adjudicated by the clinical endpoint committee.

**SVG occlusion**

Occlusion is considered as 100% stenosis. Anastomoses of Y-grafts and jump grafts are defined as separate SVGs. Both anastomoses are defined as occluded if the proximal part of the graft is occluded but the remain graft beyond the first anastomosis is patent.

**Bleeding Academic Research Consortium (BARC) classification**

Type 0: no bleeding evidence

Type 1: bleeding events does not need patients to seek treatment of a healthcare professional or hospitalization.

Type 2: any clinically overt sign of haemorrhage, requiring diagnostic studies, hospitalization or treatment by a health professional, meets one of the following
criteria and does not meet criteria for type 3, type 4 or type 5 BARC bleeding classification.

- Bleeding must require intervention, including medical practitioner-guided treatment, surgery or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug.
- Bleeding leads to hospitalization, prolonging hospitalization or increasing level of care.
- Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing).

Type 3: Clinically overt bleeding requiring medical therapy, as listed below

- Type 3a: any transfusion due to overt bleeding; haemoglobin drop ≥3 to <5g/dL;
- Type 3b: haemoglobin drop ≥5g/dL; cardiac tamponade; surgical intervention for controlling bleeding; bleeding requiring intravenous vasoactive medication.
- Type 3c: intracranial haemorrhage; intraocular haemorrhage compromising vision.

Type 4: coronary artery bypass grafting (CABG) related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are registered)

- Chest tube output ≥2 L within a 24-hour period after CABG

Type 5: fetal bleeding

Fetal bleeding means bleeding that directly causes death with no other explainable cause.

**Coronary computed tomography angiography**

A high-quality cardiac CT scan is performed according to SCCT guidelines for the performance and acquisition of CCTA, specified for local practices and available technology. Minimal requirements for the CT scanner consisted of a single- or dual-source 64-slice CT or higher. An axial scan mode and diastolic scans/reconstructions are preferred. A regular heart rate (preferably <60 bpm) is recommended.

**Reference**

Informed Consent Form

We invite you to participate in a trial “Timing of Platelet Inhibition after Coronary Artery Bypass Grafting (TOP-CABG Trail)” initiated by Fuwai Hospital of Chinese Academy of Medical Sciences, which has been approved by the Ethics Committee of Fuwai Hospital of Chinese Academy of Medical Sciences (Tel. +86-010-88396281). Please read the instructions carefully to understand your rights and obligations in the research and to clarify the design and risks of the trial. Participation in the trial is completely voluntary and will not affect your treatment during your stay in the hospital, whether you participate in this trial or not. When the researcher explains and discusses the informed consent form to you, you can ask questions at any time.

If you are currently participating in other clinical studies, please let the researchers know.

The leader of this multicenter trial is professor Shengshou Hu (Fuwai Hospital, Chinese Academy of Medical Science), and the sponsor of this trial is the National Clinical Research Centre of Cardiovascular Diseases.

Why is this trial carried out?

The purpose of this trial is to evaluate the effect of antiplatelet therapy strategies on SVG patency and bleeding risk through long-term follow-up of patients after coronary artery bypass grafting (CABG). The antiplatelet drugs used in this trial are aspirin and Ticagrelor.
Why are you invited to participate in this trial?

Because you have coronary atherosclerotic heart disease and you need to undergo CABG surgery and antiplatelet drugs, we invite you to participate in this trial. Researchers decide whether or not to be selected according to your actual situation.

You meet the inclusion criteria of the subjects in this trial: 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.

You do not violate the exclusion criteria for subjects in this trial: 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 hemodynamic instability. 5. Patients with sick sinus syndrome, or 2nd or 3rd atrioventricular block. 6. Patients with contraindications for coronary computed tomography angiography or coronary angiography (e.g., 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 (e.g., history of bleeding diathesis within three months prior presentation, severe gastrointestinal bleeding within one year prior presentation, peptic ulcer without gastrointestinal bleeding in past three 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 six months of CABG or placement of a bare-metal stent in a coronary or cerebral artery within one month of CABG. 11. Thrombocytopenia before CABG (< 100 x 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. 13. Use of strong inhibitors of CYP3A4. 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.

**How many patients will the trial recruit?**

This trial is a multicenter clinical trial and plans to recruit 2300 subjects across the country.

**What do you need to do?**

Researchers will explain to you the background, purpose, steps, benefits and risks of the research, and ask you to sign the informed consent form. The first screening for in- and exclusion criteria is conducted before surgery. A second screening is conducted within 5 days post-surgery and only the patients who are tolerant to DAPT will be randomized. You will be randomized on postoperative day five by using by central randomization system based on interactive web response, to De-DAPT referred to as...
ticagrelor (90mg twice daily) + aspirin (100 mg once daily) during first three months after CABG, then switching to aspirin (100 mg once daily) + ticagrelor placebo (twice daily) for nine months or to DAPT group with ticagrelor (90mg twice daily) + aspirin (100 mg once daily) for one year. Patients, treating physicians and investigators are blinded to allocation. You will be evaluated at one, three, six, nine, and twelve months after CABG. Evaluation in month one is performed by telephone or through an outpatient hospital visit (patient preference). In month three, six, nine, and twelve through an outpatient hospital visit, researchers will provide you with drugs for the next cycle. and to collect the occurrence of major adverse cardiovascular events and drug compliance. In month twelve after CABG, you need to take coronary computed tomography angiography (CCTA) to evaluate SVG, which is free of charge. The project team is responsible for recruiting patients and monitoring the random grouping process, but they do not directly participate in the random process. The following medical records will be collected during hospitalization: age, sex, body mass index (BMI), aspirin resistance, surgical history, anastomosis of grafts, cardiopulmonary bypass, duration of cardiac arrest, postoperative complications, history of diabetes, history of hypertension, history of hyperlipidemia, history of chronic obstructive pulmonary disease, history of peripheral artery diseases, history of PCI, cerebrovascular accident, gastric ulcer, history of massive hemorrhage, left ventricular ejection fraction, drinking history, smoking history, creatinine clearance rate, postoperative hospital stay, total hospitalization cost.

**How long will this trial last?**
This trial is expected to last for 3 years. You will participate in this trial for one year.

**What are the risks and adverse reactions of the participants in this trial?**

Participating in this trial will not have any impact on your outpatient or hospitalization. In the follow-up, you can avoid any questions you do not want to answer. Your information will be transmitted in encrypted form and stored in the confidential database of the National Clinical Research Centre of Cardiovascular Diseases. Although there is a risk of contrast agent allergy in CCTA, according to the trial, the incidence is extremely low, and radiologists have enough experience in dealing with it. Therefore, there is no additional risk to you for such problems. Venous blood collection has the risk of hematoma or infection at the blood collection site, but such risk is extremely low, and the research doctor will provide you with timely medical treatment for such problems. The experimental drugs are aspirin and ticagrelor. Aspirin has the following side effects: upper and lower gastrointestinal discomfort, rare gastrointestinal inflammation, gastroduodenal ulcer, and very rare gastrointestinal bleeding and perforation; aspirin may increase the risk of surgery-related bleeding. The use of aspirin in this trial followed the guidelines for aspirin use in CABG perioperation and conformed to aspirin indications. Patients with severe glucose-6-phosphate dehydrogenase deficiency may have hemolytic and hemolytic skin reactions; occasional skin itching, rash, urticaria, cardiovascular and respiratory discomfort; extremely rare severe anaphylactic shock; extremely rare transient liver injury with elevated transaminase. The most common side effects of ticagrelor are increased
bruising tendency, spontaneous hematoma, bleeding quality and dyspnea, which do not affect medication. If this happens, you can contact the project team doctor at any time. The doctor will provide you with timely advice or treatment. The rare side effects of ticagrelor are hypotension, dizziness, headache, gout, and bleeding. If you have the above side effects during the trial, you can contact doctors of the trial at any time, and the doctor will provide you with timely medical treatment.

Reproductive risk

For female patients: if you are breastfeeding, pregnant, or preparing for pregnancy, you cannot participate in this trial. If you are pregnant or breastfeeding, there may be risks to you and your baby that are not yet clear. For women who are using antiplatelet drugs, there is no information on whether antiplatelet drugs are safe for breastfeeding or unborn babies.

In order to participate in this trial, you must have contraception. If you have sex, you should use contraceptive methods that are acceptable to you, doctors, and the research team. You must continue contraception until 60 days after the last administration of the experimental medication.

During the course of this trial, if you are pregnant or think it is possible to become pregnant, it is important to inform the researcher immediately. If you are pregnant, you will be discontinued and the researcher will discuss with you what you should do. Researchers will provide you with contact information for the project, and you may be asked questions about pregnancy and babies even at the end of the trial.

For male patients: participating in this trial may damage your sperm and harm the
child you conceived during the trial. This kind of damage is currently unpredictable.

Please inform your sexual partner of the risk to unborn babies. She should know that if she is pregnant, you need to inform your doctors immediately, and she should inform her doctor immediately.

**Other risks**

There may also be risks, drug interactions or adverse reactions that are currently unpredictable.

If the trial involves a questionnaire, please indicate the psychological discomfort that may be caused. For example, some questions in the questionnaire may make you feel uncomfortable, and you can refuse to answer them.

If the research involves personal privacy issues, we will explain the harm that may be caused to you, such as: if you accidentally disclose personal private information, it may adversely affect your work and life.

**What are the possible benefits of participating in this trial?**

You will not benefit directly from participating in this trial. In this trial, you will receive routine postoperative education, which will provide you with relevant knowledge and information about coronary heart disease. Using your medical information for research may help us understand the pathogenesis of the disease, promote the development of safer or more effective diagnosis and treatment, and expand new scientific knowledge.

**If you do not participate in this trial, are there any other treatment options?**

You may choose not to participate in this trial, which will not have any adverse
effect on your routine treatment. At present, according to your health situation, the conventional treatment methods include taking single antiplatelet drug, or other DAPT such as aspirin combined with clopidogrel.

Cost and compensation for participation in the trial.

The experimental medication including aspirin and ticagrelor and CCTA are free of charge in one year after CABG. The trial team provides you with a transportation subsidy to take CCTA, which is based on your tickets.

What is the treatment of research-related damage?

If you have any discomfort during the experiment, please feel free to contact the researcher and he/she will give you guidance timely. The drugs provided by the trial are approved by the State Food and Drug Administration, and the drug usage do not exceed drug indications. The trial will provide medical insurance for you, and the insurance company will give you financial compensation or compensation in the event of test-related injury or death. If a serious adverse event occurred on you as a result of this trial, the insurance company will remit the compensation by telegraphic transfer to the bank account designated by you.

Is it necessary to participate in and complete this trial?

If you want to participate in this trial, you need to read this informed consent form carefully, confirm that you fully understand the relevant issues, and then sign this informed consent form. You will not lose any legal rights conferred on you by law as a result of signing this document.

If you agree to sign this document, Fuwai Hospital will obtain your research data
free of charge.

You may withdraw from the trial at any time, which will not cause discrimination or retaliation, and the corresponding medical treatment and rights will not be affected.

If you want to withdraw from the trial, please inform the researchers to complete the relevant inspection before the withdrawal, complete the withdrawal procedures in writing. After withdrawal, the researchers will no longer continue to collect and use your medical data, but the data collected anonymously before you quit cannot be deleted or withdrawn. After quitting, you can communicate with your surgeon, who will provide you with appropriate antiplatelet treatment. If you quit and find new information related to your health and rights, we may contact you again.

**Who should I contact if I have any questions or difficulties?**

You can ask any questions to researchers about this trial at any time (Dr. Qing Chu, +86-18810919868), including any discomfort that may occur during the clinical trial.

Thank you for taking the time to read this informed consent form. If you agree to participate in this clinical trial after full consideration, we hope that you will complete this clinical trial in accordance with the requirements of the researchers. Please work with your researchers to complete and sign the last page of this document before participating in this trial.
Signature Page

I have carefully read, understood, and agreed to all the terms of this informed consent form.

I have been informed of the purpose and procedures of this clinical trial, the possible risks of the trial, research compensation, my rights and interests, etc. I have had sufficient time and opportunity to ask questions and received satisfactory answers.

I agree to participate in this trial and authorize your hospital to collect my medical data for this trial.

I promise that the information I provide is true.

I know that I can withdraw from the trial at any time without affecting the medical treatment and benefits I should receive, and that the researcher may terminate my participation in the trial at any time. I agree to participate in future research, to donate remaining samples, clinical diagnosis, research data and long-term follow-up data for future research and authorize researchers to use and process my own anonymous remaining samples and data in approved cardiovascular-related genetic and non-genetic medical research.

I agree to take part in this trial.

Signature of Patient

Date

I confirm that the information in the informed consent form has been correctly
interpreted to patient.

Signature of Researcher

Date