Statistical Analysis Plan

DACAB Trial: Follow-up Extension

(DACAB-FE)

NCT03987373

V 1.0 (2021/6/5)

Wei Zhang, Doctor
Senior Statistician
Department of Biostatistics
School of Public Health
Fudan University

Date

Table of Contents

1. Background

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.

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. 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 clinical outcomes of these subjects at 5-year post-CABG.

2. Study Objectives

• 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 in previous DACAB trial in the extended five-year follow-up after CABG.

• 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.

• Exploratory Objectives

According to the imaging examination results of graft vessels at 1 year after surgery, all subjects will be divided into two natural cohorts with or without graft failure. The incidence of MACE-4, MACE-5, MACE-3, all-cause death, cardiovascular death, myocardial infarction, stroke, coronary revascularization and hospitalization for unstable angina will be compared between the two cohorts .

Similarly, all subjects will be divided into two natural cohorts with or without vein graft failure. The incidence of MACE-4, MACE-5, MACE-3, all-cause death,

cardiovascular death, myocardial infarction, stroke, coronary revascularization and hospitalization for unstable angina will be compared between the two cohorts.

The factors of planned 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.

In addition to subgroup analysis according to random grouping, the subjects will also be divided into corresponding natural cohorts according to different levels of subgroups, and the incidence of MACE-4, MACE-5, MACE-3, all-cause death, cardiovascular death, myocardial infarction, stroke, coronary revascularization and hospitalization for unstable angina will be compared between the cohorts.

3. Study Design

The primary objective of this study is to observe the clinical outcomes of subjects at 5-year post-CABG. The DACAB study was designed as a multi-center, prospective, open label, evaluator blind, randomized controlled trial.

4. Evaluation Indicators

4.1 Primary Outcome

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.

4.2 Secondary Outcome

- 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;
- 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;
- All-cause death. The outcome measure is the time to the first occurrence of all-cause death from randomization to the last visit;
- Cardiovascular death. The outcome measure is the time to the first occurrence of cardiovascular death from randomization to the last visit;
- Myocardial infarction. The outcome measure is the time to the first myocardial infarction from randomization to the last visit;
- Stroke. The outcome measure is the time to the first stroke from randomization to the last visit;
- Coronary revascularization. The outcome measure is the time to the first coronary revascularization from randomization to the last visit.;

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

4.3 Evaluation and Calculation of Endpoints

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 A accounted for graft patency (no lesions), and grade B/O accounted for the graft failure.

5. Subject Selection Criteria

All the subjects enrolled in the DACAB trial.

6. Statistical Analysis

6.1 Analysis Sets

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

6.1.1 Full Analysis Set (FAS)

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

6.1.2 Per-protocol Set (PPS)

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.

6.2 Methods of Statistical Analyses

6.2.1 General Method of Analysis

Counts and percentages for discrete variables, and mean, SD, maximum, minimum, median, 25^{th} percentiles and 75^{th} percentiles for continuous

variables will be used to summarize data.

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

A 2-sided level of significance of .05 will be applied to all statistical analyses unless specified otherwise. Statistical analyses will be performed using SAS 9.4.

6.2.2 Demographics and Baseline Characteristics

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

6.2.3 Primary Outcome

Kaplan-Meier will be used to estimate survival curves, and calculate the incidence of major adverse clinical events-4 (MACE4) for each year during the follow-up period. Log-rank test will be used to compare the differences between survival curves. COX regression model will be used to estimate hazard ratios and its 95% confidence intervals.

6.2.4 Secondary Outcome

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. GEE (Generalized Estimating Equations) was used to compare the subjects' saphenous vein graft patency rate among groups.

6.2.5 Laboratory Indicators

The results of laboratory indicators will be descriptively summarized by the group.

6.2.6 Bleeding Events

Descriptive statistical analysis will be applied to bleeding events including cerebral hemorrhage and massive gastrointestinal hemorrhage associated with antiplatelet therapy.

6.2.7 Safety Events

All safety events in this study will be listed.

6.2.8 Concomitant medications

All concomitant medications in this study will be listed.

6.2.9 Graft vessels cohorts

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. First, baseline characteristics will be compared between the two cohorts. X^2 test or Fisher's exact probability method are used to compare dichotomous data, CMH X^2 test is used to compare polytomous data; t test, ANOVA or non-parametric test are used to compare continuous data. Then, GLM method will be used to compare different outcomes after adjusting for potential confounding factors.

The outcomes of two cohorts with or without vein graft failure will be analyzed similarly with the graft failure cohort.

6.2.10 Subgroup analysis and exploratory analysis on subgroup cohorts

Based on random grouping, planned subgroup analysis will be performed

on 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.

Multivariable analysis, including GLM and propensity score methods, will be applied to exploratory analysis on subgroup cohorts.

6.2.11 Data Transformation

Date transformation rules are as follows:

1 year = 365.25 days

1 month = 30.4375 days

6.3 Sample Size

A total of 500 subjects were randomized in DACAB study (ticagrelor + aspirin, 168; ticagrelor alone, 166; aspirin alone, 166). There were 5 subjects died before 12-month visit, of these, 2 died in ticagrelor + aspirin group, and 3 died in aspirin alone group.

7. Results of Statistical Analysis

7.1 Primary and secondary objectives

7.1.1 Enrollment and Baseline characteristics

Table 1 Analysis sets

Center	ITT				FAS				PPS			
	A	A+T	T	Total	A	A+T	T	Total	A	A+T	T	Total
1												
2												
3												
4												
5												
Total												

Table 2 Subjects not included in PPS

Random number	Group

Reason: Subjects in the DACAB study who stopped the study drug for more than 60 days.

Table 3 Demographic and baseline characteristics (FAS)

Indicator	*A*	*T+A*	*T*	*P*
Age				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Sex				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Male	*** (***)	*** (***)	*** (***)	
Female	*** (***)	*** (***)	*** (***)	
Height				
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Weight				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
BMI				0.***

Indicator	*A*	*T+A*	*T*	*P*
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Clinical status				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Stable angina	*** (***)	*** (***)	*** (***)	
Unstable angina	*** (***)	*** (***)	*** (***)	
Non – ST-elevation myocardial infarction	*** (***)	*** (***)	*** (***)	
History of myocardial infarction				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
Time since onset of myocardial infarction (day)				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
<21	*** (***)	*** (***)	*** (***)	
21-90	*** (***)	*** (***)	*** (***)	
>90	*** (***)	*** (***)	*** (***)	
CCS class				0.***

Indicator	*A*	*T+A*	*T*	*P*
N(missing)	*** (***)	*** (***)	*** (***)	
0	*** (***)	*** (***)	*** (***)	
I	*** (***)	*** (***)	*** (***)	
II	*** (***)	*** (***)	*** (***)	
III	*** (***)	*** (***)	*** (***)	
IV	*** (***)	*** (***)	*** (***)	
NYHA class				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
I	*** (***)	*** (***)	*** (***)	
II	*** (***)	*** (***)	*** (***)	
III	*** (***)	*** (***)	*** (***)	
IV	*** (***)	*** (***)	*** (***)	
History of hypertension				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of hyperlipidemia				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of smoking				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	

Indicator	*A*	*T+A*	*T*	*P*
No	*** (***)	*** (***)	*** (***)	
History of diabetes				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of peripheral vascular disease				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of cerebrovascular accident				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of peptic ulcer disease				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of chronic kidney disease				0.***
N(missing)	*** (***)	*** (***)	*** (***)	

Indicator	*A*	*T+A*	*T*	*P*
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
LVEDD(mm)				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
LVEF(%)				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
LVEF class				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
30%-50%	*** (***)	*** (***)	*** (***)	
>50%	*** (***)	*** (***)	*** (***)	
SYNTAX score				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Low(0-22)	*** (***)	*** (***)	*** (***)	
Intermediate(23-32)	*** (***)	*** (***)	*** (***)	
High(>=33)	*** (***)	*** (***)	*** (***)	
EuroScore score				0.***

Indicator	*A*	*T+A*	*T*	*P*
N(missing)	*** (***)	*** (***)	*** (***)	
Low(0-2)	*** (***)	*** (***)	*** (***)	
Medium(3-5)	*** (***)	*** (***)	*** (***)	
High(>=6)	*** (***)	*** (***)	*** (***)	
Aspirin				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
beta_Blocker				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
ACEI or ARB				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
Statins				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
Proton pump inhibitor				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	

Indicator	*A*	*T+A*	*T*	*P*
No	*** (***)	*** (***)	*** (***)	
Cardiopulmonary bypass usage				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
Total grafts	***	***	***	
Graft type				
- LIMA	*** (***)	*** (***)	*** (***)	
- RA	*** (***)	*** (***)	*** (***)	
- SVG	*** (***)	*** (***)	*** (***)	
Mean total grafts/case	***	***	***	
Mean SVG/case	***	***	***	

Table 4 Baseline laboratory examinations (FAS)

Indicator	*A*	*T+A*	*T*	*P*
Glycosylated hemoglobin				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Low density lipoprotein				
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Ditto for other laboratory examination indicators				

7.1.2 Primary Outcome

Table 5 Occurrence of MACE4 during follow-up (FAS)

		Event rate during follow-up				
Group	*Overall occurrence of the event*	*12 months*	*24 months*	*36 months*	*48 months*	*60 months*
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%

Note: Overall occurrence of the event includes all the events during the follow-up period, KM was used to estimate the event rates in different visit.

Table 6 Survival Analysis for MACE4 event during follow-up (FAS)

Group	*HR(95% CI)*	*Logrank P*
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****

Figure 1. Kaplan-Meier curves of MACE4 during the follow-up (FAS)

Table 7 Occurrence of MACE4 during follow-up (PP)

		Event rate during follow-up				
Group	*Overall occurrence of the event*	*12 months*	*24 months*	*36 months*	*48 months*	*60 months*
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%

Note: Overall occurrence of the event includes all the events during the follow-up period, KM was used to estimate the event rates in different visit.

Table 8 Survival Analysis for MACE4 event during follow-up (PP)

Group	*HR(95% CI)*	*Logrank P*
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****

Figure 2. Kaplan-Meier curves of MACE4 during the follow-up (PP)

7.1.3 Secondary Outcomes

Table 9 Occurrence of secondary outcomes during the follow-up (FAS)

		Event rate during follow-up				
Indicator/Group	*Overall occurrence of the event*	*12 months*	*24 months*	*36 months*	*48 months*	*60 months*
MACE5						
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%
MACE3						
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%
All-cause death						
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%
Cardiovascular death						
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%

		Event rate during follow-up				
Indicator/Group	*Overall occurrence of the event*	*12 months*	*24 months*	*36 months*	*48 months*	*60 months*
Myocardial infarction						
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%
Stroke						
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%
Coronary revascularization						
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%
Hospitalization for unstable angina						
A	*** (***)	**%	**%	**%	**%	**%
T+A	*** (***)	**%	**%	**%	**%	**%
T	*** (***)	**%	**%	**%	**%	**%

Note: Overall occurrence of the event includes all the events during the follow-up period, KM was used to estimate the event rates in different visit.

Table10 Survival analysis for secondary outcomes during follow-up (FAS)

Indicator/Group	*HR(95% CI)*	*Logrank P*
MACE5		
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****
MACE3		
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****
All-cause death		
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****
Cardiovascular death		
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****
Myocardial infarction		
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****
Stroke		

Indicator/Group	*HR(95% CI)*	*Logrank P*
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****
Coronary revascularization		
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****
Hospitalization for unstable angina		
T+A VS. A	*** (***,***)	0. ****
T VS. A	*** (***,***)	0. ****
T+A VS. T	*** (***,***)	0. ****

Table 11 Grafts during follow-up (FAS)

Indicator	*A*	*T+A*	*T*	*P*
CTA/CAG visit time (month)				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Reexamination situation of grafts				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Examined	*** (***)	*** (***)	*** (***)	
Not examined	*** (***)	*** (***)	*** (***)	

Table 12 Patency of different grafts (FAS)

	LIMA	*SVG*	*RA*	*Total*
7 days after surgery				
Patency (A)	***	***	***	***
Failure (O/B)	**	**	**	**
Patency rate	***%	***%	***%	***%
7 days-1 month after surgery				
Patency (A)	***	***	***	***
Failure (O/B)	**	**	**	**
Patency rate	***%	***%	***%	***%
1 month-1 year after surgery				
Patency (A)	***	***	***	***
Failure (O/B)	**	**	**	**
Patency rate	***%	***%	***%	***%
1 year-5 years after surgery				
Patency (A)	***	***	***	***
Failure (O/B)	**	**	**	**
Patency rate	***%	***%	***%	***%

Table 13 Comparison of graft patency rates in different treatment group (using grafts as subjects)

	Patency rate(95%CI]			*A+T VS. A*			*T VS. A*			*A+T VS. T*		
	A	*A+T*	*T*	*Rate difference (95%CI)*	*RR(95%CI)*	*p*	*Rate difference (95%CI)*	*RR(95%CI)*	*p*	*Rate difference (95%CI)*	*RR(95%CI)*	*p*
Total grafts	***	***	***									
Patency rate 7 days after surgery	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***
Patency rate 7 days-1 month after surgery	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***
Patency rate 1 month-1 year after surgery	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***
Patency rate 1-5 years after surgery	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***
Saphenous vein graft	***	***	***									

	Patency rate(95%CI]			*A+T VS. A*			*T VS. A*			*A+T VS. T*		
	A	*A+T*	*T*	*Rate difference (95%CI)*	*RR(95%CI)*	*p*	*Rate difference (95%CI)*	*RR(95%CI)*	*p*	*Rate difference (95%CI)*	*RR(95%CI)*	*p*
Patency rate 1-5 years after surgery	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***	***% (***% to ***%)	0.** (0.** to 0.**)	0.***

Note: rate difference, RR and p value were estimated by GEE.

7.1.4 Laboratory examination during follow-up

Table 14 Laboratory examinations during follow-up (FAS)

Indicator	A	T+A	T	P
Glycosylated hemoglobin				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Low density lipoprotein				
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Ditto for other laboratory examination indicators				

7.1.5 Concomitant medications and bleeding events

Table 15 Concomitant medications during follow-up

Indicator	*A*	*T+A*	*T*	*P*
Drug1				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Use	*** (***)	*** (***)	*** (***)	
Not use	*** (***)	*** (***)	*** (***)	
Drug2				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Use	*** (***)	*** (***)	*** (***)	
Not use	*** (***)	*** (***)	*** (***)	
Ditto for other drugs				

Table 16 Bleeding events during follow-up

Indicator	*A*	*T+A*	*T*	*P*
Cerebral hemorrhage				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Occur	*** (***)	*** (***)	*** (***)	
Not occur	*** (***)	*** (***)	*** (***)	
Massive gastrointestinal hemorrhage				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Occure	*** (***)	*** (***)	*** (***)	
Not occur	*** (***)	*** (***)	*** (***)	

7.1.6 Subgroup analysis

Table 17 Subgroup analysis(MACE4 events)

Subgroup factor	A+T VS. A			T VS. A			A+T VS. T		
	HR(95%CI)	P	Interaction P	HR(95%CI)	P	Interaction P	HR(95%CI)	P	Interacion P
Age									
<=65 years old									
>65 year old									
Sex									
Male									
Female									
Baseline ACS									
Yes									
No									
History of hypertension									
Yes									
No									
History of diabetes									
Yes									
No									
History of dyslipidemia									
Yes									
No									
History of smoking									
Yes									
No									
Baseline SYNTAX score									

<=22

23-32

>=33

Ditto for other

subgroups

表 18 Subgroup analysis(MACE5)

Note: The format is the same as Table 17.

表 19 Subgroup analysis(MACE3)

Note: The format is the same as Table 17.

表 20 Subgroup analysis(All-cause death)

Note: The format is the same as Table 17.

表 21 Subgroup analysis(Cardiovascular death)

Note: The format is the same as Table 17.

表 22 Subgroup analysis(Myocardial infarction)

Note: The format is the same as Table 17.

表 23 Subgroup analysis(Stroke)

Note: The format is the same as Table 17.

表 24 Subgroup analysis(Coronary revascularization)

Note: The format is the same as Table 17.

表 25 Subgroup analysis(Hospitalization for unstable angina)

Note: The format is the same as Table 17.

7.2 Exploratory Objectives

7.2.1 Baseline characteristics

Table 26 Demographic and baseline characteristics (grouped by total grafts failure at 1 year)

Indicator	*Overall*	*Patency*	*Failure*	*P*
Age				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Sex				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Male	*** (***)	*** (***)	*** (***)	
Female	*** (***)	*** (***)	*** (***)	
Height				
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Weight				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	

Indicator	*Overall*	*Patency*	*Failure*	*P*
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
BMI				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
Clinical status				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Stable angina	*** (***)	*** (***)	*** (***)	
Unstable angina	*** (***)	*** (***)	*** (***)	
Non – ST-elevation myocardial infarction	*** (***)	*** (***)	*** (***)	
History of myocardial infarction				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
Time since onset of myocardial infarction (day)				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
<21	*** (***)	*** (***)	*** (***)	
21-90	*** (***)	*** (***)	*** (***)	

Indicator	*Overall*	*Patency*	*Failure*	*P*
>90	*** (***)	*** (***)	*** (***)	
CCS class				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
0	*** (***)	*** (***)	*** (***)	
I	*** (***)	*** (***)	*** (***)	
II	*** (***)	*** (***)	*** (***)	
III	*** (***)	*** (***)	*** (***)	
IV	*** (***)	*** (***)	*** (***)	
NYHA class				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
I	*** (***)	*** (***)	*** (***)	
II	*** (***)	*** (***)	*** (***)	
III	*** (***)	*** (***)	*** (***)	
IV	*** (***)	*** (***)	*** (***)	
History of hypertension				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of hyperlipidemia				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of smoking				0.***

Indicator	*Overall*	*Patency*	*Failure*	*P*
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of diabetes				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of peripheral vascular disease				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of cerebrovascular accident				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of peptic ulcer disease				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
History of chronic kidney disease				0.***
N(missing)	*** (***)	*** (***)	*** (***)	

Indicator	*Overall*	*Patency*	*Failure*	*P*
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	
LVEDD(mm)				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
LVEF(%)				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
mean(sd)	*** (***)	*** (***)	*** (***)	
median	***	***	***	
Min-Max	***~***	***~***	***~***	
p25-p75	***~***	***~***	***~***	
LVEF class				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
30%-50%	*** (***)	*** (***)	*** (***)	
>50%	*** (***)	*** (***)	*** (***)	
SYNTAX score				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Low(0-22)	*** (***)	*** (***)	*** (***)	
Intermediate(23-32)	*** (***)	*** (***)	*** (***)	
High(>=33)	*** (***)	*** (***)	*** (***)	
EuroScore score				0.***

Indicator	*Overall*	*Patency*	*Failure*	*P*
N(missing)	*** (***)	*** (***)	*** (***)	
Low(0-2)	*** (***)	*** (***)	*** (***)	
Medium(3-5)	*** (***)	*** (***)	*** (***)	
High(>=6)	*** (***)	*** (***)	*** (***)	
Aspirin				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Use	*** (***)	*** (***)	*** (***)	
Not use	*** (***)	*** (***)	*** (***)	
beta_Blocker				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Use	*** (***)	*** (***)	*** (***)	
Not use	*** (***)	*** (***)	*** (***)	
ACEI or ARB				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Use	*** (***)	*** (***)	*** (***)	
Not use	*** (***)	*** (***)	*** (***)	
Statins				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Use	*** (***)	*** (***)	*** (***)	
Not use	*** (***)	*** (***)	*** (***)	
Proton pump inhibitor				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Use	*** (***)	*** (***)	*** (***)	

Indicator	*Overall*	*Patency*	*Failure*	*P*
Not use	*** (***)	*** (***)	*** (***)	
Cardiopulmonary bypass usage				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Yes	*** (***)	*** (***)	*** (***)	
No	*** (***)	*** (***)	*** (***)	

Table 27 Demographic and baseline characteristics (grouped by saphenous vein grafts failure at 1 year)

Note: Same as table 26, grouped only according to saphenous vein grafts failure at 1 year.

7.2.2 Major clinical events

Table 28 Occurrence of clinical events during the follow-up (grouped by total grafts failure at 1 year)

		Event rate 2-5 years during follow-up			
Indicator/Group	*Overall occurrence of the event*	*24 months*	*36 months*	*48 months*	*60 months*
MACE4					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%
MACE5					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%
MACE3					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%
All-cause death					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%
Cardiovascular death					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%

		Event rate 2-5 years during follow-up			
Indicator/Group	*Overall occurrence of the event*	*24 months*	*36 months*	*48 months*	*60 months*
Myocardial infarction					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%
Non-silent MI					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%
Stroke					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%
Coronary revascularization					
Patency	*** (***)	**%	**%	**%	**%
Failure	*** (***)	**%	**%	**%	**%

Table 29 Survival analysis for clinical events (grouped by total grafts failure at 1 year)

Indicator/Group	*HR(95% CI)*	*Adjusted P*
MACE4		
Failure VS. Patency	*** (***,***)	0. ****
MACE5		
Failure VS. Patency	*** (***,***)	0. ****
MACE3		
Failure VS. Patency	*** (***,***)	0. ****
All-cause death		
Failure VS. Patency	*** (***,***)	0. ****
Cardiovascular death		
Failure VS. Patency	*** (***,***)	0. ****
Myocardial infarction		
Failure VS. Patency	*** (***,***)	0. ****
Non-silent MI		
Failure VS. Patency	*** (***,***)	0. ****
Stroke		
Failure VS. Patency	*** (***,***)	0. ****
Coronary revascularization		
Failure VS. Patency	*** (***,***)	0. ****

Table 30 Occurrence of clinical events (grouped by saphenous vein grafts failure at 1 year)

Note: same as table 28, grouped only according to saphenous vein grafts failure at 1 year.

Table 31 Survival analysis for clinical events (grouped by saphenous vein grafts failure at 1 year)

Note: same as table 29, grouped only according to saphenous vein grafts failure at 1 year.

Table 32 Grafts patency during 1-5 years follow-up

Indicator	*Overall*	*Patency (A)*	*Failure (O/B)*	*Adjusted P*
Total grafts at 1 year				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Patency (A)	*** (***)	*** (***)	*** (***)	
Failure (O/B)	*** (***)	*** (***)	*** (***)	
Saphenous vein grafts at 1 year				0.***
N(missing)	*** (***)	*** (***)	*** (***)	
Patency (A)	*** (***)	*** (***)	*** (***)	
Failure (O/B)	*** (***)	*** (***)	*** (***)	

7.3 Supplementary tables

Table 33 List of safety events

Table 34 List of concomitant medications