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Statistical Analysis Plan (SAP)

Colchicine for patients with aortic stenosis undergoing transcatheter aortic valve replacement (Co-STAR): a randomized-controlled trial

Co-STAR

Administrative Information

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Contributors

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Revision history

Revision	Justification	Timing

Approved by

Name	Affiliation	Study Role	Date and Signature (wet ink)
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Contents

1. Introduction

1.1 Background and rationale

Transcatheter aortic valve implantation (TAVI) is a well-established alternative to surgical aortic valve replacement (SAVR) for the treatment of patients with symptomatic severe aortic stenosis (AS). While peri-procedural complications such as stroke, vascular complications and bleeding have substantially declined with the refinement of transcatheter valves and increasing experience, new-onset atrial fibrillation (NOAF) and atrioventricular conduction disturbances continue to occur in almost half of all patients and represent an ongoing challenge for the expansion of TAVI towards younger patients at low surgical risk. Colchicine has proven safe and effective in the prevention of atrial fibrillation after cardiac surgery. Injury to the atrioventricular (AV) node and left bundle branches (LBB) due to a transient inflammation and tissue edema is an important mechanism involved in the development of conduction disturbances after TAVI. The anti-inflammatory effects of colchicine may mitigate the occurrence of atrioventricular conduction disturbances and thus the need for the implantation of a permanent pacemaker post TAVI.

1.2 Objectives

The objective of the present study is to investigate the efficacy of colchicine for the prevention of NOAF and conduction disturbances requiring the implantation of a permanent pacemaker in patients undergoing TAVI; compared to placebo.

2. Study methods

2.1 Trial design

Investigator-initiated, randomized, double-blind, placebo-controlled, monocentric clinical study; patients are randomized to receive colchicine vs placebo in a 1:1 ratio.

2.2 Randomization

Randomization will be performed after heart team decision, all eligibility criteria have been checked, and written informed consent has been obtained. The allocation schedule is based on block randomization (block size of 8) and will be stratified on presence or absence of right bundle branch block to prevent unequally balanced groups with regard to the known risk factors for the development of conduction disturbances requiring the implantation of a permanent pacemaker. Each patient will be assigned a unique identification number (record ID within REDCap), which will be linked to all recorded trial data providing encrypted data of the individual for data analysis. Randomization lists, preparation of IMP and unblinding procedures are organized by Bern University Hospital Pharmacy (ISPI); and provided with unique IMP identifiers (so called BOX numbers, also entered into REDCap xx-xxx; e.g. 02-009); boxes contain 14 pills (either colchicine or placebo) to cover the period one day before TAVI up to 12 days post-TAVI (each patient should take 14 pills in total).

2.3 Sample size

Based on a cohort predominantly treated with self-expanding transcatheter heart valves, we estimate the incidence proportion for the primary composite endpoint at 30 days at 42% in the control arm. Assuming a 45% relative risk reduction in the colchicine arm, the cumulative incidence is estimated at 23.1%. Based on these assumptions, 96 patients are required per study group to show superiority of the intervention with a power of 80% at two-tailed significance level of $\alpha = 0.05$. Accounting for a low attrition rate, 100 patients will be required per study group.

2.4 Framework

Superiority testing of the primary outcome in the intention-to-treat population ITT (randomized to colchicine vs randomized to placebo based on the box number inside the Eligibility check).

2.5 Statistical interim analyses and stopping guidance

The statistical interim reports (open and closed report, see below) will be produced by an independent statistician who also advices the data safety monitoring board DSMB on the interpretation of the report and the interim analyses.

Asymmetric stopping boundaries will be used as stopping rules in the interim analysis performed after enrolment of 120 patients with their 30 days follow-up assessment of the primary outcome and mortality, stroke and infections requiring prolonged index hospitalization or re-hospitalization completed.

Pocock-type boundaries will be applied when monitoring for harm. If the interim-analysis shows harm for the colchicine group with a Type I error rate of 0.029 or smaller with respect to any of the following endpoints, the trial will be stopped:

- the primary composite endpoint

- all-cause mortality

- any stroke

- infections requiring prolonged index hospitalization or re-hospitalization

Stopping rules for the trial due to benefit of the colchicine administration will adhere to the Peto boundaries with a required p-value of 0.001 or smaller for the difference in the primary endpoint rate at 30 days in the interims-analysis.

No adjustment of the significance level of the final analyses will be performed due to interim analysis.

An *open report* of these 120 patients aggregated (not showing the arms) will be produced containing the baseline table, adherence table, and the outcome table (with primary outcome and components, death, stroke and infections requiring prolonged index hospitalization or re-hospitalization); and this open report will be shared with the Sponsor. A *closed report* will be produced for the members of the DSMB only, where the colchicine and placebo arms will be coded (e.g. X and Y). The meaning of X and Y will be disclosed to the DSMB members separately from the sending of the closed report, e.g. by separate email or telephone call or during the DSMB meeting).

2.6 Timing of primary analysis

All outcomes will be analyzed collectively after the 30 days visits have been completed and adjudication of the events has been completed. Secondary publications using the 1 year data can be completed after that final visit has been completed and the database has been locked.

2.7 Timing of outcome assessments

Time points at which the outcomes are measured is at the 30-days visit (30 days to 37 days) or 1 year visit (+21 days); if this window can not be met (e.g. because patient cannot come to the appointment or has deceased), then the nearest last assessment of the primary and secondary outcomes will be used, which is relevant for the ECG derived outcomes. In contrast, adjudicated events which are derived with an event date can be exactly censored at and including 30 days since TAVI implantation (e.g. not counting the stroke at 35 days for the 30 days follow-up outcomes publication, instead count that stroke inside the 1 year follow-up outcomes publication).

2.8 Blinding

All investigators, study teams, trial statistician, the data managers, the research assistants, study nurses, the monitor, the laboratory analyst, and other personnel are blinded to the IMP the patient is actually receiving (as provided by ISPI). The DSMB and the interim statistician are not blinded, see below.

For necessary unblinding sealed envelopes per randomization number / box number are kept in a separate folder with the Investigator Site File. An authorized investigator can thus unblind at any time necessary. The key to the Patient ID and Randomization Number are kept in the Investigator Site File (Master Subject List).

Trial statistician supports data cleaning and provides aggregated tables (all patients combined) to the Sponsor after the primary endpoint at 30 days available. If the Sponsor agrees the data appear plausible and no more queries to confirm/correct data are needed, the trial statistician will provide the Sponsor with Tables where the arms are coded (e.g. X and Y). The X and Y codes can be provided by the interim statistician without yet unblinding anybody. Again, if the Sponsor agrees the data appear plausible and no more queries to confirm/correct data are needed, the trial statistician will provide the Sponsor with Tables where the arms are unblinded (colchicine and placebo).

Note that during the interim analysis of the 120 patients the interim statistician and the DSMB members are not blinded. They all need to sign a Confidentiality and Non-Disclosure Statement, which can be stored in the trial master file TMF.

3. Data management

3.1 Data export

The CRFs in this trial are implemented electronically (eCRF) using a dedicated electronic data capturing (EDC) system hosted at the CTU Bern server REDCap https://redcap.ctu.unibe.ch/index.php. Data can be exported directly from this system into the required format (e.g. Stata or R), including the automated code to attach the codebook.

3.2 Data validation

The Sponsor will receive overview Tables (see Tables below) with the sample sizes and the Sponsor decide whether missing data should be queried to get these data more complete. The Sponsor will receive outlier analysis of the variables mentioned in the Tables below, and the Sponsor can decide which outliers should be queried. The trial statistician will check the dates entered into REDCap and check that dates make sequentially sense:

- TAVI date and dates of assessment after TAVI vs tagged before/pre, post, day 0 etc from TAVI are consistent
- Historical dates are actually before/on date of TAVI, e.g. date of surgery.
- IMP first intake date is expected to start one day before TAVI.
- The TAVI date is day zero, adherence of IMP intake are recorded per day: -1 to 12 and should match the first intake date of IMP.
- Event dates and adjudicated event dates are equal or after date of TAVI implant and plausible (e.g. up to last follow-up date currently recorded).

Box numbers (xx-xxx) indicated in the Eligibility eCRF will be compared to the Adherence eCRF and queried if different to confirm a post-randomization switch was performed by mistake (as this would indicate patient was taking pills not from the randomized box, but from a different box).

For any other data not mentioned in the Tables below, the Sponsor will consult directly with the trial statistician whether they need additional checking for missingness and outliers etc.

The queries will be programmed inside a separate statistical code following the Data validation SOP (CTU_STA_SOP-02).

3.3 Data preparation

Data will be prepared using the codebook exported from REDCap and following the SOP (CTU_STA_SOP-10 or later).

Outcomes are coded directly inside the adjudication eCRF (*CEC Event*):

1 = Conduction disturbance requiring the implantation of a permanent pacemaker

2 = New onset atrial fibrillation

3 = Other new arrhythmia resulting in hemodynamic instability or requiring therapy

4 = Death

5 = Stroke

6 = Bleeding

7 = Acute kidney injury

8 = Systemic embolism

9 = Myocardial infarction

10 = Clinical valve thrombosis

11 = New infection

12 = Other new conduction disturbance

Each of these also with additional variables describing subtypes (see eCRF).

Whether the event is *relevant for the 30 days or 1 year analyses* is coded:

Did the event occurring within 30 days after TAVI? yes/no

Did the event occurring within 1 year after TAVI? yes/no

These two items will be double-checked with the date of the event and queried with the adjudicators in case of uncertainty/typo errors, as the event date of death, stroke, bleeding, myocardial infarction, acute kidney injury are expected to be exacty recordable and therefore to comply with the TAVI date (day 0 to +30 days: for 30 days analyses; day 0 to +365 days: for 1 year analyses).

In contrast, the event dates of conduction disturbances, systemic embolism, clinical valve thrombosis, new infection, other new conduction disturbance may also be later than 30 days (for 30 days analyses) or 365 days (for 1 year analyses), as they will depend on the nearest assessments available and may not comply with these exact windows (but depend rather on e.g. nearest available ECG for conduction assessment, nearest available echocardiography or other imaging for embolism and valve thrombosis, nearest available laboratory measurements and final diagnoses for infections).

3.4 Data sharing (if applicable)

Data sharing will be conducted following the data sharing SOP of CTU Bern (version CTU_STA_SOP-08 or later).

4. Statistical principles

Statistical analyses will be conducted according to the CTU Bern Data Analysis and Reporting SOP (CTU_STA_SOP-10), the interim analyses additionally according to the extra SOP for interim analyses (CTU_STA_SOP-09).

4.1 Confidence intervals and *P* values

Confidence intervals (95% lower and upper limit) will be reported, all applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

4.2 Analysis populations

The primary analyses will be conducted on the intention to treat population with at least one assessment of conduction disturbances post-TAVI nearest to the 30 days visit available, or if not available, who had a permanent pacemaker implant.

4.2.1 Full analysis set (FAS)

The full analysis set (FAS) will include all randomized subjects. Following the intent-to-treat ITT principle, subjects will be analyzed according to the treatment they are assigned to at randomization. The primary analyses are on the *modified intention-to-treat subjects*, as patients with no-post TAVI assessment of conduction disturbances with no permanent pacemaker implant post-TAVI are excluded.

4.2.2 As-treated

The as-treated population is defined as those patients which have been taking the study medication for the first 7 days after initiation (day -1 to 5); but including patients who terminated intake before day 5 due/related to occurrence of the primary outcome or if they had side-effects or if they deceased.

4.2.3 Per-protocol (PP)

The *per-protocol population* (PP) consists of all subjects in the modified ITT who do not have any major protocol deviations that could confound the interpretation of analyses conducted on the FAS. The following are the major protocol deviations used:

Table: List and derivation of major protocol deviations used to exclude the patient from the Per-protocol population.

Protocol deviation	eCRF sheet	Variable	Variable type	Derivation
Inclusion, exclusion, device and IMP				
Any violation of inclusion or exclusion criteria	Eligibility check, Medication, Lab, ECG baseline or pre-procedure	Not all criteria can be checked using the eCRF, avaibable are `age`, `creatinine clearance`, `hemoglobin`, `steroids`, `immunosuprresiva`, `atrial_rhythm`		`age <65`, `creatinine clearance <=30ml/min`, `hemoglobin<80g/L`, `steroids=yes`, `immunosuprresiva=yes`, `atrial_rhythm<>sinus`
No TAVI device	Procedure	`initiated`	Binary (yes/no)	`no`
	Procedure	`type_of_valve`	Categorical	`None`
No IMP taken or any pill missed between day -1 and 5	Adherence	`day_minus_one` to `day_12`	Binary (yes/no)	`No pills` or any -1 to 5 days with `no` (out of 14 in total)
Took wrong IMP	Adherence vs Eligibility check	`box_{form}`	Text xx-xxx	`box` in Adherence not equal to `box` in Eligibility check
Incomplete primary outcome assessment if both these apply (up and including 30 days visit)				
New onset atrial fibrillation	ECG	`ecg_pp_day`, `ecg_7d_duration_days`	Integer	No ECG are conducted at any time post-TAVR (day 0 or later post-TAVR)
Conduction disturbance requiring the implantation of a permanent pacemaker	CEC Event	`cec_type_of_event`	Categorical	Not equal to `yes`

The rationale is that patients with an implant are expected to benefit from colchicine if the critical period around valve implantation is well covered (thus day -1 to 5) when most conduction disturbances occur sometimes resulting in the need for a permanent pacemaker implant. Patients may die before the primary endpoint could be assessed reliably or withdraw consent before any post-TAVR ECG could be collected, so that is why they are also excluded from the Per-protocol population (whereas the adjudicators may decide that in the absence of clear evidence, no conduction disturbance was recorded, e.g. no disturbances during the TAVI procedure, but ECG post-procedure of too low quality to confirm this finding).

4.2.4 Safety population

The safety population consists of all subjects in the FAS who took at least one dose of study medication (colchicine or placebo). Subjects will be analyzed according to the treatment actually taken (i.e. considering the `box` number (xx-xxx) inside the Adherence eCRF – if this box number differs from the `box` number indicated in the Eligibility eCRF).

4.3 Estimands

The main estimand will be the Mantel-Haenszel risk difference with 95% confidence interval (CI) comparing colchicine vs placebo for the primary outcome: Composite of New onset atrial fibrillation AF (NOAF) or the occurrence of conduction disturbances requiring the implantation of a permanent pacemaker in the first 30 days post TAVI; in the modified ITT population. The modified ITT population is the population analysed as randomization, but with the additional criterium that the primary endpoint could be assessed (see 4.2.1.).

Secondary endpoints are also analysed in the modified ITT population (see 4.2.1.), using risk differences; except for inflammatory markers where mean differences with 95% confidence intervals and ANOVA F-tests will be produced.

The components of the primary outcome:

- The incidence of NOAF (at 30 days)

- The incidence of conduction disturbances requiring the implantation of a permanent pacemaker (at 30 days).

And also:

- The incidence and predictors of conductance disturbances: new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), high-grade atrioventricular block, third-degree AV block, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block, intraventricular conduction delay (at 30 days).

- The incidence of new arrhythmias resulting in hemodynamic instability or requiring therapy (defined as electrical/medical cardioversion or initiation of a new medication e.g. oral anticoagulation, rhythm, or rate controlling therapy) (at 30 days).

- The proportion of patients with at least one prosthetic leaflet with > 50% motion reduction or with at least one prosthetic leaflet with thickening (at 30 days).

- The proportion of prosthetic leaflets with > 50% motion reduction or leaflet thickening (at 30 days).

- The incidences of major clinical adverse events such as all-cause mortality, stroke, transient ischemic attack, bleeding event, kidney injury, systemic embolism, myocardial infarction, infections, clinical valve thrombosis (at 30 days).

These analyses will be repeated for the 1 year follow-up visit.

The separate inflammatory markers will be analysed in the ITT population with non-missing values, using mean differences (95% CI) and ANOVA F-test:

- The difference in inflammatory marker levels in patients treated with colchicine or placebo at day 1 post TAVI.

Sensitivity analyses will be conducted for all incidences in the Per-protocol population and the As-treated populations (see for definitions section 4.2). Sensitivity analyses will be conducted for the inflammatory markers in the Per-protocol population taking IMP at day -1, 0 and 1 around TAVR.

5. Trial Population

5.1 Screening data

Reporting of screening data of TAVI patients will be collected to describe the representativeness of the Co-STAR trial sample.

5.2 Eligibility

Summary of eligibility criteria are as follows (copied from the Protocol):

Inclusion criteria:

1. Age ≥ 65 years

2. Symptomatic severe aortic stenosis defined by an aortic valve area (AVA) ≤1.0 cm2 or an AVA indexed to body surface area <0.6cm2/m2

3. Selected to undergo transfemoral TAVI based on heart team decision

Exclusion criteria:

1. Life expectancy <1 year irrespective of valvular heart disease

2. Kidney disease with a creatinine clearance ≤30 ml/min

3. Known severe liver disease

4. Known neuromuscular disease

5. Clinically significant anaemia with haemoglobin <80g/L

6. Known inflammatory bowel disease or chronic diarrhea

7. Known ongoing bacterial infection

8. Known galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

9. Current treatment with colchicine, steroids or biologicals for any indication

10. Concomitant intake of Cyclosporine, Amiodaron, Clarithromycin, Erythromycin, Omeprazol, Verapamil or other strong inhibitors of CYP3A4 or P-Glycoprotein

11. Concomitant intake of Carbamazepin, Phenobarbital, Phenytoin, Rifampicin or other strong inductors of CYP3A4 and P-Glycoprotein

12. Permanent pacemaker or implantable cardioverter defibrillator

13. History of atrial fibrillation

14. Absence of sinus rhythm on hospital admission

15. Planned non-cardiac surgery within 30 days

16. Known intolerance to colchicine

17. Inability to provide informed consent

18. Known or suspected non-compliance, drug or alcohol abuse

19. Participation in another clinical trial with an active intervention

20. Any other planned cardiac intervention performed in the 7 days before TAVI, concomitantly with TAVI or in the 30 days after TAVI except for percutaneous coronary interventions.

5.3 Recruitment

A CONSORT patient flow diagram will be drawn following the CONSORT 2010 standards (http://www.consort-statement.org/consort-2010).

5.4 Baseline patient characteristics

Please note: P-values, standard errors, and confidence intervals are not shown in the baseline tables since any significant difference can be explained by the play of chance if the randomization was performed properly.

Table 1. Baseline characteristics

	All patients	Colchicine	Placebo
	N = xx	N = xx	N = xx
Stratification arm	n = xx	n = xx	n = xx
no RBBB	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Right Bundle Branch Block RBBB	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Age [years]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x
Male gender	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Diabetes mellitus	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Dyslipidemia	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Hypertension	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Chronic obstructive pulmonary disease (COPD)	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Solid tumor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Leukaemia/Lymphoma/Multiple Myeloma	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Peptic ulcer disease	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Previous clinically significant bleeding	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Extracardiac arteriopathy	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Frailty	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
History of endocarditis	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Coronary artery disease	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
History of myocardial infarction	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
History of PCI	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Tabacco use	n = xx	n = xx	n = xx
Never	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Current	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Former	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Previous stroke or TIA	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Ischemic stroke	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Hemorrhagic stroke	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Transient ischemic attack	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Hemiplegia	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
History of atrial flutter	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
History of cardio-thoracic surgery	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
CABG	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Valve	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
NYHA Functional classification	n = xx	n = xx	n = xx
NYHA I	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
NYHA II	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
NYHA III	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
NYHA IV	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
CCS	n = xx	n = xx	n = xx
no angina	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
CCS 1	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
CCS 2	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
CCS 3	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
CCS 4	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
Syncope	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)
STS for mortality [%]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x

Depicted are means ± standard deviations or counts (percentages).

Solid tumor : include if ≤5 years from diagnosis, excludes non-melanomatous skin cancers and in-situ cervical carcinoma.

Peptic ulcer disease: includes patients who required treatment for ulcer disease and those who bled from ulcers.

Previous clinically significant bleeding: any overt hemorrhage, that requires medical attention by a healthcare professional.

Extracardiac arteriopathy: claudication, carotid occlusion or >50% stenosis, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb arteries or carotids.

Coronary artery disease: history or presence of a stenosis > 50% in at least one major epicardial coronary vessel.

STS risk score for mortality at 30 days: https://www.sts.org/resources/risk-calculator

5.5 Medication

Details of the medication at each visit is presented.

Table 2. Medications

	All patients N = xx	Colchicine N = xx	Placebo N = xx	p-value
Baseline				
Aspirin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Clopidogrel	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Prasugrel	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Ticagrelor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Vitamin K Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
NOAC	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Dabigatran	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Edoxaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Apixaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Rivaroxaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Statin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
ACE Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
AT II Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Sartan & Neprilysin-Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Betablocker	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Calcium-Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Amiodarone	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Aldosterone-Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Diuretics	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Proton-Pump Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Insulin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Oral Antidiabetics	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
SGLT2-Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Steroids	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Immunosuppressive drugs - other than steroids	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	
Inhaled bronchodilator	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	

Discharge				
Aspirin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Clopidogrel	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Prasugrel	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Ticagrelor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Vitamin K Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
NOAC	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Dabigatran	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Edoxaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Apixaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Rivaroxaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Statin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
ACE Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
AT II Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Sartan & Neprilysin-Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Betablocker	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Calcium-Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Amiodarone	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Aldosterone-Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Diuretics	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Proton-Pump Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Insulin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Oral Antidiabetics	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
SGLT2-Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Steroids	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Immunosuppressive drugs - other than steroids	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Inhaled bronchodilator	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Follow-up 30 days				
Aspirin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Clopidogrel	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Prasugrel	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Ticagrelor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Vitamin K Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
NOAC	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Dabigatran	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Edoxaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Apixaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Rivaroxaban	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Statin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
ACE Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
AT II Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Sartan & Neprilysin-Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Betablocker	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Calcium-Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Amiodarone	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Aldosterone-Antagonist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Diuretics	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Proton-Pump Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Insulin	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Oral Antidiabetics	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
SGLT2-Inhibitor	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Steroids	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Immunosuppressive drugs - other than steroids	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Inhaled bronchodilator	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx

Depicted are counts (percentages), p-values from Fisher's exact tests.

5.6 Procedure

Details of the TAVI procedure is presented. Note that IMP intake should start one day before the TAVR.

Table 3. Transcatheter aortic valve replacement procedure

	All patients	Colchicine	Placebo	p-value
	N = xx	N = xx	N = xx	
Procedure				
Procedure was initiated	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Procedure time (minutes)	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Total contrast volume administered [ml]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Cerebral protection device used	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Pre-TAVI balloon valvuloplasty	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Implanted device	n = xx	n = xx	n = xx	x.xxx
CoreValve Evolut PRO PLUS	count (%)	count (%)	count (%)	x.xxx
Edwards Sapien 3	count (%)	count (%)	count (%)	x.xxx
Device size [mm]	n = xx	n = xx	n = xx	x.xxx
Device size [mm] (23)	count (%)	count (%)	count (%)	x.xxx
Device size [mm] (26)	count (%)	count (%)	count (%)	x.xxx
Device size [mm] (29)	count (%)	count (%)	count (%)	x.xxx
Balloon postdilatation	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Concomitant coronary intervention	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Pre-procedure imaging				
Aortic valve gradient (peak-to-peak) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Aortic valve gradient (mean) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Aortic pressure (systolilc) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Aortic pressure (diastolic) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Ventricular pressure (systolic) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Ventricular pressure (end-diastolic) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Post-procedure imaging				
Aortic valve gradient (peak-to-peak) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Aortic valve gradient (mean) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Aortic pressure (systolilc) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Aortic pressure (diastolic) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Ventricular pressure (systolic) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Ventricular pressure (end-diastolic) [mmHg]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Aortic regurgitation post-implantation (angiographically)	n = xx	n = xx	n = xx	x.xxx
None	count (%)	count (%)	count (%)	x.xxx
Mild	count (%)	count (%)	count (%)	x.xxx
Moderate	count (%)	count (%)	count (%)	x.xxx
Procedural complications				
Valve migration	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Valve embolization	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Implantation of multiple valves	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Valve retrieval	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Aortic dissection	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Annular rupture	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Left ventricular perforation	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Cardiac tamponade	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Coronary artery obstruction	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Conversion to open heart surgery	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Conversion to alternate access site	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Access vessel complication	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Bleeding	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Vascular stent implantation	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Vascular surgery	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Death	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Discharge				
Nr of days in-hospital for TAVR	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
Discharge location				x.xxx
home	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
rehabilitation clinic	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
other hospital	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
nursing home	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx

Depicted are means ± standard deviations or counts (percentages), p-values from t-tests, Fisher's exact tests or chisquare tests if more than two categories.

5.7 Adherence

Adherence is recorded for every day the IMP should be taken (one pill per day), from day -1 (one day before planned TAVI), day 0 (day the TAVI procedure is executed), day 1 to day 12 post-TAVI; so 14 IMP pills (containing colchicine or placebo) should be ingested.

Table 4. IMP adherence

	All patients N = xx	Colchicine N = xx	Placebo N = xx	p-value
IMP intake per day since TAVR (ingested according to diary)				
Day -1	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 0	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 1	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 2	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 3	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 4	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 5	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 6	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 7	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 8	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 9	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 10	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 11	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Day 12	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Adherence				
The patient prematurely stopped the daily medication	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Why did the patient stop the drug?	n=xx	n=xx	n=xx	x.xxx
adherent, stopped according to planned regimen	count (%)	count (%)	count (%)	x.xxx
allergic reaction	count (%)	count (%)	count (%)	x.xxx
side effect other than allergy	count (%)	count (%)	count (%)	x.xxx
mistake to take or obtain the drug	count (%)	count (%)	count (%)	x.xxx
unclear reason	count (%)	count (%)	count (%)	x.xxx
other reason	count (%)	count (%)	count (%)	x.xxx
Who decide to stop with IMP?	n=xx	n=xx	n=xx	
the investigator	count (%)	count (%)	count (%)	x.xxx
another medical doctor	count (%)	count (%)	count (%)	x.xxx
another medical professional	count (%)	count (%)	count (%)	x.xxx
patient active decision	count (%)	count (%)	count (%)	x.xxx
patient mistake	count (%)	count (%)	count (%)	x.xxx

Depicted are counts (percentages), p-values from Fisher's exact tests or chisquare tests.

5.8 Inflammatory markers

The current plan is to analyses 6 inflammatory markers, if new important markers are published in the meantime, then these will also be analysed and added to the Table. The inflammatory markers will be analysed one day after the TAVI. A sensitivity analyses of patients taking IMP on day -1, 0 and 1 will be performed. Note that inflammatory markers are secondary outcomes (i.e. proof-of-principle that colchicine should reduce inflammation compared to placebo).

Table 5. Inflammatory markers after TAVR (secondary outcomes)

	All patients N = xx	Colchicine N = xx	Placebo N = xx	p-value
CRP [mg/L]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
hsCRP [mg/L]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
IL-6 [pg/ml]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
IL-8 [ng/ml]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
TNF-alpha [pg/ml]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx
IL-1 beta [pg/ml]	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	n = xx, xx.x ± x.x	x.xxx

Depicted are means ± standard deviations, p-values from t-tests.

5.9 Follow-up 30 days

Whether the follow-up is performed and if yes with whom and current functional class and anginal status will be presented.

Table 6. Follow-up 30 days

	All patients N = xx	Colchicine N = xx	Placebo N = xx	p-value
Follow-up performed (Yes)	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Type of contact	n=xx	n=xx	n=xx	
Patient face-to-face	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Patient by telephone	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Cardiologist	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Family physician	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Nurse/other medical staff	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Spouse/husband/life partner	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Other	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Dyspnea functional classification	n=xx	n=xx	n=xx	
NYHA I	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
NYHA II	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
NYHA III	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
NYHA IV	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
CCS	n=xx	n=xx	n=xx	
no angina	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
CCS 1	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
CCS 2	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
CCS 3	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
CCS 4	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx
Syncope	n = xx, count (%)	n = xx, count (%)	n = xx, count (%)	x.xxx

Depicted are counts (percentages), p-values from Fisher's exact test or chisquare tests if more than two categories.

5.10 Adjudicated primary and secondary outcomes at 30 days

The adjudicated (see CEC Event eCRF) primary and secondary outcomes will be analysed, considering only the first event per event (sub)type. A supplemental table considering all events and incidence rate ratios will be produced upon request (e.g. for 1 year follow-up) – as it is unlikely that many of the events-of-interest will occur multiple times within 30 days.

Table 7. Adjudicated primary and secondary outcomes at 30 days in the modified ITT

	Colchicine N = xx	Placebo N = xx	Risk difference (95% CI)	p-value
Primary outcome and components				
New-onset Atrial fibrillatior or Implantation of permanent pacemaker due to conduction disturbances*	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
New-onset Atrial fibrillatior	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Implantation of permanent pacemaker due to conduction disturbances	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Secondary outcomes				
new or worsened first-degree atrioventricular (AV) block	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
second-degree AV block (Mobitz I or Mobitz II)	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
high-grade AV block	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
third-degree AV block	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
right bundle branch block	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
left bundle branch block	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
left anterior fascicular block	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
left posterior fascicular block	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
intraventricular conduction delay	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
new arrhythmias resulting in hemodynamic instability or requiring therapy¶	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
at least one prosthetic leaflet with either > 50% motion reduction or with leaflet thickening	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
nr of leaflets with either > 50% motion reduction or with leaflet thickening				x.xxx
1	count (%)	count (%)	x.xx (x.xx to x.xx)	
2	count (%)	count (%)	x.xx (x.xx to x.xx)	
3	count (%)	count (%)	x.xx (x.xx to x.xx)	

Major adverse clinical adverse events				
Death	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Cardiovascular death	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Stroke or TIA	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
ischemic Stroke	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
hemorhagic Stroke	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
undetermined Stroke	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Transient ischemic attack TIA	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Bleeding event BARC 2 to 5	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
BARC 3 or 5 bleeding	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Bleeding event TIMI	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
TIMI minor or major	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Bleeding event GUSTO	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
GUSTO moderate or severe	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Acute Kidney Injury	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Systemic embolism	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
extremities	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
non-CNS organ	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Myocardial infarction	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Infection	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
bacterial	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
viral	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
other	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
infection requiring prolonged index hospitalization or re-hospitalization	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx
Clinical valve thrombosis	count (%)	count (%)	x.xx (x.xx to x.xx)	x.xxx

*Primary outcome. Risk differences with Mantel-Haenszel tests. Only the first event of each event type is considered.

¶defined as electrical/medical cardioversion or initiation of a new medication e.g. oral anticoagulation, rhythm, or rate controlling therapy.

AV = atrioventricular.

Similar tables for the Supplement will be produced for the Per-protocol and As-treated populations.

5.11 Safety evaluation at 30 days

Incidence rate of gastrointestinal side effects and clinically severe side effects possibly related to study drug intake will be reported (also separate for whether the event was serious yes or no):

- Sensory motor neuropathy
- Leukopenia
- Granulocytopenia
- Thrombocytopenia
- Leukopenia
- Aplastic anaemia
- Allergic reaction
- Acute kidney injury
- Stevens-Johnson-Syndrom
- Myopathy
- Rhabdomyolysis

Events are entered using the codes from the CTCAE catalog (see https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm) and this coding will be cross-checked with the Sponsor to derive correctly the above main categories of known drug reactions to colchicine; and other summary categories as needed.

Table: List of main safety event items.

Protocol deviation	eCRF sheet	Variable	Variable type	Derivation
CTACAE Term				
Coding of event according to CTACAE	Adverse Event	`drug_ctcae_catalog`	Text from CTACAE dictionary	See https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
Details of the adverse event				
SAE	Adverse Event	`drug_sae`	Binary	0=no AE; 1=yes SAE
Grading	Adverse Event	`drug_severity`	Categorical	1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=fatal
Causality with IMP	Adverse Event	`drug_imp1_causality`	Categorical	1 = definite, 2=probable, 3=possible, 4=unlikely, 5=not related

A table will be produced summarizing incidence rates and incidence rate ratios (comparing takes colchicine at least once vs takes placebo at least once). If SAEs occurred, they can be described inside the Table separately, or if rare, as single listings. If events were definitely or probably related to IMP, they can be described inside the Table separately, or if rare, as single listings. If grading was severe to fatal, they can be described inside the Table separately, or if rare, as single listings.

Single listing could read e.g.: n=2 nausae of which one SAE in one patient taking colchicine.

A supplemental table with more detailed event descriptions can be prepared for the Sponsor if requested.

Table 8. Safety evaluation at 30 days

	Colchicine	Placebo	Incidence rate ratio (95% CI)	p-value
	N = xx, person month at risk	N = xx, person month at risk		
{CTCAE term: e.g. nausea, pleural effusion} {grading: mild/moderate/severe/life-threatening/fatal} {causality: definite or probable} {SAE: yes/no} etc.	#events in # patients (%)	#events in # patients (%)	x.x (x.x to x.x)	x.xx

Includes patients which took at least one IMP. Incidence rates per person month at risk (patient evaluable for adverse events and alive). Incidence rate ratio with 95% confidence interval from Poisson regressions with offset nr of days under observation (robustified).

Single listing if rare: n=xx event in xx patients randomised to colchicine; etc. etc.

6. Analysis

6.1 Outcome definitions

The main estimand will be the Mantel-Haenszel risk difference with 95% confidence interval (CI) comparing colchicine vs placebo for the primary outcome: Composite of New onset atrial fibrillation AF (NOAF) or the occurrence of conduction disturbances requiring the implantation of a permanent pacemaker in the first 30 days post TAVI; in the modified ITT population (see 4.2.1.).

Secondary endpoints are also analysed in the modified ITT population (see 4.2.1.), using risk differences; except for inflammatory markers where mean differences with 95% confidence intervals and ANOVA F-tests will be produced.

The components of the primary outcome:

- The incidence of NOAF (at 30 days)
- The incidence of conduction disturbances requiring the implantation of a permanent pacemaker (at 30 days).

And also:

- The incidence and predictors of conductance disturbances: new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), high-grade atrioventricular block, third-degree AV block, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block, intraventricular conduction delay (at 30 days).
- The incidence of new arrhythmias resulting in hemodynamic instability or requiring therapy (defined as electrical/medical cardioversion or initiation of a new medication e.g. oral anticoagulation, rhythm, or rate controlling therapy) (at 30 days).
- The proportion of patients with at least one prosthetic leaflet with > 50% motion reduction or with at least one prosthetic leaflet with thickening (at 30 days).
- The proportion of prosthetic leaflets with > 50% motion reduction or leaflet thickening (at 30 days).
- The incidences of major clinical adverse events such as all-cause mortality, stroke, transient ischemic attack, bleeding event, kidney injury, systemic embolism, myocardial infarction, infections, clinical valve thrombosis (at 30 days).

These analyses will be repeated for the 1 year follow-up visit.

The separate inflammatory markers will be analysed in the ITT population with non-missing values, using mean differences (95% CI) and ANOVA F-test:

- The difference in inflammatory marker levels in patients treated with colchicine or placebo at day 1 post TAVI.

The events are listed inside the *CEC Event* eCRF with the binary yes/no indicators whether they occurred within 30 days and whether they occurred within 1 year from the TAVR.

The inflammatory markers are listed inside the *Inflammatory markers Day 1* eCRF (CRP in mg/L; hsCRP in mg/L; IL-6 in pg/mL; IL-8 in ng/mL; TNF-alpha in pg/mL; IL-1 beta in pg/ml).

6.2 Analysis methods

Continuous variables will be presented as mean ± standard deviation or median and interquartile range depending on their distribution. Categorical variables will be stated as number and proportion. Characteristics will be compared colchicine vs placebo by means of unpaired t-tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. Reported p-values will be two-sided. If a normal distribution cannot be assumed, additional nonparametric tests will be considered to compare patient characteristics.

6.2.1 Primary analyses

Risk differences with 95% confidence intervals will be compared between groups using the Mantel-Haenszel method (for adjudicated events, counting only the first event). The Mantel-Haenszel risk difference will be stratified on presence or absence of right bundle branch block (RBBB, see *Eligibility check* eCRF) using the Cochran method, if both the colchicine and placebo arm have at least 10 patients in both stratification groups (RBBB=yes and RBBB=no) and these 20 patients or more combined in the smallest stratification group have at least 6 events combined. The primary analyses are in the modified ITT population (see 4.2.1.); and includes only adjudicated events counting the first event of each type only (up to 30 days).

6.2.2 Secondary analyses

Risk differences with 95% confidence intervals will be compared between groups using the Mantel-Haenszel method (for adjudicated events, counting only the first event). The Mantel-Haenszel risk difference will be stratified on presence or absence of right bundle branch block (RBBB, see *Eligibility check* eCRF) using the Cochran method, if both the colchicine and placebo arm have at least 10 patients in both stratification groups (RBBB=yes and RBBB=no) and these 20 patients or more combined in the smallest stratification group have at least 6 events combined.

For multiple events analyses Poisson regression with offset nr of days under observation (robustified variance estimation) will be performed and results will be presented as total nr of events/any patient with event (% any patient with event) and incidence rate ratios with 95% confidence intervals comparing colchicine vs placebo. Inflammatory markers will be compared colchicine vs placebo using ANOVAs and F-tests.

Inflammatory markers will be analysed using ANOVA with corresponding F-tests.

Secondary analyses of all adjudicated events will be performed in the modified ITT population (see 4.2.1.); and includes only adjudicated events counting the first event of each type only, up to 365 days of follow-up.

6.2.3 Sensitivity analyses

Sensitivity analyses of the primary and secondary outcomes will be performed in the Per-protocol and As-treated population for the adjudicated events (at 30 days).

If requested, up to 1 year adjudicated events can also be analysed in the Per-protocol and As-treated populations, but since colchicine is only provided for 12 days post-TAVR, these populations are less relevant for the longer follow-up.

Sensitivity analyses for the inflammatory markers will be performed in the population which took pills on day -1, 0 and 1 around TAVR (as these markers are measured on day 1). If the markers are not measured on day 1, but later, they will be used if pills were taken up to and including the day the markers were measured.

6.2.4 Subgroup analyses

Pre-specified subgroup analyses with appropriate interaction tests will evaluate the effect of colchicine on the primary composite endpoint stratified by sex, valve-type (self/mechanical expanding vs balloon-expanding), device-landing zone calcification (none/mild vs moderate/severe), pre- and postdilatation (performed vs not performed), and right-bundle branch block (presence vs absence).

For adjudicated events Maentel-Haenszel stratified by the subgroup factor will be used and the approximate heterogeneity test will be reported to evaluate an interaction (modifying) effect on the risk difference comparing colchicine vs placebo.

For inflammatory markers a two-way ANOVA will be performed including the interaction randomization (colchicine or placebo) x subgroup (e.g. yes or no) and the F-test for this interaction effect (df=1).

Table: Derivation of subgroups

Subgroup	eCRF sheet	Variable	Categorization
Sex	Baseline	`sex`	1=female, 2=male
Valve-type	Procedure	`type_of_valve`	Balloon expandable = Edwards; Self/mechanically expandable =Medtronic Corevalve, Acurate, SJM Portico, NAVITOR
Device-landing zone calcification	Imaging Baseline	`lvot_calcification`	0=none/1=mild 2=moderate/3=severe
Pre-dilatation = Pre-TAVI balloon valvuloplasty	Procedure	`balloon_predilatation`	0=no, 1=yes
Post-dilatation = Balloon postdilatation	Procedure	`postdilatation`	0=no, 1=yes
RBBB right-bundle branch block	Eligibility check	`rbbb_arm`	0=no, 1= Right Bundle Branch Block

Subgroups	Colchicine Nr of events/Nr of patients N = xx	Placebo Nr of events/Nr of patients N = xx	Risk Ratio [Colchicine/Placebo] (95% CI)	Risk difference [Colchicine/Placebo] (95% CI)		p-value	p-value for interaction
RBBB							x.xx
Yes	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
No	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
Gender							x.xx
Male	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
Female	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
Device-landing zone calcification							x.xx
moderate/severe	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)	forrest plot	x.xx	
none/mild	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
Valve-type							x.xx
Self- or Mechanical expanding	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
Balloon-expanding	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
Pre-dilatation							x.xx
Yes	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
No	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
Post-dilatation							x.xx
Yes	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	
No	x/xx (xx%)	x/xx (xx%)	x.xx (x.xx - x.xx)	x.xx (x.xx - x.xx)		x.xx	

Figure 2. Subgroup analyses of the Primary endpoint at 30 days in the pre-specified subgroups

6.2.5 Additional analyses

Additional exploratory statistical analyses will be performed on the (tele)monitoring of the ECG per day (e.g. baseline, pre, day -1, 0, 1, 2, 3, 4 etc. since TAVR):

Heart Rate [/min]

Atrial Rhythm (sinus, paced, atrial fibrillation or flutter, other)

Ventricular Rhythm (conducted from atria, paced, junctional or ventricular escape rhythm)

Atrio-Ventricular Conduction Disorder (AV block with type)

Intra-Ventricular Conduction Delay (=Bundle Branch Block with left/right, complete/incomplete etc.)

PQ interval [ms]

QRS duration [ms]

Additional exploratory statistical analyses will be performed on the laboratory measurements/monitoring per day (e.g. baseline, pre, day -1, 0, 1, 2, 3, 4 etc. since TAVR):

Creatinine [µmol/L]

Bilirubin [µmol/L]

ASAT [U/L]

ALAT [U/L]

Gamma-GT [U/L]

Leucocytes [G/L]

Hemoglobin [g/L]

Hematocrit [%]

Thrombocytes [G/L]

INR international normalized ratio

6.2.6 Assessment of statistical assumptions

Occasional high inflammation may typically lead to a right-skewed distribution, if this is the case ANOVA or GLM with robustified variances or corrected for heterogeneity in the variances will be used. If this appears to be not satisfactory checking the residuals from the models, markers may be (log)transformed to reach an approximate normal distribution before comparing randomized to colchicine vs placebo. Very high inflammation may typically lead to right-skewed outliers, if this is the case, a sensitivity analysis is proposed discarding these outliers from the analyses.

6.3 Interim analyses

Asymmetric stopping boundaries will be used as stopping rules in the interim analysis performed after enrolment of 120 patients with 30 days follow-up completed and all events of that period adjudicated. Risk differences with 95% confidence intervals will be analysed using the Mantel-Haenszel method (for adjudicated events, counting only the first event). The Mantel-Haenszel risk difference will be stratified on presence or absence of right bundle branch block (RBBB, see *Eligibility check* eCRF) using the Cochran method, if both the colchicine and placebo arm have at least 10 patients in both stratification groups (RBBB=yes and RBBB=no) and these 20 patients or more combined in the smallest stratification group have at least 6 events combined.

Pocock-type boundaries will be applied when monitoring for harm. If the interim analysis shows harm for the colchicine group with a Type I error rate of 0.029 or smaller with respect to any of the following adjudicated endpoints, the trial will be stopped:

- the primary composite endpoint (new-onset atrial fibrillation or new permanent pacemaker implant)

- all-cause mortality

- any stroke

- infections requiring prolonged index hospitalization or re-hospitalization

(the *CEC Event* eCRF with occurred within 30 days ticked “yes”, for infection please consider the additional item indicating hospitalized: `cec_infection_hosp`=yes)

Stopping rules for the trial due to benefit of the colchicine administration will adhere to the Peto boundaries with a required p-value of 0.001 or smaller for the difference in the primary endpoint rate at 30 days in the interims-analysis.

6.4 Missing data

If a patient withdraws from the study or is lost to follow-up, the subject will be censored at the time when the last follow-up examination took place. Analyses will be performed according to the complete case principle assuming that data from patients, who do not undergo the follow-up examination, will be missing completely at random. Note that most conduction disturbances and pacemaker implants occur within a few days from the TAVI, so it is expected that the telemonitoring until discharge will be sufficient to capture most of the primary endpoints, also if the post-discharge 7-day long-term rhythm monitoring is less complete.

6.5 Safety evaluation

The safety evaluation will be performed in the Safety population (patients taking at least one pill and analysed according to the actual product ingested, colchicine or placebo). The CTACAE coding will be used to categorize events in groups and subgroups. Total number of events per (sub)group of event, total number of patients with at least one event per (sub)group of event, incidence rates per person-month at risk (i.e. patient under observation and adverse events were recordable; excludes after death and withdrawal of consent and lost to follow-up).

6.6 Subproject

Subprojects may include cumulative incidence curves for outcomes which are time-to-event up to 1 year of follow-up, with or without competing risk with death. Subprojects may include detailed biomarkers/inflammations assessments beyond those already mentioned. Subprojects may include analyses of follow-up imaging of the valve (e.g. to assess performance).

6.7 Statistical software

Statistical packages used will be Stata version 17.0 or later, and R version 4.0.3 or later.

6.8 Quality control

The primary endpoint and secondary outcomes (adjudicated events tagged as occurring within 30 days) will be double programmed (see Table 7). The inflammation markers will not be double-programmed, only code review.

A quality control of the interim analysis will be performed comparing the overall 120 patients results obtained by the trial statistician vs the overall 120 patients results from the interim statistician (see Open report). The interim statistician will involve another independent statistician not otherwise involved in the trial for both the Closed and the Open report; and this additional independent statistician can either do a complete code review, or if the code appears to difficult to review, this additional independent statistician can also perform double programming of the four outcomes used for harm. The primary endpoint will be used for both harm and benefit.

7. Changes from the protocol

The SAP is consistent with the principle features of the statistical methods described in the protocol. Any deviation from the protocol is detailed hereunder with reason.

Table: Changes from protocol

Header	Change	Reason

8. References

European Medicines Agency, Committee for Human Medicinal Products; Draft ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, step 2b - Revision 1. 30 August 2017.

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