Antiplatelet therapy after coronary artery bypass surgery: five year follow-up of randomised DACAB trial

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ABSTRACT

OBJECTIVE

To assess the effect of different antiplatelet strategies on clinical outcomes after coronary artery bypass grafting.

DESIGN

Five year follow-up of randomised Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Grafting (DACAB) trial.

SETTING

Six tertiary hospitals in China; enrolment between July 2014 and November 2015; completion of five year follow-up from August 2019 to June 2021.

PARTICIPANTS

500 patients aged 18-80 years (including 91 (18.2%) women) who had elective coronary artery bypass grafting surgery and completed the DACAB trial.

INTERVENTIONS

Patients were randomised 1:1:1 to ticagrelor 90 mg twice daily plus aspirin 100 mg once daily (dual antiplatelet therapy; n=168), ticagrelor monotherapy 90 mg twice daily (n=166), or aspirin monotherapy 100 mg once daily (n=166) for one year after surgery. After the first year, antiplatelet therapy was prescribed according to standard of care by treating physicians.

MAIN OUTCOME MEASURES

The primary outcome was major adverse cardiovascular events (a composite of all cause death, myocardial infarction, stroke, and coronary revascularisation), analysed using the intention-to-treat principle. Time-to-event analysis was used to compare the risk between treatment groups. Multiple post hoc sensitivity analyses examined the robustness of the findings.

RESULTS

Follow-up at five years for major adverse cardiovascular events was completed for 477 (95.4%) of 500 patients; 148 patients had major adverse cardiovascular events, including 39 in the dual antiplatelet therapy group, 54 in the ticagrelor monotherapy group, and 55 in the aspirin monotherapy group. Risk of major adverse cardiovascular events at five years was significantly lower with dual antiplatelet therapy versus aspirin monotherapy (22.6% *v* 29.9%; hazard ratio 0.65, 95% confidence interval 0.43 to 0.99; P=0.04) and versus ticagrelor monotherapy (22.6% *v* 32.9%; 0.66, 0.44 to 1.00; P=0.05). Results were consistent in all sensitivity analyses.

CONCLUSIONS

Treatment with ticagrelor dual antiplatelet therapy for one year after surgery reduced the risk of major adverse cardiovascular events at five years after coronary artery bypass grafting compared with aspirin monotherapy or ticagrelor monotherapy.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03987373

WHAT IS ALREADY KNOWN ON THIS TOPIC

Dual antiplatelet therapy with ticagrelor is more effective than aspirin monotherapy in preventing saphenous vein graft failure after coronary artery bypass graft surgery (CABG)

However, the effect of dual antiplatelet therapy on clinical outcomes, including major adverse cardiovascular events (MACE), after CABG remains unclear

In the DACAB trial, dual antiplatelet therapy with ticagrelor plus aspirin significantly improved vein graft patency rate at one year compared with aspirin monotherapy

WHAT THIS STUDY ADDS

Ticagrelor dual antiplatelet therapy for one year significantly reduced the five year risk of MACE after CABG, compared with aspirin monotherapy or ticagrelor monotherapy

This five year follow-up extension study of the DACAB trial suggests that one year of dual antiplatelet therapy improves clinical outcomes after CABG

Introduction

Aspirin monotherapy is recommended after coronary artery bypass graft surgery to improve graft patency and reduce major adverse cardiovascular events.[1-4] Findings from randomised and observational studies suggest that dual antiplatelet therapy is more effective than aspirin monotherapy in preventing saphenous vein graft failure.[5-9] However, the evidence is inconclusive with regard to the effect of dual antiplatelet therapy on clinical outcomes,[4 7 10-18] and current clinical guidelines recommend dual antiplatelet therapy only in selected patients at high ischaemic risk after coronary artery bypass grafting.[3 19-22]

The Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB)[23] trial was a multicentre, randomised, open label trial comparing ticagrelor dual antiplatelet therapy, ticagrelor monotherapy, and aspirin monotherapy for one year after coronary artery bypass grafting. Vein graft patency (primary outcome) at one year was significantly higher in patients randomised to dual antiplatelet therapy compared with patients randomised to aspirin monotherapy (88.7% *v* 76.5%; P<0.001) and numerically higher compared with patients randomised to ticagrelor monotherapy (88.7% *v* 82.8%; P=0.068).

The DACAB trial was not powered for clinical outcomes. At one year after coronary artery bypass grafting, the rate of major adverse cardiovascular events

(cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was 1.8% in the dual antiplatelet therapy group, 2.4% in the ticagrelor monotherapy group, and 5.4% in the aspirin monotherapy group. The rate of major bleeding was 1.8% in the dual antiplatelet therapy group and 1.2% in the ticagrelor monotherapy group; no major bleeding event was reported in the aspirin monotherapy group.

We have now extended the clinical follow-up of patients included in the DACAB trial to five years (DACAB-Follow-up Extension (DACAB-FE) study), with the aim of investigating the effect of different antiplatelet strategies on clinical outcomes at five years after coronary artery bypass grafting.

Methods

Study design

The DACAB trial was a prospective, multicentre, open label, evaluator blind, randomised, controlled trial that compared the effect of dual antiplatelet therapy with ticagrelor plus aspirin, ticagrelor monotherapy, and aspirin monotherapy on saphenous vein graft patency in patients aged 18 to 80 years who had elective coronary artery bypass graft surgery in six Chinese tertiary hospitals.[23] The study design and full inclusion/exclusion criteria have been described previously.[23] Briefly, eligible patients were enrolled from 31 July 2014 through 3 November 2015 and randomised 1:1:1 to ticagrelor 90 mg twice daily plus aspirin 100 mg once daily (dual antiplatelet therapy), ticagrelor monotherapy 90 mg twice daily, or aspirin monotherapy 100 mg once daily for one year after coronary artery bypass graft surgery.[23] After the first year, antiplatelet therapy was based on the recommendation of the individual treating physician (including aspirin monotherapy, adenosine diphosphate receptor inhibitor monotherapy (ticagrelor or clopidogrel), and dual antiplatelet therapy).

All patients in the DACAB trial were included in the DACAB-FE study. This study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice.

Data collection

Annual clinical follow-up at local sites was recommended according to clinical status. A face-to-face or telephone visit with the central clinical trial unit was scheduled for all surviving patients at five years (within three months either side) after coronary artery bypass grafting, at which the original medical records of clinical events, related laboratory test results, electrocardiograms, and ultrasonic cardiography results and the use of concomitant medications were collected. Electrocardiograms were read centrally by the Clinical Endpoint Committee, which independently adjudicated the outcome. For deceased patients, the cause of death was adjudicated using the national China Centre for Disease Control database.

Outcomes and endpoints

The primary outcome was major adverse cardiovascular events (a composite of all cause death, myocardial infarction, stroke, and coronary revascularisation). Secondary outcomes included an extended major adverse cardiovascular events outcome (a composite of all cause death, myocardial infarction, stroke, coronary revascularisation, and hospital admission for unstable angina) and a restricted major adverse cardiovascular events outcome (a composite of cardiovascular death, myocardial infarction, and stroke), as well as their individual components. All outcomes were measured at the time to first occurrence from randomisation to last visit. Detailed outcome definitions are provided in the supplementary appendix.

The safety outcome, analysed post hoc, was major bleedings events based on the Thrombolysis in Myocardial Infarction (TIMI) risk criteria (combination of coronary artery bypass grafting related bleeding and non-coronary artery bypass grafting related major bleeding, such as intracranial bleeding, clinically overt signs of haemorrhage with haemoglobin drop ≥5 g/dL, and fatal bleeding). The secondary safety outcome was serious adverse events resulting in hospital admission or emergency department visits. We added net adverse clinical events, a composite of major adverse cardiovascular events and major bleeding events, as a post hoc outcome.

Statistical analysis

The sample size for the DACAB trial was based on a calculated statistical power of 80% to detect a significant difference in the primary outcome of vein graft patency.[23] For the DACAB-FE study, we did no formal power calculation. In the DACAB-FE primary analysis, patients were analysed according to randomised treatment groups in the DACAB trial (intention to treat).

We summarised baseline characteristics by using counts and percentages for discrete variables and mean with standard deviation and median with interquartile range for continuous variables. We reported outcomes as frequencies, incidence per 1000 patient months, and cumulative incidence.

We used Kaplan-Meier curves to describe the event-free survival in the groups and univariate Cox regression models to compare the risk of outcomes between treatment groups. We tested the Cox proportionality assumption by means of scaled Schoenfeld residuals. We reported estimates as hazard ratios and 95% confidence intervals. We used competing risk analysis with a Fine-Gray framework for all outcomes except major adverse cardiovascular events, extended major adverse cardiovascular events, and all cause death.[24] Patients with no events were right censored at their last visit. For patients who were lost to follow-up, we used the date of the last visit or the most recent known clinical outcome in the primary analysis.

We used a univariate Cox regression model to analyse treatment effects in key patient subgroups (age group; sex; coronary syndrome status; history of myocardial infarction, hypertension, diabetes, hyperlipidaemia, and peripheral arterial disease; pump use; and bleeding risk based on the CRUSADE

score[25]). Additional subgroup analyses were based on history of stroke, chronic pulmonary disease, chronic kidney disease, smoking, SYNTAX score, EuroSCORE, Lp(a) lipoprotein concentrations, left main disease, internal mammary artery use, and completeness of revascularisation. We tested treatment effect modification by using interaction terms.

Sensitivity analyses

We did multiple post hoc sensitivity analyses. To evaluate the effect of one year of dual antiplatelet therapy on late events, we did landmark analysis starting at one year after randomisation by using univariate Cox proportional hazard models. We did this analysis in participants who remained in the trial and had not had a primary endpoint event during the first year. We repeated the main analysis including only patients who received the planned dose of study drug without interruption for more than 60 days during the first year (per protocol).

In addition, we did two as-treated analyses. In the first analysis, we compared patients on the basis of the antiplatelet treatment that they received in year 1 and in years 2-5 by using adjusted multivariable Cox regression model. We identified the covariates included in the model by using a causal directed acylic graph (supplementary figure S1). Considering the limitations of conditional models and the likelihood of reverse causation bias, we fitted a marginal structural model through stable inverse probability weighting in the second analysis.[26] We divided the entire follow-up period into seven time segments (0-2 months, 2-4 months, 4-6 months, 6-8 months, 8-10 months, 10-12 months, and 12-60 months) and regarded antiplatelet treatment at different time segments as time dependent exposure. The covariates included in the effect estimation were the same as in the first as-treated analysis (see as-treated analysis methods section of supplementary appendix for more details).

In another post hoc analysis, we compared major adverse cardiovascular events, all cause death, cardiovascular death, and myocardial infarction between patients with all patent grafts and patients with at least one failed graft at one year imaging. To investigate a potential dependency of the treatment effect by the enrolling centres, we used a multivariable Cox regression model with an interaction term between treatment and study centre.

We applied a two sided significance level of 0.05 to all statistical analyses without multiplicity adjustment. We used SAS version 9.4 for statistical analyses.

Patient and public involvement

Although patients and the public were not directly involved in this paper owing to the lack of funding and covid-19, we spoke to patients about the study and asked one representative of the patients to read the manuscript and give us advice before submission.

Results

Patient characteristics

The primary analysis included 500 patients whose demographics and baseline characteristics have been previously published.[23] Among these patients,

Table 1 | Demographic and baseline characteristics of included patients. Values are numbers (percentages) unless stated otherwise

Characteristic	Overall (n=500)	Ticagrelor plus aspirin (n=168)	Ticagrelor monotherapy (n=166)	Aspirin monotherapy (n=166)
Mean (SD) age, years	63.1 (8.2)	63.0 (8.1)	62.9 (8)	63.5 (8.1)
Sex:				
Male	409 (81.8)	134 (80)	134 (81)	141 (85)
Female	91 (18.2)	34 (20)	32 (19)	25 (15)
Mean (SD) body mass index	25.2 (3.3)	25.3 (3.2)	25.2 (3.0)	25.2 (3.6)
Coronary syndrome status:				
Chronic coronary syndrome	168 (33.6)	55 (33)	63 (38)	50 (30)
Acute coronary syndrome	332 (66.4)	113 (67)	103 (62)	116 (70)
Medical history:				
Myocardial infarction	156 (31.2)	53 (32)	60 (36)	43 (26)
Stroke	61 (12.2)	26 (15)	13 (8)	22 (13)
Hypertension*	369 (73.8)	127 (76)	122 (73)	120 (72)
Diabetes†	217 (43.4)	75 (45)	75 (45)	67 (40)
Hyperlipidaemia‡	364 (72.8)	121 (72)	124 (75)	119 (72)
Smoking	246 (49.2)	85 (51)	74 (45)	87 (52)
Peripheral artery disease	82 (16.4)	26 (15)	27 (16)	29 (17)
Chronic kidney disease§	89 (17.8)	31 (18)	25 (15)	33 (20)
Median (IQR) LVEF, %	62.0 (57.0-67.0)	61.0 (56.0-67.0)	62.0 (58.0-66.0)	63.0 (56.0-68.0)
Pump use	121 (24.2)	39 (23)	36 (22)	46 (28)
IMA graft use	418 (83.6)	141 (84)	144 (87)	133 (80)

IMA=internal mammary artery; IQR=interquartile range; LVEF=left ventricular ejection fraction; SD=standard deviation.
*Defined as systolic/diastolic blood pressure ≥140/90 mm Hg.
†Defined as glycated haemoglobin (HbA_{1c}) >6.5%.
‡Defined as baseline low density lipoprotein cholesterol >1.8 mmol/L with or without statin therapy.
§Defined as baseline serum creatinine >100 µmol/L.

168 received dual antiplatelet therapy during the first year after coronary artery bypass grafting, 166 received ticagrelor monotherapy, and 166 received aspirin monotherapy. Most of the patients enrolled were men (81.8%), and the mean age was 63.1 years. Table 1 summarises the baseline characteristics of the included patients.

Follow-up

The first five year visit occurred in August 2019 and the last in June 2021. Completeness of follow-up for the primary outcome of major adverse cardiovascular events at five years was 95.4% (477/500 patients; fig 1). Median follow-up time was 61.1 months (supplementary table S1). For the five year assessment, 197 (39.4%) patients were followed up in person and 280 (56.0%) by telephone interview. Electrocardiographic or echocardiographic assessment was obtained in 428 (85.6%) patients at one year and in 402 (80.4%) patients at five years.

Antiplatelet and other concomitant medications

Within the first year from randomisation, 17 (3.4%) patients discontinued the allocated study drug for longer than 60 days, of whom five (3%) had been randomised to dual antiplatelet therapy, eight (5%) to ticagrelor monotherapy, and four (2%) to aspirin monotherapy. At the five year follow-up, 324 (64.8%) of 500 patients were receiving aspirin monotherapy: 103 (61%) in the dual antiplatelet therapy group, 102 (61%) in the ticagrelor monotherapy group, and 119 (72%) in the aspirin monotherapy group. Full details of concomitant medications at one year and at five years are shown in supplementary figure S2 and supplementary tables S2 and S3.

Primary outcome

Major adverse cardiovascular events occurred in 148 patients: 39 in the dual antiplatelet therapy group, 54 in the ticagrelor monotherapy group, and 55 in the aspirin monotherapy group. At the five year follow-up, the rate of major adverse cardiovascular events was 22.6% in the dual antiplatelet therapy group, 32.9% in the ticagrelor monotherapy group, and 29.9% in the aspirin monotherapy group (table 2). Patients in the dual antiplatelet therapy group had a significantly lower risk of major adverse cardiovascular events compared with patients in the aspirin monotherapy group (hazard ratio 0.65, 95% confidence interval 0.43 to 0.99; P=0.04) and in the ticagrelor monotherapy group (0.66, 0.44 to 1.00; P=0.05); we found no significant difference between patients in the

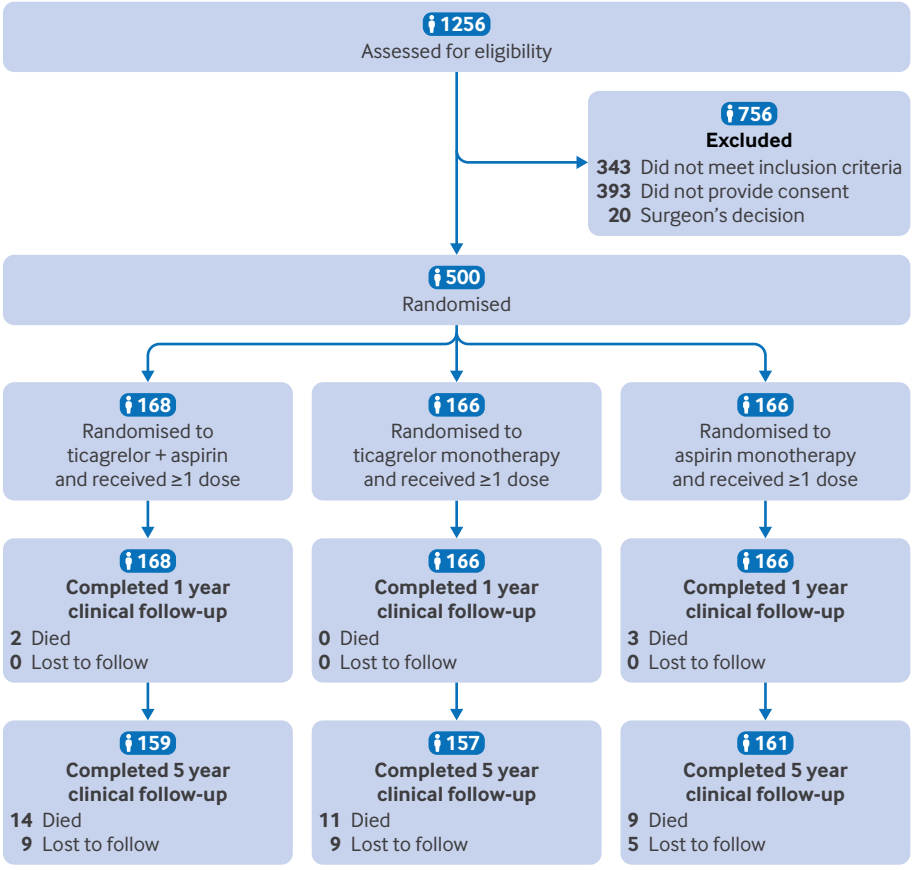

Fig 1 | Flow of patients through Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Grafting (DACAB) trial and DACAB follow-up extension study

ticagrelor monotherapy group and those in the aspirin monotherapy group (0.99, 0.68 to 1.44; P=0.97) (table 3 and fig 2). The global Schoenfeld residuals test verified the Cox proportionality assumption (P=0.63).

Sensitivity analyses

Results were consistent in all the sensitivity analyses. In the landmark analysis restricted to patients who were event-free at one year, patients in the dual antiplatelet therapy group had a numerically lower risk of late (2-5 years) major adverse cardiovascular events compared with patients in the aspirin monotherapy group (hazard ratio 0.76, 0.43 to 1.34; P=0.34) and patients in the ticagrelor monotherapy group (0.74, 0.42 to 1.30; P=0.31) (supplementary figure S3). In the per protocol analyses, patients in the dual antiplatelet therapy group had a significantly lower risk of major adverse cardiovascular events compared with patients in the aspirin monotherapy group (hazard ratio 0.63, 0.42 to 0.96; P=0.03) and patients in the ticagrelor monotherapy group (0.62, 0.41 to 0.94; P=0.03).

The baseline characteristics and the incidence of primary and secondary outcomes in the first as-treated analysis are summarised in supplementary tables S4 and S5. Patients who received dual antiplatelet therapy in the first year and aspirin monotherapy in years 2-5 had a significantly lower risk of major adverse cardiovascular events compared with those who received aspirin monotherapy during the first year and in years 2-5 (hazard ratio 0.54, 0.33 to 0.88; P=0.01) and those who received adenosine diphosphate receptor inhibitor monotherapy in the first year and aspirin monotherapy in years 2-5 (0.56, 0.34 to 0.93; P=0.03) (supplementary table S6). In the marginal structural model with stable inverse probability weighting (mean weight was 1.006, minimum weight was 0.2489, and maximum weight was 1.3255), use of dual antiplatelet therapy in the first year and aspirin monotherapy in years 2-5 was associated with a significantly lower risk of major adverse cardiovascular events compared with the use of aspirin monotherapy for the whole study period (hazard ratio 0.45, 0.28 to 0.72; P<0.001) and the use of adenosine diphosphate receptor inhibitor monotherapy for the first year followed by aspirin monotherapy in years 2-5 (0.65, 0.44 to 0.95; P=0.04).

The rate of major adverse cardiovascular events and myocardial infarction was higher in patients with at least one failed graft compared with patients with all grafts patent at one year (44.1% *v* 24.7% (P<0.001) and 31.5% *v* 14.0% (P<0.001), respectively; supplementary table S7). We found no significant differences in the rates of major adverse cardiovascular events between participating centres (supplementary table S8).

Secondary outcomes

The extended major adverse cardiovascular events outcome occurred in 39 patients in the dual antiplatelet therapy group, 55 patients in the ticagrelor monotherapy group, and 56 patients in the aspirin monotherapy group; the rates at five years were 22.6%, 32.9%, and 30.5%, respectively (table 2). The risk of extended major adverse cardiovascular events was

Table 2 | Incidence of primary and secondary outcomes in randomised treatment groups

	Ticagrelor plus aspirin (n=168)			Ticagrelor monotherapy (n=166)			Aspirin monotherapy (n=166)		
Outcome	No (%) with events	Events per 1000 patient months	Cumulative incidence at 5 years—% (95% CI)	No (%) with events	Events per 1000 patient months	Cumulative incidence at 5 years—% (95% CI)	No (%) with events	Events per 1000 patient months	Cumulative incidence at 5 years—% (95% CI)
MACE*	39 (23)	4.5	22.6 (16.9 to 29.8)	54 (33)	7.0	32.9 (26.2 to 40.7)	55 (33)	7.0	29.9 (23.5 to 37.6)
0-1 year	17 (10)	9.2	10.1 (6.4 to 15.8)	28 (17)	16.5	16.9 (12.0 to 23.6)	29 (17)	17.2	17.5 (12.5 to 24.2)
2-5 years†	22 (15)	3.2	17.1 (11.2 to 25.5)	26 (20)	4.3	21.7 (14.8 to 31.1)	26 (19)	4.2	32.9 (20.1 to 50.8)
Extended MACE‡	39 (23)	4.5	22.6 (16.9 to 29.8)	55 (33)	7.1	32.9 (26.2 to 40.7)	56 (34)	7.2	30.5 (24.1 to 38.2)
Restricted MACE§	27 (16)	3.0	15.8 (11.1 to 22.4)	44 (27)	5.5	26.2 (20.2 to 33.8)	45 (27)	5.5	26.6 (20.6 to 34.3)
All cause mortality	16 (10)	1.7	9.3 (5.7 to 15.0)	11 (7)	1.1	6.3 (3.5 to 11.4)	12 (7)	1.2	6.2 (3.4 to 11.1)
CV mortality	9 (5)	0.9	5.1 (2.7 to 9.8)	6 (4)	0.6	3.4 (1.5 to 7.5)	7 (4)	0.7	4.0 (1.9 to 8.3)
MI	18 (11)	1.9	10.9 (7.0 to 16.9)	36 (22)	4.4	21.8 (16.3 to 29.2)	32 (19)	3.7	19.6 (14.3 to 26.7)
Non-silent MI	10 (6)	1.0	6.0 (3.3 to 11.1)	14 (8)	1.5	8.5 (5.1 to 14.1)	16 (10)	1.7	9.7 (6.1 to 15.5)
Silent MI	9 (5)	0.9	5.4 (2.9 to 10.2)	22 (13)	2.5	13.5 (9.1 to 19.9)	18 (11)	1.9	10.5 (6.7 to 16.5)
Stroke	6 (4)	0.6	3.5 (1.6 to 7.6)	6 (4)	0.6	3.4 (1.6 to 7.6)	15 (9)	1.5	8.7 (5.3 to 14.2)
Ischaemic	1 (1)	0.1	0.6 (0.1 to 3.9)	5 (3)	0.5	2.7 (1.1 to 6.6)	12 (7)	1.2	6.6 (3.8 to 11.7)
Haemorrhagic	5 (3)	0.5	3.1 (1.3 to 7.3)	1 (1)	0.1	0.6 (0.1 to 4.4)	3 (2)	0.3	1.9 (0.6 to 5.7)
Coronary revascularisation	7 (4)	0.7	3.7 (1.7 to 7.7)	8 (5)	0.8	4.1 (2.0 to 8.3)	10 (6)	1.0	5.2 (2.8 to 9.8)
Hospital admission for unstable angina	4 (2)	0.4	2.2 (0.8 to 6.0)	8 (5)	0.8	4.5 (2.2 to 8.9)	8 (5)	0.8	4.5 (2.3 to 9.0)
Major bleeding	8 (5)	0.8	4.9 (2.5 to 9.6)	4 (2)	0.4	2.5 (0.9 to 6.5)	7 (4)	0.7	4.3 (2.1 to 8.9)
NACE¶	42 (25)	5.0	24.4 (18.5 to 31.8)	55 (33)	7.2	33.5 (26.8 to 41.4)	58 (35)	7.6	31.7 (25.2 to 39.5)

CI=confidence interval; CV=cardiovascular; MACE=major adverse cardiac events; MI=myocardial infarction; NACE=net adverse clinical events.
*Composite of all cause mortality, myocardial infarction, stroke, and coronary revascularisation.
†Analysis population is risk population at beginning of second year: 151 in ticagrelor plus aspirin group, 133 in ticagrelor monotherapy group, and 134 in aspirin monotherapy group.
‡Composite of all cause mortality, myocardial infarction, stroke, coronary revascularisation, and hospital admission for unstable angina.
§Composite of cardiovascular mortality, myocardial infarction, and stroke.
¶Composite of all cause mortality, myocardial infarction, stroke, coronary revascularisation, and major bleeding.

Table 3 | Risk comparison of primary and secondary outcomes between randomised treatment groups

	Ticagrelor plus aspirin *v* aspirin monotherapy		Ticagrelor plus aspirin *v* ticagrelor monotherapy		Ticagrelor monotherapy *v* aspirin monotherapy	
Outcome	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
MACE*	0.65 (0.43 to 0.99)	0.04	0.66 (0.44 to 1.00)	0.05	0.99 (0.68 to 1.44)	0.97
0-1 year	0.56 (0.31 to 1.01)	0.05	0.58 (0.32 to 1.06)	0.07	0.96 (0.57 to 1.61)	0.88
2-5 years	0.76 (0.43 to 1.34)	0.34	0.74 (0.42 to 1.30)	0.31	1.03 (0.60 to 1.77)	0.91
Extended MACE†	0.64 (0.43 to 0.96)	0.03	0.65 (0.43 to 0.98)	0.04	0.99 (0.68 to 1.44)	0.96
Restricted MACE‡	0.56 (0.35 to 0.90)	0.02	0.57 (0.35 to 0.91)	0.02	0.98 (0.65 to 1.48)	0.94
All cause mortality	1.35 (0.64 to 2.86)	0.44	1.49 (0.69 to 3.21)	0.30	0.91 (0.40 to 2.06)	0.82
CV mortality	1.30 (0.49 to 3.49)	0.60	1.52 (0.54 to 4.23)	0.43	0.86 (0.29 to 2.53)	0.78
MI	0.54 (0.30 to 0.95)	0.03	0.47 (0.27 to 0.82)	0.01	1.14 (0.71 to 1.82)	0.58
Non-silent MI	0.62 (0.28 to 1.34)	0.22	0.70 (0.32 to 1.56)	0.39	0.88 (0.44 to 1.77)	0.72
Silent MI	0.51 (0.23 to 1.13)	0.10	0.38 (0.18 to 0.83)	0.01	1.32 (0.70 to 2.49)	0.39
Stroke	0.39 (0.15 to 1.00)	0.05	0.99 (0.32 to 3.06)	0.99	0.39 (0.15 to 1.00)	0.05
Ischaemic	0.08 (0.01 to 0.62)	0.02	0.20 (0.02 to 1.67)	0.14	0.41 (0.15 to 1.16)	0.09
Haemorrhagic	1.67 (0.40 to 6.98)	0.48	4.99 (0.59 to 42.42)	0.14	0.34 (0.04 to 3.22)	0.34
Coronary revascularisation	0.69 (0.26 to 1.81)	0.45	0.87 (0.32 to 2.39)	0.78	0.80 (0.32 to 2.01)	0.63
Hospital admission for unstable angina	0.49 (0.15 to 1.63)	0.25	0.49 (0.15 to 1.61)	0.24	1.01 (0.38 to 2.69)	0.98
Major bleeding	1.14 (0.42 to 3.14)	0.80	1.99 (0.60 to 6.61)	0.26	0.57 (0.17 to 1.96)	0.38
NACE§	0.67 (0.45 to 1.00)	0.05	0.70 (0.47 to 1.05)	0.09	0.95 (0.66 to 1.38)	0.80

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MACE=major adverse cardiac events; MI=myocardial infarction; NACE=net adverse clinical events
*Composite of all cause mortality, myocardial infarction, stroke, and coronary revascularisation.
†Composite of all cause mortality, myocardial infarction, stroke, coronary revascularisation, and hospital admission for unstable angina.
‡Composite of cardiovascular mortality, myocardial infarction, and stroke.
§Composite of all cause mortality, myocardial infarction, stroke, coronary revascularisation, and major bleeding.

lower in patients in the dual antiplatelet therapy group compared with patients in the aspirin monotherapy group (hazard ratio 0.64, 0.43 to 0.96; P=0.03) and in the ticagrelor monotherapy group (0.65, 0.43 to 0.98; P=0.04) (table 3 and fig 3).

The restricted major adverse cardiovascular events outcome occurred in 27 patients in the dual antiplatelet therapy group, 44 patients in the ticagrelor monotherapy group, and 45 patients in the aspirin monotherapy group; the rates at five years were 15.8%, 26.2%, and 26.6%, respectively (table 2). The risk of restricted major adverse cardiovascular events was lower in patients in the dual antiplatelet therapy group compared with patients in the aspirin monotherapy group (hazard ratio 0.56, 0.35 to 0.90; P=0.02) and in the ticagrelor monotherapy group (0.57, 0.35 to 0.91; P=0.02) (table 3 and fig 4).

The rates of all cause mortality and cardiovascular mortality at five year were numerically higher in the patients in dual antiplatelet therapy group compared with patients in the aspirin monotherapy group (9.3% *v* 6.2% and 5.1% *v* 4.0%, respectively) and in the ticagrelor monotherapy group (9.3% *v* 6.3% and 5.1% *v* 3.4%, respectively) (table 2). The individual clinical outcomes are summarised in table 2 and supplementary tables S9 to S13.

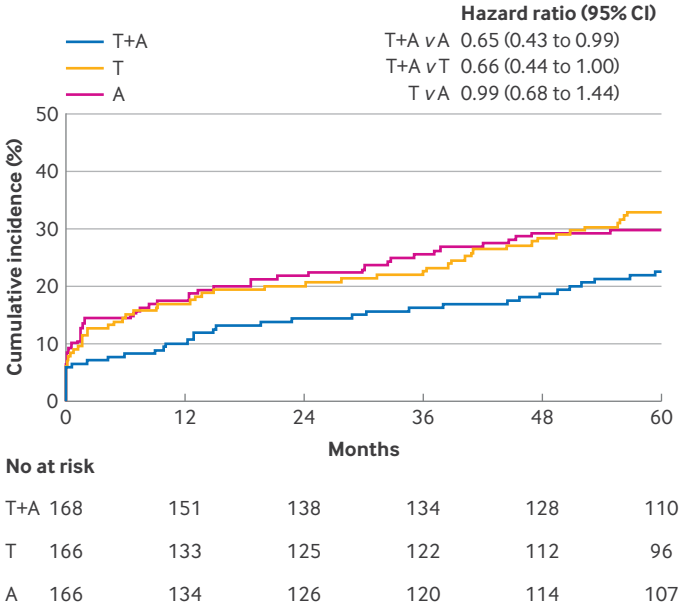

Fig 2 | Kaplan-Meier estimate of time to primary major adverse cardiovascular events outcome. A=aspirin monotherapy; CI=confidence interval; HR=hazard ratio; T=ticagrelor monotherapy; T+A=ticagrelor plus aspirin

Safety outcomes

Nineteen patients experienced major bleeding events, including eight in the dual antiplatelet therapy group, four in the ticagrelor monotherapy group, and seven in the aspirin monotherapy group; the rates at five years were 4.9%, 2.5%, and 4.3%, respectively (table 2). The risk of major bleeding was not significantly different between patients in the dual antiplatelet therapy group and patients in the aspirin monotherapy group (hazard ratio 1.14, 0.42 to 3.14; P=0.80) and in the ticagrelor monotherapy group (1.99, 0.60 to 6.61; P=0.26) (table 3). The other adverse events were similar between groups (supplementary table S14).

Net adverse clinical outcomes (post hoc analysis)

The risk of net adverse clinical events was significantly lower in patients in the dual antiplatelet therapy group

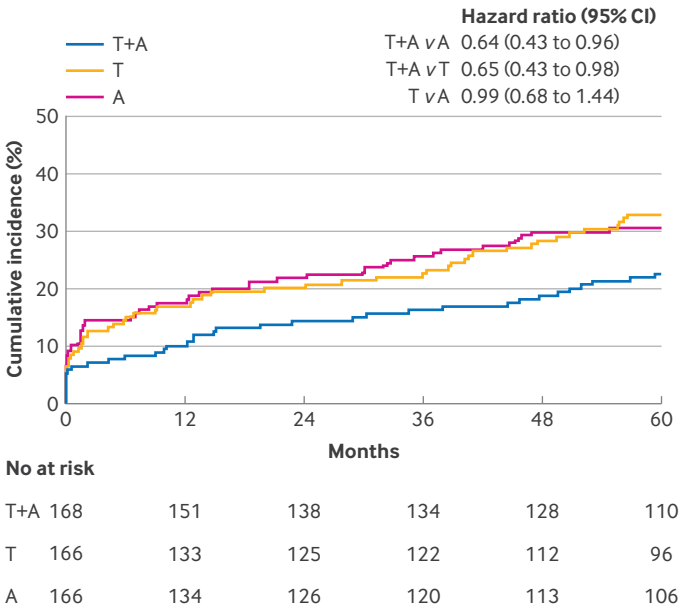

Fig 3 | Kaplan-Meier estimate of time to extended major adverse cardiovascular events. A=aspirin monotherapy; CI=confidence interval; HR=hazard ratio; T=ticagrelor monotherapy; T+A=ticagrelor plus aspirin

compared with patients in the aspirin monotherapy group (24.4% *v* 31.7% at five years; hazard ratio 0.67, 0.45 to 1.00; P=0.05) (table 2 and table 3). We found no significant difference in net adverse clinical events between patients in the dual antiplatelet therapy and ticagrelor monotherapy groups (24.4% *v* 33.5% at five years; hazard ratio 0.70, 0.47 to 1.05; P=0.09) (tables 2 and table 3).

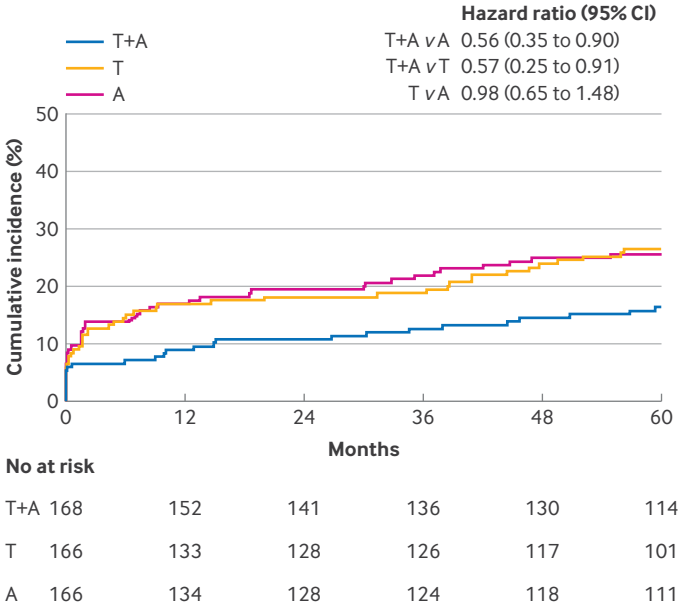

Fig 4 | Kaplan-Meier estimate of time to restricted major adverse cardiovascular events. A=aspirin monotherapy; CI=confidence interval; HR=hazard ratio; T=ticagrelor monotherapy; T+A=ticagrelor plus aspirin

Subgroup analysis

Subgroup treatment effect interactions are reported in table 4 and supplementary table S15.

Discussion

In this extended follow-up study of the DACAB trial, the risk of major adverse cardiovascular events up to five years after coronary artery bypass grafting was lower with dual antiplatelet therapy with ticagrelor plus aspirin for one year compared with aspirin monotherapy or ticagrelor monotherapy. The beneficial effect of ticagrelor dual antiplatelet therapy seemed to continue after the first year and was consistent across key clinical subgroups, including different baseline bleeding risks.

Strengths and limitations of study

This study provides evidence of clinical benefit with the use of ticagrelor dual antiplatelet therapy for one year after coronary artery bypass grafting. Given the substantial rate of cardiovascular events after coronary artery bypass grafting despite standard aspirin therapy, evidence for the clinical effect of ticagrelor dual antiplatelet therapy is of critical importance to inform clinical practice. Strengths of this study include the evaluation of three different antiplatelet strategies, the high adherence to the randomised treatment during the first year, the high rate of complete five year follow-up, and the combined evaluation of clinical events and imaging.

The main limitation is that the randomised allocation to antiplatelet therapy was for the first year only. However, coronary artery bypass graft thrombosis typically occurs within the first year after surgery,[27 28] and the prevention of graft occlusion in the first postoperative year could conceivably have long term effects on reducing the risk of major adverse cardiovascular events[29]; in addition, the long term benefit of one year of ticagrelor dual antiplatelet therapy was confirmed in all the sensitivity analyses.

In clinical practice, patients with coronary artery bypass grafts are generally followed by a specialist early after surgery and then referred to their general physician, and changes in medical therapy are frequent during this transition and also driven by the patient's health status. The change in antiplatelet treatment could be seen as an intercurrent event, and we presented the intention-to-treat analysis and two as-treated analyses to describe the effect of the interventions both from a treatment policy estimand perspective and from a hypothetical strategy perspective. However, the intention-to-treat analysis is of principal interest for inference as it describes the practical consequences of the specific antiplatelet treatment over the first year (and collider stratification, confounding by indication, and unmeasured bias may be present in the as-treated analyses).

Other limitations include the fact that owing to restrictions associated with the covid-19 pandemic, more than half of the patients completed the five year follow-up remotely, rather than attending

Table 4 | Subgroup analyses of primary major adverse cardiac events outcome between randomised treatment groups using univariate Cox regression

Subgroup	Patients with events/total patients (%)			Ticagrelor plus aspirin *v* aspirin monotherapy		Ticagrelor plus aspirin *v* ticagrelor monotherapy		Ticagrelor monotherapy *v* aspirin monotherapy	
	Ticagrelor plus aspirin	Ticagrelor monotherapy	Aspirin monotherapy	HR (95% CI)	P value*	HR (95% CI)	P value*	HR (95% CI)	P value*
All patients	39/168 (23)	54/166 (33)	55/166 (33)	0.65 (0.43 to 0.99)		0.66 (0.44 to 1.00)		0.99 (0.68 to 1.44)	
Age:					0.71		0.58		0.85
≤70 years	33/140 (24)	41/133 (31)	42/130 (32)	0.68 (0.43 to 1.08)		0.70 (0.45 to 1.11)		0.98 (0.63 to 1.50)	
>70 years	6/28 (21)	13/33 (39)	13/36 (36)	0.56 (0.21 to 1.47)		0.52 (0.20 to 1.36)		1.08 (0.50 to 2.32)	
Sex:					0.72		0.11		0.05
Male	29/134 (22)	46/134 (34)	43/141 (30)	0.66 (0.41 to 1.06)		0.56 (0.35 to 0.89)		1.19 (0.78 to 1.80)	
Female	10/34 (29)	8/32 (25)	12/25 (48)	0.55 (0.24 to 1.28)		1.27 (0.50 to 3.23)		0.44 (0.18 to 1.07)	
Coronary syndrome status:					0.29		0.64		0.53
CCS	9/55 (16)	17/63 (27)	16/50 (32)	0.44 (0.19 to 0.99)		0.55 (0.24 to 1.23)		0.84 (0.42 to 1.66)	
ACS	30/113 (27)	37/103 (36)	39/116 (34)	0.76 (0.47 to 1.22)		0.69 (0.43 to 1.11)		1.10 (0.70 to 1.72)	
History of MI:					0.49		0.93		0.51
Yes	13/53 (25)	20/60 (33)	12/43 (28)	0.83 (0.38 to 1.81)		0.68 (0.34 to 1.37)		1.23 (0.60 to 2.52)	
No	26/115 (23)	34/106 (32)	43/123 (35)	0.60 (0.37 to 0.98)		0.65 (0.39 to 1.09)		0.92 (0.59 to 1.44)	
History of hypertension:					0.19		0.25		0.90
Yes	32/127 (25)	38/122 (31)	38/120 (32)	0.77 (0.48 to 1.23)		0.75 (0.47 to 1.21)		1.01 (0.64 to 1.58)	
No	7/41 (17)	16/44 (36)	17/46 (37)	0.39 (0.16 to 0.95)		0.44 (0.18 to 1.08)		0.94 (0.48 to 1.87)	
History of diabetes:					0.86		1.00		0.86
Yes	17/75 (23)	24/75 (32)	22/67 (33)	0.62 (0.33 to 1.17)		0.66 (0.35 to 1.22)		0.97 (0.54 to 1.72)	
No	22/93 (24)	30/91 (33)	33/99 (33)	0.68 (0.40 to 1.17)		0.67 (0.39 to 1.16)		1.02 (0.62 to 1.67)	
History of hyperlipidaemia:					0.43		0.40		0.10
Yes	27/121 (22)	35/124 (28)	41/119 (34)	0.59 (0.36 to 0.96)		0.74 (0.45 to 1.22)		0.81 (0.52 to 1.27)	
No	12/47 (26)	19/42 (45)	14/47 (30)	0.90 (0.41 to 1.97)		0.51 (0.25 to 1.06)		1.65 (0.82 to 3.31)	
History of PAD:					0.27		0.87		0.14
Yes	7/26 (27)	10/27 (37)	15/29 (52)	0.42 (0.17 to 1.03)		0.70 (0.27 to 1.85)		0.55 (0.25 to 1.23)	
No	32/142 (23)	44/139 (32)	40/137 (29)	0.74 (0.47 to 1.18)		0.66 (0.42 to 1.04)		1.14 (0.74 to 1.75)	
Pump use:					0.97		0.51		0.50
Yes	11/39 (28)	11/36 (31)	17/46 (37)	0.67 (0.31 to 1.44)		0.85 (0.37 to 1.97)		0.80 (0.37 to 1.71)	
No	28/129 (22)	43/130 (33)	38/120 (32)	0.65 (0.40 to 1.07)		0.61 (0.38 to 0.98)		1.08 (0.70 to 1.68)	
CRUSADE score:					0.53		0.40		0.84
Low risk	34/154 (22)	48/149 (32)	50/152 (33)	0.63 (0.41 to 0.97)		0.63 (0.41 to 0.98)		1.00 (0.68 to 1.49)	
High risk	5/14 (36)	6/17 (35)	5/14 (36)	0.92 (0.27 to 3.17)		1.16 (0.35 to 3.79)		0.85 (0.26 to 2.78)	

ACS=acute coronary syndrome; CCS=chronic coronary syndrome; CI=confidence interval; HR=hazard ratio; MI=myocardial infarction; PAD=peripheral artery disease.
*P value for interaction.

an in-person visit, and this may have affected in particular the ascertainment of silent myocardial infarctions. Moreover, given the small number of events, the analysis of the individual outcomes may be underpowered. Finally, the use of the internal mammary artery for coronary artery bypass grafting was lower compared with that in Western registries, which may affect the generalisability of results, but this is consistent with contemporary Chinese cardiac surgical practice.[30]

Comparison with other studies

Previous studies on the clinical effect of dual antiplatelet therapy, aspirin monotherapy, and ticagrelor monotherapy after coronary artery bypass graft surgery reported mixed results.[7 12-14 31 32] In the CASCADE study, at a median follow-up of 7.6 years, treatment with clopidogrel plus aspirin for one year was associated with a numerical reduction in major adverse cardiovascular events compared with aspirin monotherapy.[13] In the prematurely terminated TICAB trial, no significant differences in the incidence of major adverse cardiovascular events one year after coronary artery bypass grafting were observed in patients who were treated with ticagrelor monotherapy and those treated with aspirin monotherapy, although the study may have been underpowered to detect even moderate treatment effects.[32] In a subgroup analysis of the PLATO trial, among patients with acute coronary syndromes who had coronary artery bypass grafting, ticagrelor plus aspirin for one year was superior to clopidogrel plus aspirin in reducing the risk of major adverse cardiovascular events at 12 months after surgery.[31] However, this was an observational analysis in a subgroup of patients enrolled in a prospective randomised trial.[31]

Clinical implications

In the one year imaging analysis of the DACAB trial, ticagrelor dual antiplatelet therapy was associated with a significantly higher saphenous vein graft patency rate compared with aspirin monotherapy, but too few events occurred to allow meaningful intergroup comparisons of clinical outcomes, although the absolute rate of major adverse cardiovascular events was lower in the ticagrelor dual antiplatelet therapy group than in the aspirin monotherapy group.[23] The attrition rate of coronary bypass grafts is known to be higher in the first year after surgery (mostly owing to early thrombosis and reactive intimal hyperplasia) and

relatively lower during postoperative years 2-5.[28 33] Our analysis suggests that ticagrelor dual antiplatelet therapy during the first postoperative year may protect coronary bypass grafts from early occlusion, leading to sustained postoperative clinical benefit. We hypothesise that this benefit is due to the protective effect of patent surgical grafts against coronary artery disease progression and acute coronary events.[34]

We observed an absolute increase in mortality in patients who received dual antiplatelet therapy. This increased incidence of mortality was based on a low number of events and was not accompanied by an increase in bleeding events; further investigation is needed. An increase in the risk of major bleeding events was noted in a recent meta-analysis comparing ticagrelor dual antiplatelet therapy with aspirin monotherapy in coronary artery bypass grafting patients,[9] but this was not seen in our study, in which a significant net clinical benefit was seen with the use of ticagrelor dual antiplatelet therapy for one year after surgery; however, our sample size may have been underpowered for safety outcomes. Treatment decisions must be based on clinical and surgical characteristics of the individual patient.

Future directions

Future studies should investigate the effect of short term ticagrelor dual antiplatelet therapy after coronary artery bypass grafting, as well as its optimal duration. Furthermore, research comparing the efficacy and safety of ticagrelor dual antiplatelet therapy with aspirin monotherapy or ticagrelor monotherapy in specific patient populations, such as people with diabetes or older people, or in patients taking concomitant drugs, would provide additional guidance to clinicians treating patients after coronary artery bypass graft surgery.

Conclusions

The DACAB-FE study provides evidence of a significant five year clinical benefit of one year of ticagrelor dual antiplatelet therapy after coronary artery bypass grafting compared with aspirin monotherapy or ticagrelor monotherapy.

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Data sharing: All data that underlie the results reported in this article will be provided on reasonable request.

Transparency: The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of this study were presented at the 2021 American Heart Association annual meeting and the 2023 annual meeting of the European Association for Cardio-Thoracic Surgery and will be disseminated through scientific publications in peer reviewed journals and presentations at national meetings in China. The results will also be shared with the clinicians at participating sites via an investigator meeting.

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Web appendix: Supplementary materials
Web appendix: Protocol