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# Compare the Efficacy of Different antiplatelet therapy strategy after Coronary Artery Bypass Graft Surgery: Follow-up Extension

# ( DACAB Trial: Follow-up Extension, DACAB-FE)

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| ACS | Acute Coronary Syndrome |
| AE | Adverse Event |
| CABG | Coronary Artery Bypass Graft |
| CCS | Canadian Cardiovascular Society |
| DBL | Database Lock |
| ECG | Electrocardiogram |
| FAS | Full Analysis Set |
| IEC | Independent Ethics Committee |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MSCTA | Multi-slice Computed Tomography Angiography |
| OPCAB | Off-pump Coronary Artery Bypass |
| PLATO | Platelet Inhibition and Patient Outcomes Trial |
| PI | Principal Investigator |
| PPS | Per-Protocol Set |
| SAE | Serious Adverse Event |
| UCG | Ultrasonic Cardiogram |
| TIMI | Thrombolysis in Myocardial Infarction |
| UCG | Ultrasound Cardiogram |

# 1. INTRODUCTION

## 1.1 Background

In the last 30 years, antiplatelet agents were used to prevent vein graft thrombosis after CABG.[1] Aspirin, as the standard therapy, was recommended to be long-term use to reduce post-surgery adverse events[2,3]. 2012 STS guidelines[4] and the 2016 AHA post-CABG secondary prevention guidelines[5] recommended that dual antiplatelet therapy (DAPT) should be started or continued for ACS patients receiving CABG to reduce cardiovascular adverse events, meanwhile, improve the patency rate of vascular graft in the early postoperative period. The latest 2016 ACC/AHA[6] and 2017 ESC/EACTS[7] DAPT guidelines made similar recommendations, but the level of evidence is Level C. On the other hand, for patients with stable coronary heart disease (SCAD/SIHD) receiving CABG, it is controversial on whether post-CABG DAPT can improve clinical outcomes or the patency rate of vascular graft.

DACAB trial is an open label multi-center randomized clinical trial. The patients enrolled in DACAB trial were randomly assigned to the (1) ticagrelor+aspirin (T+A) group, (2) ticagrelor(T) group and (3) aspirin (A) group. Patients were treated and followed up for 12 months. The primary endpoint was the patency rate of saphenous vein graft （SVG） after 1 year of CABG. Secondary endpoint included MACEs within 1 year after CABG. There are 500 patients were enrolled from July 2014 through November 2015 and follow-up was completed in January 2017, 168 patients in the T+A group, 166 in T group and 166 in A group. The results showed that the 1-year SVG patency rate (primary endpoint) of T+A group was 88.7% (432/487, T+A vs A, p=0.0006), the T group was 82.8% (371/485, T vs A, p=0.0962), and the A group was 76.5% (404/488). The incidence of MACE during 1 year of follow-up was 1.8% in T+A group, 2.4% in T group，and 5.4% in A group. The DACAB trial demonstrated that compared with aspirin monotherapy, the combination of ticagrelor and aspirin significantly improved 1-year SVG patency after CABG. Meanwhile, the combination of ticagrelor and aspirin therapy or ticagrelor monotherapy showed a favor trend with reducing the MACEs compared with aspirin monotherapy. The results of DACAB trial were reported in the Late Breaking Clinical Trial at the American Heart Association Annual Meeting in November 2017 and published at JAMA journal (JAMA 2018, 319[16]:1677-1686）[8,9].

Would the observed differences in SVG patency at 1 year post CAGB translate into long-term clinical benefit? This remain to be a great interest to follow up these patients. Previous studies showed that SVG patency might predict the long-term prognosis, however, results were inconsistent. Differences in sample sizes and study design might be the potential explanation for the discrepancies (Table 1). Therefore, in present study, we intend to collect and analyze the long-term data in patients who were enrolled and survived in DACAB trial. We would observe the cardiovascular outcomes in three groups at 5-year post-CABG, which would have great clinical implications.

**Table 1: Correlation between graft patency rate and long-term prognosis**

| Author, Study Type | Patient Group | Result | Comments |
|---|---|---|---|
| Lytlel[10]<br><br>Retrospective Study | 1296 patients with (723) and without (573) SVGs stenosis. At a mean follow-up of 6.9 years | A stenotic graft to the left anterior descending artery was a strong predictor of decreased survival ($p < 0.001$), decreased reoperation-free survival ($p < 0.001$), and decreased event-free survival ($p < 0.001$). | Late vein graft stenosis are more dangerous than native coronary stenosis. Late stenosis in saphenous vein grafts to the left anterior descending coronary artery predict a high rate of death and cardiac events and are an indication for reoperation. |
| Fitzgibbon GM[11]<br><br>Retrospective Study | A total of 1,388 patients underwent a first coronary artery bypass graft procedure, 234 had a second bypass procedure, and 15 had a third bypass procedure | The presence of diseased but patent grafts, particularly those with high profile lesions (>50% graft stenosis), increased reoperation morbidity and mortality. | Vein graft patency and occlusion were closely correlated with the need for reoperation and survival. |
| Halabi AR[12]<br><br>Retrospective Study | 1243 patients who underwent angiography after CABG | Our primary outcome measure was the composite of death, myocardial infarction, or repeat revascularization. Of 1,243 patients included in the analysis, 27.9% had no, 11.9% had noncritical, 20.8% had critical, and 39.3% had occlusive SVG disease. At 10 years, the corresponding adjusted composite event rates were 41.2%, 56.2%, 81.2%, and 67.1%, respectively ($p < 0.0001$). | Early vein graft failure was associated with death, MI, or revascularization. |
| Lopes RD[13]<br><br>Retrospective Study | 1829 patients who underwent coronary artery bypass graft surgery and had an angiogram performed up to 18 months after surgery | The composite of death, myocardial infarction, or revascularization occurred more frequently among patients who had any VGF compared with those who had none (adjusted hazard ratio, 1.58; 95%CI, | That SVG failure was associated with an increase in revascularization but not with death or myocardial infarction at long-term follow-up. |

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| | | 1.21–2.06; *P*=0.008).<br>This was due mainly to more frequent revascularization with no differences in death (adjusted hazard ratio, 1.04; 95% CI, 0.71–1.52; *P*=0.85) or death or myocardial infarction (adjusted hazard ratio, 1.08; 95% CI, 0.77–1.53; *P*≤0.65). | |
| Shavadia J[14]<br><br>Retrospective Study | 5,276 patients undergoing CABG surgery | A strong trend toward reduced patient survival was noted with "arterial graft failure" (arterial ± vein GF) compared to "vein graft failure only" (no arterial GF) (adjusted hazard ratio 2.2, 95% CI 0.98-5.0, P = .056). | LITA-to-LAD graft stenosis ≥70%, but SVG failure was associated with a worse long-term prognosis. |
| Yamasaki M[15]<br><br>Retrospective Study | Two hundred thirty-four patients underwent late invasive angiography after coronary artery bypass operations. The study population consists of 163 patients with thrombolysis in myocardial infarction (TIMI) 3 flow of both the RA graft and study SVGs. | MACE was higher in patients with significant graft stenosis than in patient without stenosis (10 of 28 [35.7%] versus 7 of 135 [5.2%]; p < 0.0001). | The incidence of adverse clinical events and need for revascularization were significantly higher in patients with graft stenosis. |

## 1.2 Study Purpose

This study is designed to compare the clinical outcomes of the subjects enrolled in the DACAB trial 5 years after CABG (randomization).

# 2. STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective is to compare the incidence of major adverse clinical events-4 (MACE-4, a composite of all-cause death, myocardial infarction, stroke, and coronary revascularization) among 3 randomized regimens (T+A, T alone, A alone) in previous DACAB trial in the extended five-year follow-up after CABG.

## 2.2 Secondary Objectives

The secondary objectives are to compare the incidence of MACE-5 (a composite of all-cause death, myocardial infarction, stroke, coronary revascularization and hospitalization for unstable angina); MACE-3 (a composite of cardiovascular death, myocardial infarction and stroke); all-cause death; cardiovascular death; myocardial infarction; stroke; coronary revascularization; hospitalization for unstable angina and graft failure among 3 randomized regimens in previous DACAB trial in the five-year follow-up after CABG.

## 2.3 Exploratory Objectives

According to the imaging examination results of graft vessels at 1 year after surgery, all subjects were divided into two natural cohorts with or without graft failure. Similarly, all subjects were divided into two natural cohorts with or without vein graft failure.

The exploratory objectives are to compare the incidence of MACE-4; MACE-5; MACE-3; all-cause death; cardiovascular death; myocardial infarction; stroke; coronary revascularization and hospitalization for unstable angina between the two cohorts with or without graft/vein graft failure at one-year angiographic follow-up.

Planned exploratory subgroup analysis consists of gender, age stratification, ACS presentation, hypertension, diabetes mellitus, history of high low-density lipoprotein cholesterol (LDL-C), history of high lipoprotein(a), prior myocardial infraction, stroke, peripheral vascular disease, COPD, history of CKD-3 or higher, smoking, left main coronary artery disease, SYNTAX Score stratification, EuroScore stratification at baseline, on-pump or off-pump, whether to use the internal thoracic artery, complete revascularization or not.

# 3. STUDY PLAN AND PROCEDURES

## 3.1 Overall Study Design and Flow Chart

This study will include the subjects who enrolled in DACAB trial to compare clinical outcomes 5 years after CABG. After completing 12-month randomized treatment from DACAB trial, investigators would not make any interventions or impact on subjects' therapeutic strategy.

Aspirin monotherapy would be given to most subjects according to the current guidelines. However, other antiplatelet regimens might be given for subjects by their attending physician based on the subject's individual condition. Subjects would spontaneously undergo regular laboratory test such as biochemical parameters, ECG, UCG, coronary computed tomography angiography imaging (CCTA) or coronary angiography (CAG) and clinical follow-up according to clinical need and their individual condition. At 5-year (± 3 month) after CABG, a face-to-face visit is scheduled to be performed to collect the occurrence of clinical events, including types and time of events. The first 5-year visit would be performed around August 2019.

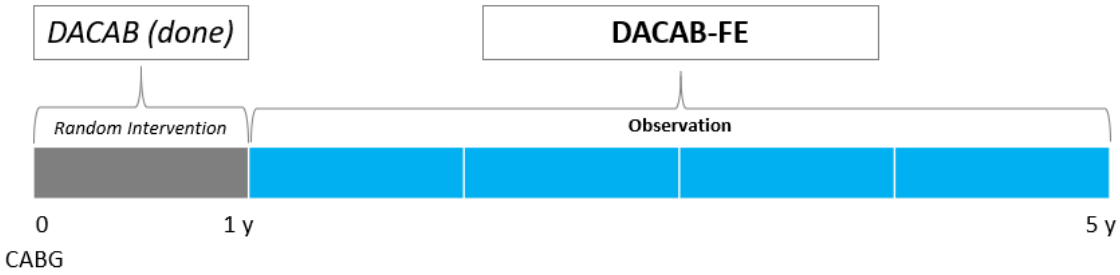


**Figure 1: Schematic Overview of the Study**

### 3.2 Rationale for Study Design, Doses and Control Groups

This study is a non-interventional, observational study. The follow-up data of subjects will be collected at 5-year after CABG.

## 4. SUBJECT SELECTION CRITERIA

### 4.1 Inclusion / Exclusion Criteria

All the subjects enrolled in the DACAB trial.

## 5. COLLECTION OF STUDY VARIABLES

### 5.1 Recording of Data

The investigator will ensure that the data is recorded on the paper form of Case Report Forms (CRF) as specified in the study protocol and in accordance with the instructions provided.

General information such as subject's age and gender, medical history should be recorded. Medical record and laboratory test, such as biochemical parameters (cardiac troponin, brain natriuretic peptide, etc.), ECG, UCG, CT/MRI, coronary CTA or coronary angiography related to the end points of this study will be collected and recorded to assist in the determination of endpoint events.

The investigator ensures the accuracy, completeness, and legibility of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed paper CRF. A copy of the completed paper CRF will be archived at the study site.

## 5.2 Data Collection at 5-year Visit

The data of subjects will be collected at the visit at 5-year (± 3 month) after CABG. The collected data includes: vital signs; current medications; types and time of events; original medical record and laboratory test results related to clinical events. For deceased patients, the death and cause of death will be determined by telephone interview with their relatives firstly. The related medical records would be acquired from their relatives to further determination the cause of death, if available. Electronic medical records would be approached under relatives' permission. Determination of graft patency will be determined from medical records. Original images of coronary CTA or coronary angiography will be acquired and re-assessment.

## 5.3 Outcome Measures

### 5.3.1 Primary Outcome Measure

The primary outcome is MACE-4, defined as a composite of all-cause death, myocardial infarction, stroke and coronary revascularization. The outcome measure is the time to the first occurrence of MACE-4 event from randomization to the last visit.

### 5.3.2 Secondary Outcome Measures

Including:

1) MACE-5, defined as a composite of all-cause death, myocardial infarction, stroke, coronary revascularization and hospitalization for unstable angina. The outcome measure is the time to the first occurrence of MACE-5 event from randomization to the last visit.

2) MACE-3, defined as a composite of cardiovascular death, myocardial infarction and stroke. The outcome measure is the time to the first occurrence of MACE-3 event from randomization to the last visit.

3) All-cause death. The outcome measure is the time to the first occurrence of all-cause death from randomization to the last visit.

4) Cardiovascular death. All "undetermined death" will be assumed as "cardiovascular death". The outcome measure is the time to the first occurrence of cardiovascular death from randomization to the last visit.

5) Myocardial infarction, including STEMI, NSTEMI, or silent/unrecognized MI (eg. new pathological Q waves detected by ECG, or new reduced ventricular wall motion detected by UCG during follow-up). The outcome measure is the time to the first myocardial infarction from randomization to the last visit.

6) Stroke, including ischemic, hemorrhagic, or unknown type. The outcome measure is the time to the first stroke from randomization to the last visit.

7) Coronary revascularization, any repeated PCI or CABG, no matter ischemic driven or not. The outcome measure is the time to the first coronary revascularization from randomization to the last visit.

8) Hospitalization for unstable angina. The outcome measure is the time to the first hospitalization for unstable angina from randomization to the last visit.

9) Graft failure/vein graft failure at the last visit (Fitzgibbon Grade B/O assessed by CCTA or CAG). The outcome measure is the incidence of graft failure/vein graft failure.

## 5.4 Safety

The primary and secondary efficacy outcomes and measures serve as the primary and secondary safety outcomes and measures. Other safety outcome measures include other serious adverse events resulting in hospitalization or emergency visits.

### 5.4.1 Adverse Events Collection Reports

The present study is a non-interventional, observational study without specific Astrazeneca drug during 1 to 5 year after CABG. Actively collection of all AEs is not required. However, ADR related to Astrazeneca drugs will be spontaneously reported to Astrazeneca Patient Safety according to local regulation-Order 81. Astrazeneca Patient Safety contact information: Fax: +86 21 38683551; E-mail: China.AZDrugSafety@astrazeneca.com; Tel: +86 21 52929866，+86 21 58385073 (Emergency).

### 5.4.2 Severe Adverse Events Collection Reports

In addition to the primary and secondary outcome events, the present study also collect other severe adverse events resulting in hospitalization or emergency visits, which includes cardiac insufficiency, heart failure; arrhythmias, such as atrial fibrillation, atrial flutter, and supraventricular tachycardia; other thrombotic events, such as pulmonary embolism, deep venous thrombosis; neurological diseases, such as Alzheimer's disease, dizziness and vertigo (excluding stroke), tumors; respiratory system diseases, such as pulmonary infection, acute onset of COPD; digestive system diseases, such as gastrointestinal bleeding, tumors; urinary system diseases, such as renal insufficiency, hemodialysis, urinary tract infections, tumors; endocrine system diseases, such as diabetes, tumors; hematological system diseases, such as anemia, tumors; musculoskeletal system diseases, such as fractures, cervical and lumbar diseases, tumors; other unclassified reasons, such as social factors. Physical examination needs do not fall into this category.

# 6. ETHICAL AND REGULATORY REQUIREMENTS

## 6.1 Ethical Conduct of The Study

The final study of this study will be implemented after and under the supervision of the ethics committee/institutional review board (IRB)/independent ethics committee (IEC).

## 6.2 Ethics and Regulatory Review

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to subject participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH GCP, Chinese GCP and to the regulatory and legal requirements of the participating country. The informed consent and any additional subject information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his/her personal trial-related data will be used by principle investigator in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his / her medical records may be examined by authorized monitors (CRA) or Clinical Quality Assurance auditors, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

## 6.3 Informed Consent

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

- Ensure each subject is notified that they are free to discontinue from the study at any time

- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed Informed Consent Form is given to the subject

- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

## 6.4 Changes to The Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the National Co-ordinating Investigator and Sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment should be approved by each Ethics Committee before implementation. Local requirements should be followed for revised protocols.

Sponsor will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s).

If a protocol amendment requires a change to a center's Informed Consent Form, Sponsor and the center's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

## 6.5 Audits and Inspections

Authorized representatives of Ruijin Hospital, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

# 7. STUDY MANAGEMENT

## 7.1 Training of Study Site Personnel

The PI should ensure adequate training and updated information or notifications have been delivered to study relevant personnel including physicians and nurses.

## 7.2 Study Monitoring

### 7.2.1 Source Data

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For CRFs, all data must be derived from source documents.

### 7.2.2 Use and Completion of CRF

It is the responsibility of the Investigator to maintain adequate and accurate CRF designed by the study team to record all study data in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to study team as soon as they are entered in the CRF.

### 7.2.3 Record Retention in Study Sites

The Investigator must maintain confidential all study documentation and take measures to prevent accidental or premature destruction of these documents.

### 7.2.4 Data Protection

The subject's personal data, which are included in the study database shall be treated in compliance with all applicable laws and regulations. Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party when archiving or processing personal data pertaining to the subjects.

## 7.3 Potential Biases Controlling

The 5-year after CABG visit (on site) will be in person by a trained site coordinator and CRC. Original materials such as medical record and laboratory test results would be asked to provide for endpoint assessment. All potential endpoint events（including all-cause death, cardiovascular death, non-fatal MI, non-fatal stroke, repeated coronary revascularization）will be adjudicated by an independent Clinical Endpoint Committee (CEC) according to the 2014 ACC/AHA Cardiovascular Endpoints Data Standards. Original coronary artery imagine would

be acquired if available. All grafts outcomes will be adjudicated by an independent Image Data Review Committee (IDRC) according to the DACAB protocol.

## 7.4 Study Timetable and End of Study

- Protocol Approved: Dec2018
- First 5-year Visit: Aug2019
- Last 5-year Visit: Dec2020
- DBL: Jun2021
- CSR: Sep2021
- Publication: Dec2021

The first 5-year visit in this study is expected in Aug 2019, while the last is in Dec 2020. Database Lock will be about 6 months after the last 5-year visit. Clinical study report is planned to be finalized in Sep 2021.

# 8. EVALUATION AND CALCULATION OF ENDPOINTS

## 8.1 Calculation or Derivation of Clinical Outcomes

The primary outcome is the time to the first occurrence of any MACE-4, which is a composite of all-cause death, myocardial infarction, stroke, and coronary revascularization and measured in days since the date of randomization. Subjects who had not experienced any major adverse clinical events from randomization to the last visit will be right-censored. For those subjects who lost to follow-up at 5-year visit, the date of the last contact and the most updated clinical outcomes available in medical record or other source will be used in primary analysis. If there's no major adverse clinical events recorded for those subjects who lost to follow-up at 5-year visit, then these subjects will be right-censored at the date of their last contact. The survival curves will be estimated using Kaplan-Meier method.

The secondary outcomes (time to event) will be analyzed similarly with the primary observational endpoint.

Graft failure after CABG is in accordance with Fitzgibbon classification criteria by using MSCTA or CAG, there were a total of 3 categories, grade A, B and O, where grade B/O accounted for the graft failure.

# 9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

## 9.1 Description of Analysis Sets

Subjects will be analyzed per the randomized treatment groups they were assigned to in the previous DACAB study.

### 9.1.1 Full Analysis Set

The Full Analysis Set (FAS) in current study is same as FAS in DACAB trial.

### 9.1.2 Per-protocol Set

Per-protocol set (PPS) is defined as all subjects in the FAS with exclusion of the following subjects:

- Subject discontinued the application of study drug longer than 60 days during the treatment phase in the previous DACAB study

PPS will only be used in the analysis of primary observational endpoint. The analysis using the FAS will be regarded as primary while the analysis based on PPS will act as supportive.

## 9.2 Methods of Statistical Analyses

### 9.2.1 General Method of Analysis

Descriptive summary statistics, such as number of subjects, mean, SD, median, IQR, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize data. Summary statistics will be provided for each group in previous DACAB study.

The correlations between the observational endpoints (both primary and secondary) and the characteristics of subjects will be explored, the characteristics of subject include age, gender, medical history, etc.

The missing data will be assumed missing at random, no imputation will be applied unless specified otherwise.

The detailed statistical methods applied in analyses will be provided in Statistical Analysis Plan.

### 9.2.2 Demographics and Baseline Characteristics

Demographic and baseline characteristic variables will be descriptively summarized by the group in previous DACAB study.

### 9.2.3 Primary Outcome Measure

Kaplan-Meier method will be applied to analyze the primary outcome (MACE-4), and the rate of subjects who has the first MACE-4 occurred within 1, or 2, or 3, or 4, or 5 years after CABG will be provided.

### 9.2.4 Secondary Outcome Measures

The time to event variables in the secondary outcomes will be analyzed similarly with the primary outcome.

As 1-4 vessels were generally measured in each subject, the vein graft patency at 5 years after CABG is a categorical data measured repeatedly in subjects. The number and the percentage of the grafts in Fitzgibbon grade B/O will be summarized by the group in previous DACAB study.

## 9.3 Determination of Sample Size

A total of 500 subjects were randomized in DACAB study (ticagrelor + aspirin, 168; ticagrelor alone, 166; aspirin alone, 166). There are 5 subjects died before 12-month visit, of these, 2 died in ticagrelor + aspirin group, and 3 died in aspirin alone group. Therefore, 495 patients would be scheduled for 5-year on-site visit.

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