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Routine revascularization with percutaneous coronary intervention in patients with coronary artery disease undergoing transcatheter aortic valve implantation – the third nordic aortic valve intervention trial – NOTION-3

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Background Coronary artery disease (CAD) frequently coexists with severe aortic valve stenosis (AS) in patients planned for transcatheter aortic valve implantation (TAVI). How to manage CAD in this patient population is still an unresolved question. In particular, it is still not known whether fractional flow reserve (FFR) guided revascularization with percutaneous coronary intervention (PCI) is superior to medical treatment for CAD in terms of clinical outcomes.

Study design The third Nordic Aortic Valve Intervention (NOTION-3) Trial is an open-label investigator-initiated, multicenter multinational trial planned to randomize 452 patients with severe AS and significant CAD to either FFR-guided PCI or medical treatment, in addition to TAVI. Patients are eligible for the study in the presence of at least 1 significant PCI-eligible coronary stenosis. A significant stenosis is defined as either FFR ≤ 0.80 and/or diameter stenosis $> 90\%$. The primary end point is a composite of first occurring all-cause mortality, myocardial infarction, or urgent revascularization (PCI or coronary artery bypass graft performed during unplanned hospital admission) until the last included patient have been followed for 1 year after the TAVI.

Summary NOTION-3 is a multicenter, multinational randomized trial aiming at comparing FFR-guided revascularization vs medical treatment of CAD in patients with severe AS planned for TAVI. (*Am Heart J* 2023;255:39–51.)

Background

Aortic stenosis (AS) is present in 2% to 7% of the general population > 65 year in the Western world and is associated with increased mortality and morbidity when the AS is severe.¹ Surgical aortic valve replacement (SAVR) has been the dominant treatment for severe AS since the 1960s. However, the last decade has seen a rapid increase in transcatheter aortic valve implantation (TAVI), the use of which in 2019 surpassed SAVR in number of procedures.² There is an overlap between the etiology and risk factors of coronary artery disease (CAD) and AS explaining why they often coexist.^{3,4} The prognostic importance of coexisting CAD in patients undergoing TAVI is unclear due to varying CAD definitions, absence of physiological assessment of CAD severity, use of SYNTAX score, as well as incomplete reporting of end points based on CAD status.^{3,5} Moreover, the benefit of coronary revascularization on the overall prognosis may be minimal, as patients planned for

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TAVI are predominantly elderly patients which may have a higher risk of procedural complications and post procedural dual anti-platelet therapy and a significant competing risk of death. Finally, only a minority of the patients have angina upon presentation. Consequently, the European guidelines recommendation on coronary revascularization in patients with severe AS and concomitant CAD undergoing TAVI is weak (Class II, level of evidence C).⁶ Moreover, the recommendation is to use angiography to guide revascularization (coronary artery diameter stenosis >50% or >70%). However, in current practice, it is widely accepted that invasive fractional flow reserve (FFR) is superior to angiography alone, in terms of guiding the decision to revascularize coronary lesions in patients without significant valvular disease.⁷⁻¹⁰ Hitherto, only 1 randomized study, without a firm conclusion, have addressed this issue.¹¹ Thus, we are still lacking decisive randomized evidence on whether patients with CAD planned for TAVI should undergo coronary revascularization in addition to TAVI or could be treated with TAVI only. As TAVI is increasingly adopted worldwide, and also in younger patients at lower surgical risk, this question is of paramount importance for selecting the proper treatment for this growing patient population. Moreover, the safety of physiology (FFR) to guide coronary revascularization in patients with AS is unknown.

Hypothesis and aim

The aim of the NOTION-3 trial is to evaluate the effect of routine FFR-guided complete revascularization with PCI against conservative management of CAD in AS patients undergoing TAVI. The hypothesis is that revascularization is superior to conservative management. The study is registered on www.clinicaltrials.gov (identifier NTC03058627).

Methods

This study was funded by an unrestricted grant from Boston Scientific for investigator-initiated trials and a grant from the Danish Heart Foundation (17-R116-A7697-22073). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study design and organization

NOTION-3 is an open-label investigator-initiated, multicenter multinational randomized trial involving 12 centers in Denmark, Finland, Latvia, and Sweden. All participating centers have an annual volume of minimum 100 TAVI procedures and the steering committee consists of representatives from all participating centers. Patient enrollment started in 2017 and is expected to continue through 2022 with reporting of the primary end point in 2023 and the final follow-up in 2027.

Inclusion and exclusion criteria

Inclusion and exclusion criteria listed in [Table I](#).

Randomization and inclusion of patients

Patients fulfilling in- and exclusion criteria are, after written and oral informed consent, randomized 1:1 to either TAVI + conservative management of CAD (Conservative treatment) or TAVI + FFR-guided complete revascularization with PCI (Revascularization). Randomization is performed using a web-based electronic case report form and permuted-blocks with varying block size of 2 or 4 and stratified by center. All patients with at least 1 coronary lesion with coronary artery diameter stenosis >50% referred for TAVI after a Heart Team conference are screened for inclusion. Patients with significant CAD can be randomized immediately. Significant CAD is defined as at least 1 coronary stenosis with a positive FFR (≤ 0.80) or diameter stenosis >90%. In cases with a diameter stenosis >90% FFR is not mandatory. Patients referred for TAVI with an initial coronary angiography (CAG) with lesion(s) with diameter stenosis 50% to 90% without FFR measurement or a heart CT with suspicion of CAD will have a new CAG with FFR measured before the decision to randomize the patient in the study. These patients will provide informed consent before the FFR procedure, such that randomization can be carried out as soon as a positive FFR is measured. Patients with non-significant CAD, defined as diameter stenosis >50% with negative FFR (>0.80) can be included in the NOTION-3 Registry. CAG with or without FFR is recommended to be performed before TAVI as a stage procedure, but it is also allowed for CAG with or without FFR to be performed concomitant with the TAVI procedure or ≤ 2 days after in special cases due to local logistical reasons. FFR is used to evaluate coronary lesions with coronary artery diameter stenosis 50% to 90% and measured using a pressure wire following 2 minutes of continuous infusion of adenosine (140 ug/kg/min) in a central vein. Alternatively, intracoronary bolus administration of adenosine (100 ug for RCA or 200 ug for the left coronary artery) was used. [Figure](#) illustrates the patient flow.

Conservative treatment of the CAD

Patients randomized to conservative management of CAD are not revascularized before TAVI and no revascularization is planned after TAVI. The patients are managed according to the standard clinical care after TAVI. The CAD should be handled according to clinical assessment including evaluation of symptoms. The patients may at any time, if clinically indicated according to guidelines, be referred for a new CAG and coronary revascularization. Revascularization will in this case be considered and adjudicated as an event (unplanned revascularization). Revascularization will only be performed on clinical indications according to current guidelines for revascularization.¹²

Table I. Inclusion and exclusion criteria

Inclusion criteria

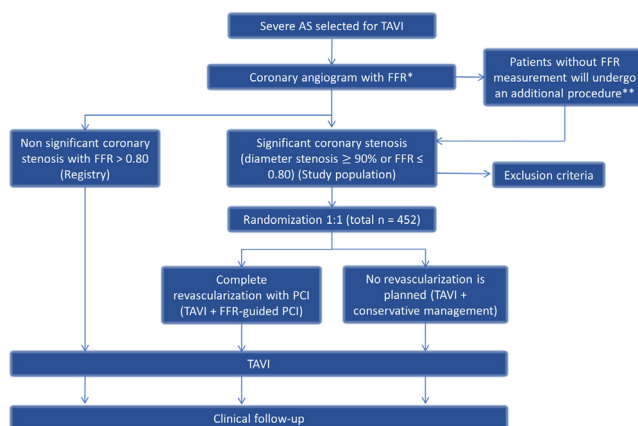
1. Age \geq 18 y
2. Severe aortic valve stenosis and selected for TAVI by a multi-disciplinary Heart Team
3. At least 1 stenosis with FFR \leq 0.80 or coronary artery diameter stenosis $>$ 90% in a coronary artery \geq 2.5 mm in diameter

Exclusion criteria

1. Life expectancy $<$ 1 y due to other severe non-cardiac disease
2. Severe renal failure with estimated glomerular filtration rate $<$ 20 ml/min
3. No PCI-eligible coronary artery stenosis
4. Admitted with a new acute coronary syndrome (ST-elevation myocardial infarction (STEMI) or non-STEMI) within 14 days
5. Significant stenosis in left main stenosis or ostial left anterior descending artery (LAD) + ostial left circumflex artery (LCx)
6. Only stenoses with thrombolysis in myocardial infarction (TIMI) grade $<$ 3
7. Potential pregnancy
8. Known allergy toward P2Y12 receptor antagonists or heparin
9. More than 1 chronic total occlusion (CTO)

CTO, chronic total occlusion; LAD, left anterior descending artery; LCx, left circumflex artery; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Figure



Flow chart for patient inclusion and randomization. AS indicates aortic stenosis; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation. *Part of routine work-up in patients considered for TAVI. **Applies only to patients with coronary artery diameter stenosis of 50% to 90%. The additional procedure was not performed until any affection of renal function had returned to habitual baseline.

Antithrombotic treatment in the Conservative treatment group

Antithrombotic treatment is prescribed according to international TAVI recommendations. In the period before, the patients without an indication for oral anticoagulation are treated with aspirin (75 mg daily) lifelong, loaded with clopidogrel (300-600 mg) pre-TAVI and continued on clopidogrel (75 mg daily) for 3 months. In case oral anticoagulant therapy is indicated, the patients are treated with oral anticoagulation (vitamin K antagonist (INR 2-3) or direct oral anticoagulant) and clopidogrel (75 mg daily) for 3 months followed by oral anticoagulant monotherapy lifelong. POPular TAVI trials^{13,14}

showed a clear overall benefit of reducing anticoagulant and antithrombotic therapy after TAVI. As a direct consequence, from early 2020, patients without an indication for oral anticoagulation are treated with aspirin (75 mg daily) lifelong alone (or clopidogrel, in case of a contraindication for aspirin or a strong indication for clopidogrel). In case life-long oral anticoagulant therapy is indicated, the patients are treated with oral anticoagulant monotherapy (vitamin K antagonist or direct oral anticoagulant) lifelong alone. It is encouraged not to use other combinations and durations of treatment. If, based on a thorough individual patient risk assessment, this is done, the reason should be clearly explained. Any additional

medication may be prescribed based on individual patient assessment.

FFR-guided complete revascularization

In patients randomized to full revascularization, PCI is performed in any suitable lesion in coronary arteries ≥ 2.5 mm in diameter and with coronary artery diameter stenosis $>90\%$ or FFR ≤ 0.80 . The protocol recommended PCI before TAVI as a stage procedure, but also allowed for PCI to be performed concomitant with the TAVI procedure or ≤ 2 days after in special cases due to local logistical reasons and recommendation. Full revascularization is intended, but incomplete revascularization is allowed if PCI is deemed not feasible in 1 or more lesions (eg, due to chronic total occlusions). PCI is performed according to current guidelines and stenting is generally encouraged but not mandatory. The choice of stent is at the discretion of the operator, but latest generation drug-eluting stents are recommended. Calcium modification techniques were left to the discretion of the operator.

Antithrombotic treatment in the revascularization group

Antithrombotic treatment is prescribed according to the recommendations in international guidelines applicable at the time of PCI treatment: Patients will be treated with aspirin (75 mg) lifelong and loaded with clopidogrel (300-600 mg) during the PCI procedure, heparin during the PCI and TAVI-procedure (ACT > 250) and maintenance dose of clopidogrel (75 mg) per day for 6 months. In case of indication for life-long treatment with oral anticoagulant, aspirin (75 mg) per day was used for 1 month and clopidogrel (75 mg) per day for 6 months. The AUGUSTUS trial¹⁵ showed clear benefit of reducing the aspirin treatment period for patients with a life-long indication for anticoagulant therapy undergoing PCI. As a direct consequence, after AUGUSTUS trial was published, the duration of aspirin was in case of lifelong indication of oral anticoagulant shorten to < 7 days.¹⁵ It is encouraged not to use other combinations and durations of treatment. If, based on a thorough individual patient risk assessment, this is done, the reason should be clearly explained.

TAVI procedure

All patients are discussed by the Heart Team consisting of 1 interventional cardiologist, 1 cardiac surgeon and 1 non-interventional cardiologist.¹⁶ Severe AS is defined as an effective orifice area < 1 cm² or 0.6 cm²/m², AND a mean transvalvular gradient > 40 mmHg or a peak systolic velocity > 4 m/s as assessed by echocardiography – a dobutamine stress echocardiography is allowed in case of LVEF $< 50\%$. A transfemoral TAVI approach with use of local anesthesia or conscious sedation only is the standard approach, but alternative access and/or use of gen-

eral anesthesia is allowed. The use of pre- and/or post dilatation, right or left ventricular pacing, the choice of transcatheter heart valve (THV) type and size, and the choice of vascular closure device type is left at the discretion of the treating physician. All patients are monitored for a minimum of 24 hours after TAVI and the decision for possible permanent pacemaker implantation and early discharge is taken in consultation with the attending physician.

Follow-up

All patients will be followed for 5 years from the date of TAVI and the primary end point will be reported when the last included patient has been followed for 1 year after TAVI. By that time, most patients will have been followed for longer than 1 year and thus an average follow-up time of 2 years is expected for the report of the primary end point. Telephone follow-up interviews will be performed at 1 and 12 months after the TAVI procedure.

End points

The primary end point is a composite of first occurring all-cause mortality, myocardial infarction, or urgent revascularization (PCI or CABG performed during unplanned hospital admission with acute coronary syndrome) until the last included patient has been followed for 1 year after the TAVI. Secondary end points are listed in [Table II](#). The end points are defined according to The Valve Academic Research Consortium-2 (VARC-2),¹⁷ and/or 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular End point Events in Clinical Trials¹⁸ (see appendix). All end points related to mortality or hospitalizations will be identified using hospital files and national registries, in which all deaths and hospital referrals are reported. The following events will be adjudicated by an independent clinical events committee (CEC): death, myocardial infarction, any unplanned revascularization, admission for heart failure, stroke, bleeding, and renal failure. Members of the CEC will review all relevant medical records and other available material. The members of the CEC have no access to information regarding treatment allocation. The CEC consists of 3 independent cardiologists. A complete list of the members is given in the appendix.

Safety monitoring

An independent data safety monitoring board (DSMB) will monitor interim analyses for both safety and efficacy study end points. The key responsibilities of the DSMB are: 1. Reviewing the study protocol; 2. Evaluating the quality of ongoing study conduct including accrual rate, adherence to protocol, accuracy and completeness of data capture; 3. Assessing safety and efficacy data by intervention group. The DSMB should meet at least once when the first 50% of the patients have been included

Table II. Primary and secondary end points

End point	
Primary end point (composite)	All-cause mortality, myocardial infarction, or urgent revascularization
Secondary end points	<ol style="list-style-type: none"> 1. Individual components of the primary end point 2. Mortality or myocardial infarction 3. Cardiovascular mortality 4. Cardiovascular mortality, myocardial infarction, or urgent PCI 5. Cardiovascular mortality or myocardial infarction 6. Peri-procedural (PCI or TAVI) myocardial infarction 7. Spontaneous myocardial infarction 8. Any revascularization 9. Target vessel revascularization 10. Target lesion revascularization 11. Definitive stent thrombosis 12. Admission for new onset of heart failure 13. Stroke or transient ischemic attack 14. Bleeding (VARC and BARC > 1) 15. Acute Kidney Injury 16. Cost effectiveness analysis 17. CCS class, 1 mo and 1 y 18. NYHA class, 1 mo and 1 y 19. Quality of life (EQ5d5L), 1 mo and 1 y 20. Delta LVEF, LV mass, end systolic and diastolic volume, peak aortic velocity and mean aortic gradient by echocardiography, 1 mo and 1 y

BARC, bleeding academic research consortium; CCS, canadian cardiovascular society; LV, left ventricle; LVEF, left ventricular ejection fraction; NYHA, New York heart association; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; VARC, valve academic research consortium.

and followed for at least 1 month after TAVI. Furthermore, the primary end point for these patients must be adjudicated by the event committee. All additional patients included at the time point of full event adjudication will also be included in the analysis. The DSMB will consist of 3 cardiologists chosen before study start. Premature termination of the study will be mandated if 1 of the treatment strategies shows statistically significant inferiority with regards to safety to a higher degree than expected. No members of the DSMB participate in recruitment or data collection and are all blinded to treatment allocations. A complete list of the members is given in the appendix.

Sample size

As the primary end point is based on follow-up until the last included patient have been followed for 1 year after the TAVI, the mean follow-up time for all patients will be longer and estimated to be 2 years. The sample size calculation is therefore based on expected events after 2 years follow-up. The event rate for the primary end point is expected to be 35% (all-cause mortality 17%, and myocardial infarction or urgent PCI 18%) in the conservative group (TAVI only). These rates are estimated based on previous observations: all-cause mortality at 2-years was 16.7% in PARTNER II;¹⁹ myocardial infarction or urgent revascularization at 2 years was 17.7% in FAME II⁹. In a STEMI cohort with concomitant multi-vessel disease complete revascularization compared to culprit only PCI

resulted in a relative reduction of urgent revascularization of 67%.²⁰ A similar relative reduction of 75% was observed following complete revascularization in a cohort of stable ischemic heart disease.⁹ Thus, the expected event rate for the primary end point in the FFR-guided complete revascularization group is 23% (all-cause mortality 16%, and myocardial infarction or urgent PCI 7%). With a statistical power of 80% and a 2-sided alpha of 5% and 1:1 randomization a total of 452 patients are required to detect a reduction in the primary end point from 35% to 23%. As the event rate in this population is uncertain an interim analysis of total number of events will be performed when 226 (50% of the patients) have been followed for at least 1 month after TAVI. The number of patients to be enrolled in the study may be adjusted according to the event rate in the conservative arm of the study.

Statistical analysis plan

The end points will be analyzed according to the intention-to-treat principle. Differences between groups in time-to-event end points will be assessed with the log-rank test (for the primary end point, patients will be censored in case they reach an event or until the last included patient has been followed for 1 year after the TAVI). Survival probabilities will be illustrated using Kaplan-Meier graphs. Hazard ratios between groups will be calculated using a Cox proportional hazard model. Differences between group means/medians will be as-

Table III. Pre-specified subgroups for analysis of primary end points

Pre-specified subgroups

Age (\geq median and $<$ median)
Sex
Known diabetes
Previous myocardial infarction
Stabil angina status before inclusion
Number of diseased vessels
Proximal lesion stenosis
Proximal LAD stenosis
Coronary artery diameter stenosis ($>90\%$ and $\leq 90\%$)
FFR value
LVEF ($>40\%$ and $\leq 40\%$)
Presence of CTO
STS score
Syntax score
Risk of bleeding (Precise-DAPT)
Type of aortic valve stent
Access for TAVI (transfemoral, apical and cervical)

CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; FFR, fractional flow reserve; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; STS, society of thoracic surgeons score; TAVI, transcatheter aortic valve implantation.

essed with parametric or non-parametric statistics. The χ^2 analysis or Fisher exact test will be used to test differences between proportions. A 2-tailed P -value $< .05$ is considered statistically significant. Additional follow-ups after 3 and 5 years are planned.

Subgroup analyses

Primary end points will also be analyzed according to several pre-specified subgroups listed in [Table III](#).

Ethical considerations

The protocol has been approved by the Danish Ethical Committee (Region Hovedstaden: H-16039929) and by local regional ethics committees in each participating country. The collection of data complies with the regulatory rules of the Danish Data Protection Agency (Region Hovedstaden, Journal issue: 2012-58-0004), and the study is being conducted in compliance with good clinical practice and with the Helsinki II Declaration as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions. All patients provide written informed consent and can withdraw from the study at any time if they chose to or if it is deemed medically indicated, by the investigator. A patient's participation in the study will be discontinued if the patient's general condition contraindicates continuing the study or if the patient turns out to be non-eligible. Existing data suggest that PCI in patients with stable CAD has no preventive effect, compared to medical treatment, on mortality. FFR in lesions with coronary artery diameter stenosis $>50\%$ on coronary angiography or cardiac CT ss performed as part of routine work-up in most cen-

ters referring patients for TAVI, and enrollment in this study will therefore not expose the patients to any additional risk. The exclusion criteria ensure that patients with severe coronary artery disease in which medical treatment is not safe is not included in the trial. The benefit from PCI is expected to constitute a reduction in the need for urgent PCI and elective PCI, although implantation of stents introduces the risk of a stent thrombosis. In this trial we find the potential clinical benefit from treatment of all coronary lesions (versus conservative management) to outweigh the risk associated with the potential repeat procedures performed in patients with CAD randomized to conservative management. The planned follow-up echocardiography is standard procedure for patients treated with TAVI, and therefore not an additional burden to the patients.

NOTION-3 Registry

In NOTION-3 only patients with either FFR positive lesions, or with lesion with coronary artery diameter stenosis $\geq 90\%$ will be randomized, whereas patients with FFR-negative lesions with coronary artery diameter stenosis $>50\%$ will be followed in a registry, NOTION-3-registry, and events detected. This will allow for evaluation of the safety of deferring PCI in patients with FFR-negative lesions. These patients will be evaluated for clinical events in line with the randomized study group. Follow-up will be done by hospital files, and telephone interview will not be performed. All patients in the registry will provide written informed consent.

Discussion

Hitherto, the ACTIVATION trial is the only completed randomized study addressing the question of revascularization with PCI vs medical therapy in patients planned for TAVI.¹¹ A total of 235 patients were randomized. At 1 year after TAVI the primary end point (composite of all-cause mortality and rehospitalization) occurred in 48 (41.5%) of patients treated with PCI, and in 47 (44.0%) treated conservatively, with events driven by rehospitalizations. The requirement for non-inferiority of PCI in combination with TAVI was not met, although no PCI showed non-inferiority at 1 year for angiographically significant stenoses in the analysis of the as-treated population, $P = .05$. Moreover, no difference was found between groups in term of secondary outcomes (stroke, myocardial infarction, or acute kidney injury), except for rate of bleeding from any cause which was higher in the PCI arm.¹¹ The trial was limited by premature termination of patient enrollment, exclusion of patients with CCS class III and no use of invasive physiology (FFR) to evaluate the significance of CAD. In NOTION-3, the CAD severity is assessed based on a physiological pressure index, FFR, which is the gold standard in stable CAD.²¹ The validity of invasive physiological assessment of coro-

nary stenosis severity pre-TAVI in patients with severe AS has been subject to some debate. The main question has been whether FFR would decrease following TAVI due to increased coronary flow, and thus lead to reclassification of lesions near the cut-off value of ≤ 0.80 . Therefore, non-hyperemic indices such as resting full-cycle ratio (RFR) and instantaneous wave-free ratio (iFR) have been suggested as alternatives to FFR in this patient population. However, pre- and long-term post-TAVI comparison of the different indices indicate that FFR may be the most robust index.^{22,23}

Antithrombotic treatment

TAVI and PCI are both moving targets and new evidence may change the recommendations for the treatment during the inclusion period. In NOTION-3 this was the case for antithrombotic treatment as the POPular TAVI trials were published in 2020 and the AUGUSTUS trial in 2019. These trials have resulted in the change described in the method section and may impact results, particularly in terms of bleeding events.

End point definitions

Since the commencement of the NOTION-3 trial, the Valve Academic Research Consortium criteria have been updated to the third version (VARC-3)²⁴ which may affect end point definitions. The expected number of end points with the new definitions is difficult to predict as there is no data from this patient population.

Summary

NOTION-3 is a multicenter randomized trial aiming to evaluate the effect of routine FFR-guided complete revascularization versus conservative management of CAD in 452 patients with severe AS undergoing TAVI. The primary end point is defined as a composite of all-cause mortality, myocardial infarction, or urgent revascularization until the last included patient has been followed for 1 year after the TAVI. The trial was started in 2017 and is expected to end in 2022 with report of the primary end point in 2023.

Conflict of interest

None reported.

Appendix

Data Safety Monitoring Board

Lars Køber, Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, Denmark and Department of Clinical Medicine, University of Copenhagen, Denmark

Nico Pijls, Catharina Hospital, Department of Cardiology, Eindhoven, The Netherlands.

Göran Olivencrona, Department of Cardiology, Clinical Sciences, Lund University, Skåne, University Hospital, Lund, Sweden.

Clinical events committee

Jørgen Jeppesen, Glostrup Copenhagen University Hospital, Department of Cardiology, Copenhagen, Denmark.

Kjell Nikus, Tampere University Hospital, The Heart Center, Tampere, Finland

Ole Fröbert, Örebro University Hospital, Department of Cardiology, Örebro, Sweden

Event charter

The following end points are defined according to the The Valve Academic Research Consortium-2 (VARC-2),²⁵ and/or 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular End point Events in Clinical Trials¹⁸:

1. Mortality
2. Myocardial infarction (MI)
3. Revascularization
4. Hospitalization for heart failure
5. Stroke or transient ischemic attack (TIA)
6. Bleeding
7. Acute kidney failure

1. MORTALITY^{18,25}

The clinical event committee (CEC) will aim to attribute the cause of death to the underlying disease process rather than the immediate mechanism. Mortality will be classified as cardiovascular and non-cardiovascular.

A. Cardiovascular death

Mortality is considered as cardiovascular unless it is clearly attributable to another cause and thus includes:

- Death due to proximate cardiac cause (eg, myocardial infarction, cardiac tamponade, worsening heart failure).
- Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease.
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure.
- All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events.
- Sudden or unwitnessed death.
- Death of unknown cause.

B. Non-cardiovascular mortality

Any death in which the primary cause of death is clearly related to another condition (eg, infection, cancer, suicide, accident, pulmonary, hepatobiliary, gastrointestinal, renal, overdose, neurological (excluding stroke

and or cardiovascular hemorrhage of central nervous system).

2. MYOCARDIAL INFARCTION (MI)^{18,25}

MI is classified as spontaneous or peri-procedural < 72 hours of TAVI and < 48 hours of CAG/PCI and CABG:

A. Spontaneous MI²⁵:

Any of the following 3:

1. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL (if cardiac biomarkers are increased at baseline (99th percentile), a further increase of at least 20% is required AND the peak value must exceed the previously stated limit), together with the evidence of myocardial ischaemia from at least 1 of the following:
 - a) Symptoms of ischaemia
 - b) ECG changes indicative of new ischaemia in 2 contiguous ECG leads
 - c) New pathological Q-waves in 2 contiguous ECG leads
 - d) Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
2. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood and accompanied by:
 - a) Presumably new ST elevation
 - b) New LBBB
 - c) Evidence of fresh thrombus by coronary angiography and/or at autopsy
 - d) Pathological findings of a MI

B. Peri-procedural MI:

1 TAVI²⁵:

Detection of at least 1 post procedural sample of cardiac biomarkers (preferable CK-MB) < 72 hours of TAVI with a peak value exceeding 15 x the upper reference limit for troponin or 5 x for CKMB (if cardiac biomarkers are increased at baseline (99th percentile), a further increase in at least 50% required AND the peak value must exceed the previously stated limit), with at least 1 of the following:

- a) New ischemic symptoms
- b) Ventricular arrhythmias
- c) New or worsening heart failure
- d) ECG changes indicative of new ischaemia or new pathological Q waves in 2 contiguous ECG leads
- e) Hemodynamic instability
- f) Imaging evidence of new loss of viable myocardium or new wall motion abnormality

2 PCI¹⁸:

Detection of at least 1 post procedural sample of cardiac biomarkers (preferable CK-MB) < 48 hours of PCI with 5 x the upper reference limit for troponin or CK-MB (if cardiac biomarkers are increased at baseline (99th percentile), a further increase in at least 20% required AND the peak value must exceed the previously stated limit), with at least 1 of the following:

- a) New ischemic symptoms
- b) New ischemic changes on ECG indicative of new ischaemia or pathological Q waves in 2 contiguous ECG leads
- c) Imaging evidence of new loss of viable myocardium or new wall motion abnormality
- d) Angiographic evidence of a flow limiting complication, such as of loss of patency of a side branch, persistent slow-flow or no-reflow, embolization

3 CABG¹⁸:

Detection of at least 1 post-procedural sample of cardiac biomarkers (preferable CK-MB) < 48 hours of CABG with a peak value exceeding 10 x the upper reference limit for troponin or CK-MB (if cardiac biomarkers are increased at baseline (99th percentile), a further increase in at least 20% required AND the peak value must exceed the previously stated limit, with at least 1 of the following:

- a) New pathological Q waves or new LBBB
- b) Imaging evidence of new loss of viable myocardium or new wall motion abnormality
- c) Angiographically documented new graft or new native coronary artery occlusion

3. Revascularization¹⁸

Revascularization includes any unplanned revascularization (PCI or CABG) performed after the initial treatment allocation. Revascularization is further classified as urgent or non-urgent. [Table I-IV](#)

Target lesion revascularization (TLR): Any repeat PCI or CABG of a lesion that was treated or deferred based on the initial randomization. The target lesion is defined as the treated segment from 5 mm proximal to 5 mm distal to the stent or from 5 mm proximal to 5 mm distal to the deferred lesion.

Target vessel revascularization (TVR): Any repeat PCI or CABG of any segment in a vessel treated or deferred based on the initial randomization. The target vessel is defined as the entire coronary vessel proximal and distal to the treated segment or proximal and distal to the deferred lesion, including any upstream and downstream side branches.

Definite stent thrombosis: The presence of thrombus in the stent or the segment 5 mm proximal or distal to the stent plus at least 1 of the following:

1. acute onset of ischemic symptoms in rest
2. new ECG changes that suggest new ischemia

Table I. Value definition MI

Values	Value definition
ECG changes indicative of new ischemia	In the absence of left ventricular hypertrophy and LBBB pattern (or other confounder such as a paced rhythm) on ECG, either a) new (or presumed new) ST elevation at the J point in 2 contiguous leads with the following cut points: 0.1 mV in all leads other than leads V1-3 where the following cut points apply: 0.2 mV in men 40 y of age; 0.25 mV in men < 40 y of age, or 0.15 mV in women; or b) new (or presumed new) horizontal or downsloping ST-segment depression 0.05 mV in 2 contiguous leads and/or T inversion 0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio > 1; or c) New LBBB.
New Q waves	New (or presumed new) a) Q wave in leads V2-3 0.02 s or QS complex in leads V 2 and 3 b) Q wave 0.03 s and 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V 4-6 in any 2 leads of a contiguous lead grouping (I, aVL; V1-6; II, III, aVF; V 7-9); or c) c) R wave 0.04 s in V1-2 and R/S 1 with a concordant positive T wave in the absence of a conduction defect.
New ischemic symptoms	Presence of acute symptoms of myocardial ischemia, at rest or accelerated ischemic symptoms, either of which the investigator determines is secondary to ischemia, such as a) chest, upper extremity, mandibular, or epigastric discomfort, or b) an ischemic equivalent such as dyspnea or fatigue.

Table II. Value definition revascularization

Values	Value definition
Worsening ischemic discomfort	Documentation of ischemic discomfort (angina, or symptoms thought to be equivalent) occurring either a) at rest, or b) in an accelerating pattern with frequent episodes associated with progressively decreasing exercise capacity.
Objective evidence of myocardial ischemia	a) Changes on resting ECG (specified below) b) Inducible myocardial ischemia (specified below) c) Coronary lesion on angiography (specified below) d) Coronary revascularization (specified below)
Changes on resting ECG	New or worsening ST or T-wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH), defined as either a) Transient ST elevation (duration <20 min): new ST elevation at the J point 0.1 mV in any 2 contiguous leads (other than leads V2 to V3); in leads V2 to V3, the following cut points apply: 0.2 mV in men 40 y of age, 0.25 mV in men <40 y of age, and 0.15 mV in women. b) ST depression and T-wave changes: new horizontal or downsloping ST depression 0.05 mV in 2 contiguous leads and/or new T inversion 0.3 mV in 2 contiguous leads with prominent R wave or R/S ratio > 1.
Inducible myocardial ischemia	a) An early positive exercise stress test result, defined as ST elevation or 2 mm ST depression before 5 METs b) Stress echocardiography (reversible wall motion abnormality) c) Myocardial scintigraphy (reversible perfusion defect) d) MRI (myocardial perfusion deficit under pharmacological stress) e) FFR positive lesion
Coronary lesion on angiography	Angiographic evidence of a lesion, new or worsening of an existing lesion, and/or thrombus in an epicardial coronary artery believed to be responsible for the myocardial ischemic symptoms/signs.
Coronary revascularization	Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization or subsequent to transfer to another institution without interceding home discharge.

3. spontaneous rise and fall in biomarkers

4. non-occlusive thrombus or

5. TIMI 0/1

A. Urgent revascularization (revascularization due to the indication ACS):

Includes any revascularization (PCI or CABG) performed during unplanned hospital admission with acute coronary syndrome (MI or unstable angina*). For definition of MI, please see section 2.

* Unstable angina requires that all the following criteria be met:

a) Worsening ischemic discomfort (specified in [Table II](#))

b) Unscheduled hospitalization

c) Objective evidence of myocardial ischemia (specified in [Table II](#))

d) Cardiac biomarkers not indicative of acute myocardial infarction

B. Non-urgent revascularization:

Includes any revascularization (PCI or CABG) that does not meet the criteria for urgent revascularization.

4. Hospitalization for heart failure¹⁸

Table III. Value definition heart failure

Values	Value definition
New or worsening symptoms of HF	a) Dyspnea b) Decreased exercise tolerance c) Fatigue d) Volume overload
Objective evidence of new or worsening HF	<u>Physical examination:</u> a) Peripheral edema b) Increasing abdominal distention or ascites c) Pulmonary rales/ crackles/crepitations d) Increased jugular venous pressure and/ or hepatojugular reflux e) S3 gallop f) Clinically significant or rapid weight gain <u>Laboratory criterion:</u> a) Biomarker increases BNP/ NT-pro BNP (> upper reference limit). In patients with chronically elevated natriuretic peptides, a significant increase above baseline is required. b) Radiological evidence of pulmonary congestion: imaging findings consistent with increased intravascular blood volume in the lungs.
Receives initiation or intensification of treatment specifically for HF	a) Augmentation of oral diuretic therapy b) Intravenous diuretic, inotrope, or vasodilator therapy c) Mechanical or surgical intervention including any LV assist device and mechanical fluid removal

Table IV. BARC definition²⁶

BARC bleeding definition

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional.
Type 2	Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least 1 of the following criteria: (1) Requiring nonsurgical, medical intervention by a health care professional (2) Leading to hospitalization or increased level of care (3) Prompting evaluation
Type 3	Type 3a <ul style="list-style-type: none"> ■ Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed) ■ Any transfusion with overt bleeding Type 3b <ul style="list-style-type: none"> ■ Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed) ■ Cardiac tamponade ■ Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) ■ Bleeding requiring intravenous vasoactive agents Type 3c <ul style="list-style-type: none"> ■ Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) ■ Subcategories confirmed by autopsy or imaging or lumbar puncture ■ Intraocular bleed compromising vision
Type 4	<ul style="list-style-type: none"> ■ Perioperative intracranial bleeding within 48 h ■ Reoperation after closure of sternotomy for the purpose of controlling bleeding ■ Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period (only allogenic transfusions are considered transfusions for CABG-related bleeds) ■ Chest tube output ≥ 2 L within a 24-h period Notes: If a CABG-related bleed is not adjudicated as at least a type-3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type-4 severity criteria, it will be classified as not a bleeding event.
Type 5	Type 5a <ul style="list-style-type: none"> ■ Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious Type 5b <ul style="list-style-type: none"> ■ Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

- A. Prolongation of hospitalization because of worsening of heart failure or presentation of the patient for an urgent, unscheduled clinic/office/emergency department visit or hospital admission (>24 hours), with a primary diagnosis of HF, AND
- B. where the patient exhibits new or worsening symptoms of HF on presentation, AND
- C. has objective evidence of new or worsening HF *, AND
- D. receives initiation or intensification of treatment specifically for HF

* Objective evidence consists of at least 2 physical examination findings OR at least 1 physical examination finding and at least 1 laboratory criterion (chest x-ray or BNP) of new or worsening HF on presentation.

5. Stroke or TIA^{18,25}

An acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Stroke: Duration of a focal or global neurological deficit >24 h; OR <24 h if available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death.

TIA (transitory ischemic attack): Duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct.

Confirmation of the diagnosis by at least 1 of the following:

- a) Neurologist or neurosurgical specialist
- b) Neuroimaging procedure (CT scan or brain MRD), but stroke may be diagnosed on clinical grounds alone

Stroke/TIA is further classified as:

- a) Ischemic
- b) Hemorrhagic
- c) Undetermined

6. Bleeding (VARC-2 and Bleeding Academic Research Consortium (BARC))²⁶

Bleeding is classified as:

- a) Life-threatening or disabling bleeding:
 - 1) Fatal bleeding (BARC type 5) OR
 - 2) Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
 - 3) Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
 - 4) Overt source of bleeding with drop in haemoglobin >5 g/dL or whole blood or

packed red blood cells (RBCs) transfusion >4 units (BARC type 3b)

b) Major bleeding (BARC type 3a):

- 1) Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of 2 or 3 units of whole blood/RBC, or requiring surgery AND
- 2) Does not meet criteria of life-threatening or disabling bleeding

c) Minor bleeding (BARC type 2 or 3a, depending on the severity):

Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life-threatening, disabling, or major, but meet at least 1 of the following criteria:

- 1) Requiring nonsurgical, medical intervention by a health care professional
- 2) Leading to hospitalization or increased level of care
- 3) Prompting evaluation

BARC type 1 is not considered as end point.

7. Acute kidney failure (VARC-2)²⁶

VARC II criteria.

Stage 1:

Increase in serum creatinine to 150% to 199% (1.5-1.99 × increase compared with baseline) OR increase of ≥0.3mg/dl (≥26.4 mmol/l) OR Urine output <0.5 ml/kg/h for >6 but <12 hour

Stage 2:

Increase in serum creatinine to 200% to 299% (2.0-2.99 × increase compared with baseline) OR Urine output <0.5 ml/kg/h for >12 but <24 hour

Stage 3:

Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) OR Urine output <0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 hour

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