Dual or single antiplatelet therapy after coronary surgery for acute coronary syndrome (TACSI trial): Rationale and design of an investigator-initiated, prospective, multinational, registry-based randomized clinical trial

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Abstract The TACSI trial (ClinicalTrials.gov Identifier: NCT03560310) tests the hypothesis that 1-year treatment with dual antiplatelet therapy with acetylsalicylic acid (ASA) and ticagrelor is superior to only ASA after isolated coronary artery bypass grafting (CABG) in patients with acute coronary syndrome. The TACSI trial is an investigator-initiated pragmatic, prospective, multinational, multicenter, open-label, registry-based randomized trial with 1:1 randomization to dual antiplatelet therapy with ASA and ticagrelor or ASA only, in patients undergoing first isolated CABG, with a planned enrollment of 2200 patients at Nordic cardiac surgery centers. The primary efficacy end point is a composite of time to all-cause death, myocardial infarction, stroke, or new coronary revascularization within 12 months after randomization. The primary safety end point is time to hospitalization due to major bleeding. Secondary efficacy end points include time to the individual components of the primary end point, cardiovascular death, and rehospitalization due to cardiovascular causes. High-quality health care registries are used to assess primary and secondary end points. The patients will be followed for 10 years. The TACSI trial will give important information useful for guiding the antiplatelet strategy in acute coronary syndrome patients treated with CABG. (Am Heart J 2023;259:1–8.)

Coronary artery bypass grafting (CABG) is the recommended treatment for coronary artery disease (CAD) patients with complex multivessel disease and is indicated both in selected patients with chronic CAD and in patients with the acute coronary syndrome (ACS), who are hemodynamically stable and in the subacute phase.[1,2]

Secondary prevention medication with antiplatelet agents is recommended after CABG to maintain the long-term benefits of revascularization, both in terms of morbidity and mortality. The Current Society of Cardiology (ESC) and European Association for Cardio-thoracic Surgery (EACTS), and American College of Cardiology (ACC), and American Heart Association's guidelines recommend that acetylsalicylic acid (ASA) should be pre-

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Submitted October 23, 2022; received in revised form January 12, 2023; accepted January 12, 2023

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0002-8703

https://doi.org/10.1016/j.ahj.2023.01.011

scribed lifelong to all patients without contraindications undergoing CABG.[3,4] Furthermore, dual antiplatelet therapy (DAPT) with ASA and a P2Y12 inhibitor is strongly recommended (Class 1) during the first 12 postoperative months in patients with ACS undergoing CABG, if the bleeding risk is low.[3,4] Regarding the choice between P2Y12 inhibitors, ticagrelor or prasugrel are in the ESC/EACTS guidelines recommended over clopidogrel for most patients with ACS, including patients after CABG.[3] Despite the strong recommendations for DAPT in ACS-CABG, adherence to the guidelines has been reported to be low. In Sweden, only 50% of patients with ACS are treated with DAPT after CABG.[5] Similar figures have been reported from Canada.[6] One plausible reason for the low adherence is the lack of prospective, randomized study results that clearly demonstrate the superiority of DAPT in comparison with ASA only. The objective of the TACSI trial is therefore to assess whether DAPT with ticagrelor and ASA compared to single antiplatelet therapy with ASA improves 12 months' outcome after isolated CABG in patients with ACS, defined as time to major adverse cardiovascular events (MACE).

Study rationale

The Class 1 recommendation for DAPT after CABG in patients with ACS in the current guidelines is based on limited evidence as illustrated by a C level of evidence.[3,4] The evidence is extrapolated from DAPT trials in non-CABG populations, subgroup analyses of ACS trials, smaller observational studies, and randomized trials with surrogate end points.[3,4] No randomized trials with clinically relevant end points supporting the current DAPT guidelines in patients undergoing CABG have been published.

The CURE trial showed that DAPT with clopidogrel and ASA was superior to ASA monotherapy in unselected patients with ACS.[7] However, in the subpopulation of patients that underwent CABG, there was no significant difference between DAPT and ASA monotherapy in the incidence of postoperative MACE, including death, myocardial infarction, and stroke.[8] Interaction analyses in the CURE trial did not reveal any significant difference between the patients undergoing CABG or not. Furthermore, a Danish observational study showed that DAPT with ASA and clopidogrel was associated with a reduced risk for death and new myocardial infarction after CABG in patients with myocardial infarction.[9]

At the time of the initiation of the TACSI trial, 2 meta-analyses that compared DAPT with ASA only after CABG had been published.[10,11] In one of the studies, based on RCTs only, there was no difference in mortality between DAPT and ASA only.[10] In the other meta-analysis, based on both RCT's and observational studies, only DAPT patients treated with clopidogrel were included.[11] Importantly in the latter study early mortality (in-hospital or 30-day) was lower with ASA + clopidogrel compared with ASA alone, while the risk of perioperative myocardial infarction was comparable. Mortality after the first 30 postoperative days was not reported. Patients treated with ASA + clopidogrel after CABG had a trend toward a higher incidence of major bleeding episodes, compared with ASA alone.[11] The conclusions of these meta-analyses were weakened by a large variation in the included studies regarding study drugs, study design, patient inclusion criteria, study quality, and length of follow-up.

Despite the uncertainty of whether DAPT improves outcomes after CABG in patients with ACS or not, the 2017 ESC/EACTS guidelines on DAPT strongly recommended that DAPT should be used after CABG in patients with ACS (class 1, LoE C).[4] DAPT should be started as soon after CABG as considered safe, and a treatment period of 12 months was advocated for patients with normal bleeding risk, while for patients with increased bleeding risk, a shorter treatment period was recommended. These recommendations have been repeated in several guidelines published after 2017.[2,12,13] Similar recommendations were also given in the ACC/American Heart Association's guidelines from 2016, which also gave a class 2B recommendation for DAPT in patients undergoing CABG with stable angina, given the reduced risk for vein graft occlusion shown in small, randomized trials.[3]

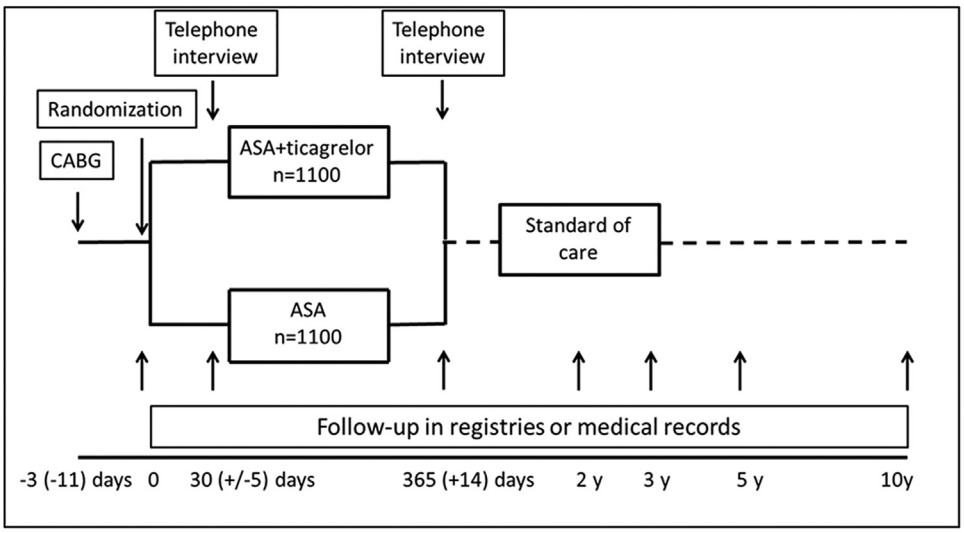
Taking all available data together, both at the time of the initiation of the TACSI trial in 2017 and today, there are still limited data supporting that a patient that undergoes CABG after an episode of ACS should be treated with DAPT. Larger randomized trials are lacking and therefore, the TACSI trial was instigated to bridge this gap in the evidence.

Methods

Study design

The "Dual antiplatelet therapy with **T**icagrelor and **A**cetylsalicylic acid (ASA) vs ASA only after isolated **c**oronary artery bypass grafting in patient**s** w**I**th acute coronary syndrome" (TACSI trial) is a 1:1 prospective, randomized, interventional, multinational, multicenter, safety/efficacy, parallel assignment, open-label treatment study. TACSI is planned to randomize 2200 patients that undergo CABG for ACS to either DAPT with ticagrelor and ASA or ASA monotherapy. A study flow chart is depicted in Figure. TACSI uses the "registry-based randomized clinical trial" (RRCT) methodology,[14,15] using existing national high-quality health care registries and databases for the capture of background and outcome variables. Additional information will be collected using telephone interviews conducted by study nurses. The study was approved by the Regional Research Ethics Committee on July 24, 2017 (registration number 564-17) and is registered at clinicaltrials.gov (registration

Figure



Study design.

Table I. Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Written informed consent Age ≥18 y Has undergone first time isolated CABG due to an episode of acute coronary syndrome (STEMI, NSTEMI, unstable angina) within 6 wk before surgery	Previously enrolled in this study Concomitant surgical procedure other than CABG Anticoagulant treatment after the operation (eg, warfarin, direct thrombin inhibitors (dabigatran), FXa inhibitors (rivaroxaban, apixaban, heparin, low-molecular weight heparin, fondaparinux) Discharge from the operating hospital to an ICU Pregnancy or lactation Known intolerance or contraindication to ticagrelor or ASA. Any disorder that may interfere with drug absorption Any condition other than coronary artery disease with a life expectancy <12 mo Known chronic liver disease, renal disease requiring dialysis or bleeding disorder AV-block II and III in patients without pacemaker Any other indication for dual antiplatelet therapy, that is, recent stent implantation Debilitating stroke within 90 d before inclusion Previous intracranial bleeding Treatment with immunosuppressants (eg, cyclosporine and tacrolimus) Treatment with strong CYP3A4-inhibitors (eg, ketoconazole, clarithromycin, nefazodon, ritonavir, or atazanavir) Any condition that in the opinion of the investigator may interfere with adherence to trial protocol

number NCT03560310) and has EudraCT number 2017-001499-43). The study will be performed in accordance with the protocol, with the latest version of the Declaration of Helsinki, with Good Clinical Practice (ICH-GCP E6(R2) and applicable regulatory requirements.

Study population and inclusion/exclusion criteria

The trial will include a representative group ($n = 2200$) of patients with ACS treated with first-time isolated CABG who fulfill the requirements according to inclusion and exclusion criteria (Table I). The patients are recruited from participating centers in Sweden, Norway, Finland, Denmark, and Iceland. Surgical procedures and postoperative care are performed according to established local routines. The patients receive oral and written information about the study and will then sign a consent form. The inclusion and randomization will take place before the patient is discharged from the operating hospital after CABG, 3-14 days after the operation. Patients are withdrawn from the study if the patient withdraws consent or if it is medically indicated as judged by the investigator. Already collected study data for these patients will be

Table IIA. Efficacy end points

Primary	Secondary
A composite end point of the time to all cause death, or myocardial infarction, or stroke, or new revascularization within 12 mo	Time to all cause death
	Time to all cause death, myocardial infarction or stroke
	Time to cardiovascular death
	Time to first myocardial infarction
	Time to first stroke
	Time to new revascularization
	Time to coronary angiography
	Time to hospitalization for heart failure
	Time to cardiovascular hospitalization
	Time to sudden death or aborted cardiac arrest
	Time to new-onset AF

Table IIB. Safety end points

Primary	Secondary
Time to major bleeding defined as bleeding requiring hospitalization	Time to minor bleeding
	Time to any bleeding
	Time to dyspnea
	Time to dyspnea causing drug interruption
	Time to new onset renal failure
	Treatment cross-over

kept in the study database, however, new data, including data from the registries will not be added. Patients prematurely withdrawn from the study are not replaced.

Study end points

Primary and secondary efficacy end points are listed in Table IIA and primary and secondary safety end points are listed in Table IIB. Events will be collected from national registries, databases and electronic patient records in the participating countries using ICD-10 codes. The codes used to define events are listed in Table III. Primary efficacy end point is a composite end point of the time to MACE, including all-cause death, myocardial infarction, stroke, or new coronary revascularization within 12 months after randomization. Neither efficacy nor safety end points will be adjudicated in this pragmatic trial. Primary safety end point is major bleeding, defined as hospitalization with bleeding as the main diagnosis. The secondary end points listed in Table IIA and IIB will be analyzed using a hierarchical order, ranking the end points according to clinical relevance. Secondary end points include the primary efficacy and safety end points at 2, 3, 5, and 10 years after randomization, and the individual components of the composite end point at 1, 2, 3, 5, and 10 years. In addition, other cardiovascular secondary end points have been included, such as hospitalization for cardiovascular causes, especially heart failure. Secondary safety end points including for example, time to new onset renal failure will also be followed for 10 years. Predefined subgroup analyses based on age, sex, diabetes, renal dysfunction, ACS subtype, LVEF, the severity of coronary disease, and prior PCI, will be performed.

Informed consent and randomization

The study is an open-label randomized study. Patients who fulfill the inclusion/exclusion criteria are approached for verbal and written information and sign an informed consent form 3 to 14 days after the operation. After consent, patients are randomized in an electronic randomization system to either intervention (DAPT using ASA 75 mg daily + ticagrelor 90 mg BID) or control (ASA 75-160 mg daily according to local protocols). No washout period or a higher loading dose for patients switching from clopidogrel or prasugrel to ticagrelor is recommended in the trial. Preoperative platelet inhibition should be stopped before CABG according to current guidelines, that is, prasugrel 7 days, clopidogrel 5 days, and ticagrelor 3 days before surgery. Aspirin should not be discontinued. Patients will be stratified at randomization to ensure that each participating center has a similar number of intervention and control patients. The study medication will be prescribed in the clinical routine by the investigator/co-investigator before discharge. In the Nordic counties prescribed medications are funded by county councils or the government with a small co-fee for the patients.

Follow-up

After 1 month (30 ± 5 days) a study nurse conduct a structured telephone interview with the patient to col-

Table III. ICD and procedure codes used to define endpoints.

Diagnoses/procedures	Codes
Myocardial infarction	
Non-ST elevation MI	I21.4
ST-elevation MI	I21.0-I21.3
Reinfarction	I22
Stroke	
Ischemic stroke	I63, I64, I69
Hemorragic stroke	I61, I62.9
Subarachnoidal bleeding	I60
Revascularization	
CABG	FN A-F
PCI	FNG02, FNG05
Heart failure	I50
Atrial fibrillation	I48
Stable angina	I20.9, I20.8
Unstable angina	I20.0, I20.1
Renal failure	N17-N19
Bleedings	K226, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6. K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K66.1, K92.0-K92.2, I61, I62, I60, I23.0; I31.2, I85.0, D50, D62, D65, D68, D69; H92.2, H35.6; M25.0, N42.1, N501A, N93.8, N93.9, N95, 04.0, R04.1, R04.2, R04.8, R04.9, N02

CABG = Coronary artery bypass grafting, MI = Myocardial infarction, PCI = Percutaneous coronary intervention.

lect data regarding cardiac events, adverse events related to the study medication, and compliance with assigned treatment. A second telephone interview with similar questions will be conducted after 1 year (365 + 14 days), which marks the end of the treatment period. The rationale for the telephone interviews is that it is difficult to capture compliance to study medications in registers and databases. Information from the telephone interviews will be entered in an electronic case report form (eCRF). If contact with the patient has not been achieved despite repeated phone calls, information will be collected from hospital records. Cardiovascular medications, antithrombotic and antidiabetic drugs, and proton pump inhibitor medications are recorded in the eCRF at baseline and followed in registries or medical records during the follow-up period. Other medications will not be registered in the study database.

Every second month, until the last patient, has completed the 12-month follow-up telephone interview, data on all-cause mortality will be collected at the study centers. Mortality registries or active follow-up in medical records will be used. If death occurs, the site to which the patient belongs will be requested to collect information about the cause of death. Information on mortality will be forwarded to the data and safety monitoring board together with group assignments. Since other events (MI, stroke, revascularization, and major bleeding) will not be collected regularly from the national registries and databases until the study is completed, the decision from the data and safety monitoring board to stop or continue the study will be based exclusively on mortality data.

A separate trial, CoCAP (NCT04783701) will investigate graft patency with coronary CTA 12 to 36 months after CABG in a subset of TACSI patients ($n = 360$).

Monitoring

Data monitoring according to Good Clinical Practice will be carried out by independent external monitors regularly at each study site during the study period. The monitors will have regular contact with the participating clinics to ensure that the trial is conducted in compliance with the protocol and applicable regulatory requirements. The monitors will also provide information and support to the centers.

Sample size calculation and statistical considerations

The sample size calculation is based on a log-rank test of the primary end point. Based on published data from trials involving DAPT in patients with ACS[16] and preliminary data from retrospective registry studies,[17] we projected event rates and hazard ratios before study initiation. In the CABG-substudy of the PLATO trial which compared ticagrelor + ASA with clopidogrel, the primary composite of postrandomization cardiovascular death, stroke, and myocardial infarction (which includes also perioperative mortality and morbidity) occurred in 10.6% of the ticagrelor patients and in 13.1% of the clopidogrel patients at 1-year (HR 0.84 (95% CI 0.60-1.16).[16] Total all-cause post-randomization mortality was reduced from 7.9% in the clopidogrel group to 4.1% in the ticagrelor group (HR 0.49 (95%CI 0.32-0.77). In a preliminary propensity score-matched analysis based on the SWEDEHEART registry in 4746 patients operated 2012

to 2015, all-cause mortality after discharge after CABG in patients with ACS at 1-year was 0.7% in patients treated with ticagrelor + ASA and 2.2% in patients treated with ASA monotherapy (HR 0.33 (95% CI 0.16-0.86).[17] Based on these data we assumed an event rate of the primary end point (MACE at 1-year) to be 8% in ASA monotherapy patients. The 2-sided significance level and the power were set to 5% and 80%, respectively. Assuming an HR of 0.615 for the primary end point in the DAPT arm, the sample size calculation yielded 1,056 patients in each arm. The total expected number of events needed is 138. To adjust for attrition, the sample size was set to 2,200. On January 10, 2023, 1,630 patients were included (74%).

The primary analysis of all study end points will be conducted according to intention-to-treat. All statistical testing will be performed at the 2-sided $\alpha = 0.05$ significance level. The primary end point, time to all cause death, myocardial infarction, stroke, or new revascularization at the end of the 12-month follow-up period, will be compared by the trial arm (ticagrelor + ASA vs ASA only) using a log-rank test ($\alpha = 0.05$) of time to the first event from the time of randomization. A Cox proportional hazards regression will be used as a sensitivity analysis and adjusted for covariates predefined in the Statistical Analysis Plan (SAP). Additional per-protocol and as-treated analysis will also be performed. The secondary end points will be analyzed using a hierarchical order, ranking the end points according to clinical relevance. The tests will be performed, as described below, without adjustment on the significance level ($\alpha = 0.05$) until a nonsignificant result is obtained. Secondary end points obtained after the nonsignificant one will for exploratory reasons also be reported. Secondary end points of time to event data will be analyzed using the same methods as the primary end points. The number of hospitalizations will be analyzed using poisson regression. Binary secondary end points will be analyzed using an ordinary χ^2-test in combination with logistic regression (with covariates predefined in the SAP) as a sensitivity analysis. Continuous secondary end points will be analyzed using ordinary *T*-tests in combination with a General Linear Model (with covariates predefined in the SAP) as a sensitivity analysis.

Discussion

The TACSI trial compares a more potent antiplatelet therapy consisting of DAPT with ASA and the P2Y12 inhibitor ticagrelor with ASA monotherapy after CABG in patients with ACS. DAPT is strongly recommended for these patients in current European and North American guidelines,[3,4] but without support from dedicated large randomized trials comparing single vs DAPT in CABG patients. The potential advantage of a more potent antiplatelet therapy is a reduced risk for thromboembolic episodes while on treatment, and a reduced risk for graft occlusion, which may have long-term benefits. On the other hand, DAPT will most likely increase the risk for major bleeding complications, which at least in other CAD populations have been associated with the same increase in mortality risk as a new myocardial infarction.[18,19] In the PEGASUS-TIMI 54 trial, which compared ticagrelor + ASA vs ASA only in a high-risk CAD population 1 to 3 years after myocardial infarction, the risk for major bleeding events was 2.6% with ticagrelor + ASA and 1% with ASA only, after a mean follow-up of 33 months.[20] The risk for intracranial and fatal bleeding was low in both groups. Minor bleeding events were more common and approximately 7% of the ticagrelor-treated patients in the PEGASUS trial stopped the medication due to bleeding. Another known side effect of ticagrelor is dyspnea which occurred in 18.9% of the patients in PEGASUS-TMI 54, leading to study-drug discontinuation in 5% of the patients. It should be clearly noted that the PEGASUS-TIMI 54 trial did not primarily include patients after CABG.

In TACSI inclusion 3 to 14 days after surgery is allowed. One may argue that patients should be randomized before CABG; in order not to miss potential outcome events. However, TACSI is a pragmatic trial that assesses the optimal long term antithrombotic strategy in a clinical reality. Start, or resumption, of antiplatelet therapy should not be performed until after hemostasis is secured. A large proportion, approximately 30% of CABG patients, also develop postoperative atrial fibrillation (POAF). If a patient randomized to DAPT and later develops POAF, the treating physician could in some cases decide there is an indication for oral anticoagulation (currently 40%-50% of POAF patients in the Nordic countries). Therefore, ticagrelor would have been stopped in most cases, since triple antithrombotic treatment currently is not recommended after CABG. This would have caused a larger bias in the trial, due to the intention-to-treat design, and therefore we choose to randomize patients after surgery. The POAF issue is also a reason why inclusion 3-14 days after CABG was allowed, since the incidence of POAF peaks at day 2-3. As it is now, a patient may develop POAF and if there is no indication for OAC, the patient can be included in TACSI before discharge.

In the present study it is not possible to use the BARC-classification, or any other classification that includes the number of transfusions or hemoglobin drop to define major bleeding; this as the national registries and databases that are used to collect end points, do not contain this information. Instead, we use hospitalization due to bleeding as the definition of major bleeding. Furthermore, we have not included any formal adjudication of events. Our aim was to conduct a large and pragmatic trial using available information in registries minimizing the need of collection of biomarkers and adjudication of clinical events. Studies and meta-analyses have failed to detect any effect

of event adjudication on study conclusions and the numbers of events included in the final analyses are minimally changed.[21,22]

As mentioned above, there was limited evidence for DAPT after CABG in patients with ACS at the time of the initiation of the TACSI trial. During the time that has elapsed since the start of trial no studies have been published that changes the current level of evidence. The DACAB study investigated graft patency after CABG comparing DAPT with ASA plus ticagrelor, ticagrelor monotherapy, and ASA monotherapy in 600 CABG patients.[23] Graft patency was significantly better in the DAPT group but there was no significant difference in MACE rate at 1 year postoperatively. In the POPULAR CABG trial, the addition of ticagrelor to standard ASA did not reduce the rate of saphenous vein graft occlusion or clinical events at 1-year.[24] None of these studies were powered for, or designed to, evaluate clinical outcomes. A meta-analysis based on randomized trials has been published indicating improved vein graft patency with DAPT in patients after CABG,[25] where clopidogrel and ticagrelor were equally effective. A more recent meta-analysis compared DAPT with ticagrelor and aspirin vs aspirin only and found improved vein graft patency in DAPT-treated patients.[26]

The TACSI trial follows patients 10 years after randomization. The long follow-up period was chosen because of 2 reasons; First, treatment effects may become evident late after randomization as exemplified by the STICH/STICHES study,[27] where the gain of CABG compared to medical therapy become evident first after ten years. If DAPT with ticagrelor enhances graft patency, as data from the meta-analysis mentioned above suggest,[26] it may have an impact on the outcome a long time after the treatment period ends. Secondly, long-term follow-up data from prospective studies in cardiac surgery patients are rare. With the present study design and access to information from national registries and databases, we will not only be able to collect long-term information about events, such as death, thromboembolic events, and major bleeding, but also on time-updated information about antithrombotic medication in a large well-defined patient cohort.

Registry-based RCTs are complement but not a substitute for traditional RCTs. RRCT's have certain advantages such as including more unselected patients, low risk for confounding, and low costs, but also challenges. Study variables might not be well-defined or missing, data quality might be variable and questionable, and there is limited possibility for the collection of detailed safety data.[14,15] Therefore, RRCTs are better fitted for the evaluation of therapeutic options used in routine clinical care, while traditional RCTs are more appropriate for studies aiming for the approval of new pharmaceutical agents and medical devices.

A large observational registry study, with an inherent risk for selection bias and residual confounding, published after the initiation of the TACSI trial, showed no significant difference in MACE (including all-cause death, myocardial infarction, and stroke) between DAPT with ASA and ticagrelor and ASA monotherapy, but an increased risk for major bleeding during the first postoperative year.[28] A meta-analysis focusing on clinical outcomes and based on both randomized trials and observational data, demonstrated that DAPT was associated with lower cardiovascular mortality after CABG but with a higher incidence of major bleeding.[29] The lower overall cardiovascular mortality was not replicated when the analysis was restricted to randomized trials. Hence, importantly these more recent studies do not change the level of evidence and the question whether patients with ACS undergoing CABG should be treated with DAPT remains elusive, and thus the need for the TACSI trial.

Funding

The trial is funded by Swedish Research Council (grant 2017-00495 to AJ), The Swedish Heart Lung Foundation (grants 2017-0459 to AJ; 2018-0560 to AJ, 2021-0433 to AJ) the Swedish state under an agreement between the Swedish government and the county councils concerning economic support of research and education of doctors (ALF agreement) (grants ALFGBG 925251 to AJ; ALFGBG 725131 to AJ; ALFGBG 966204 to AJ. There is no industrial involvement or support.

Author contributions

Carl Johan Malm: investigation, writing - original draft. **Joakim Alfredsson:** conceptualization, study design, methodology, writing - review and editing. **David Erlinge:** conceptualization, study design, methodology, writing - review and editing. **Tomas Gudbjartsson:** investigation; writing - review and editing. **Jarmo Gunn:** Investigation; writing - review and editing. **Stefan James:** conceptualization, study design, methodology, writing - review and editing. **Christian H. Møller:** investigation; writing - review and editing. **Susanne J. Nielsen:** conceptualization, study design, methodology, writing - review and editing. **Ulrik Sartipy:** conceptualization, study design, methodology, writing - review and editing. **Theis Tønnessen:** investigation; writing - review and editing. **Anders Jeppsson:** conceptualization, study design, funding acquisition, methodology, writing - review and editing.

Disclosures

AJ reports personal fees from AstraZeneca and LFB Biotechnologies outside the present study. None of the other authors report any conflict of interests.

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