A randomized comparison of a rivaroxaban-based strategy with an antiplatelet-based strategy following successful TAVR for the prevention of leaflet thickening and reduced leaflet motion as evaluated by four-dimensional, volume-rendered computed tomography (4DCT)

GALILEO 4D

– Substudy of the GALILEO trial –

PROTOCOL

Version 3.0, dated May 29th, 2017

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1. TIME SCHEDULE

Visit number [a]		**#1**	**#3**
Period	**Screening**		**Planned treatment**
Visit	**Screening**	**Baseline / Randomization** [c]	**On-site visit**
Day	1-7 days [b] prior to randomization	0	90
Window {day[s])			± 15 d
Study assessments			
Informed consent (IC) [d]	(X)		
Demographics [e]	(X)		
Medical history	(X)		
Functional NYHA class	(X)		**X**
Prior medication	(X)		
TAVR assessment	(X)		
Inclusion / exclusion criteria	(X)	(X)	
Concomittant medication		(X)	(X)
Physical exam		(X)	(X)
Vital signs [f]		(X)	(X)
Echocardiogram (TTE or TEE) [g]	(X)		**X**
12-lead ECG		(X)	(X)
4D-computed tomography			**X**
Study medication			
Prescribing/dispensing assigned therapy		(X) [h]	(X)
NOAF assessment and adjustment of treatment [i]		(X)	(X)
(Serious) adverse events [j]	(X)	(X)	(X)
Laboratory assessments (local labs)			
Hematology [k]	(X)		
Liver tests [l]	(X)		
Renal function [m]	(X)		

(X) Items assessed in the main GALILEO study

X Items assessed in the GALILEO-4D substudy only

[a] Visit number #2 at 30 days after randomization is only mandatory in the main GALILEO trial.

[b] Consenting subjects must be randomized within 1-7 days post-TAVR and before hospital discharge.

[c] Once randomized, a subject has entered the study and all randomized subjects will be followed for this substudy until the 4DCT-scan has been performed, even if they did not take assigned study medication or prematurely discontinued study medication. In case of early permanent discontinuation of study medication, all relevant information must be captured in the eCRF as soon as possible after stopping the assigned study medication. The timing of the on-site visit must be kept unchanged.

(d) A separate informed consent form will need to be signed for the GALILEO-4D substudy.

(e) Demographics: year of birth, sex and race/ethnicity, if allowed per local regulations.

(f) Vital signs: blood pressure, heart rate, weight, and height. Note that height only needs to be determined at screening.

(g) The mean transaortic valve pressure gradient should be determined from either routine transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) recordings before discharge and at 90 ± 15 days after randomization.

(h) The first study drug administration.

(i) In case of NOAF after randomization, sujects in: (a) the rivaroxaban-based treatment strategy will be switched to rivaroxaban 15 or 20 mg once-daily, based on kidney function. eGFR will be used as reported in lab printouts or calculated from serum creatinine levels using the MDRD formula. Subjects with moderate renal impairment and eGFR < 50 and ≥ 30 mL/min/1.73 m^2 will receive an adjusted dose of rivaroxaban of 15 mg once-daily. Both of these doses must be taken with food. (b) Subjects in the antiplatelet-based treatment strategy will switch to vitamin K antagonist after INR assessment (INR target 2-3).

(j) Only serious adverse events (SAE) and adverse events (AE) that lead to permanent discontinuation of the assigned study medication are to be reported. The investigator must report immediately (within 24 hours of the investigator's awareness) all (serious) adverse events. (S)AE reporting will be done via the main GALILEO study.

(k) Hematology tests include hemoglobin, platelet count and white cell count.

(l) Liver tests include AST/ALT, total bilirubin and its components, and alkaline phosphatase

(m) Renal function will be estimated by creatinine clearance (Cr-Cl; MDRD formula using serum creatinine levels).

2. BACKGROUND

Transcatheter aortic valve replacement (TAVR) has become an established therapeutic option for patients with symptomatic, severe aortic valve stenosis, who are ineligible or at high risk for conventional surgical aortic valve replacement (SAVR).[1-4] Results from the NOTION (Nordic Aortic Valve Intervention Trial) randomized clinical trial showed that TAVR may also be a viable option for patients with a lower risk profile.[5]

Very recently, Makkar et al. (2015) reported that leaflet thickening and reduced leaflet motion is not uncommon after both TAVR and SAVR – with an incidence of ~ 20%. Although reduced leaflet motion did not result in higher transvalvular gradients, the authors emphasized that this phenomenon should be further investigated for its effect on clinical outcomes (e.g. stroke) and valve durability. As this valve leaflet thickening and reduced motion could be reversed by oral anticoagulant (OAC) treatment and was not observed in patients on chronic OAC therapy, the authors hypothesized that this phenomenon could be related to possible leaflet thrombosis or a "thrombotic film" on the leaflets.[6]

In the most recent ESC guidelines, the need for a 3-month period of postoperative OAC therapy has been challenged in patients with aortic bioprostheses (class IIb, level of evidence C), with the use of low-dose aspirin now favoured as an alternative.[7] Although the rates of thrombo-embolic events among patients given OAC after surgical bioprosthetic aortic valve implantation appear to be lower than the event rates among patients given aspirin alone, OAC treatment is associated with more bleeding.[8] With the limited evidence to date based primarily on observational studies, the trade-off between reduced thromboembolic events with OAC and increased bleeding remains uncertain.

Currently, treatment of TAVR patients with dual anti-platelet therapy (DAPT; aspirin and clopidogrel) for 3-6 months is widely accepted and recommended[9] – however, this recommendation is not based on hard evidence and the usefulness of DAPT is questioned. Two small studies revealed that the risk for cardiovascular events was not reduced, while the risk for bleeding increased in the DAPT group compared to single antiplatelet therapy.[10,11] However, antiplatelet-based therapy alone might not be the optimal treatment for TAVR patients.

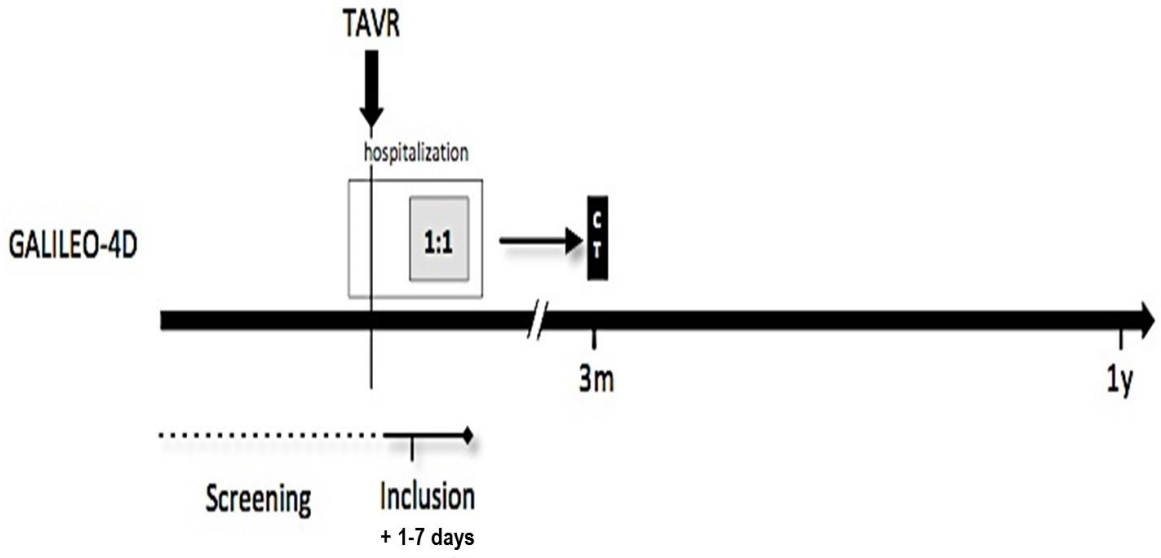
As to date, the optimal therapy for TAVR patients is not known and only based on consensus, there is an unmet need to identify the best medical treatment in patients undergoing TAVR. As novel oral anti-coagulants (NOACs) such as rivaroxaban may reduce the risk for TAVR-related thrombotic events, without increasing the bleeding risk, this study aims to evaluate whether a rivaroxaban-based strategy, following successful TAVR, compared to an antiplatelet-based strategy, is superior in reducing subclinical valve leaflet thickening and motion abnormalities – as detected by four-dimensional, volume-rendered computed tomography (4DCT).

3. PURPOSE

The purpose of this project is to evaluate whether a rivaroxaban-based strategy, following successful TAVR, compared to an antiplatelet-based strategy, is superior in reducing subclinical valve leaflet thickening and motion abnormalities – as evaluated by 4DCT imaging at three months following TAVR.

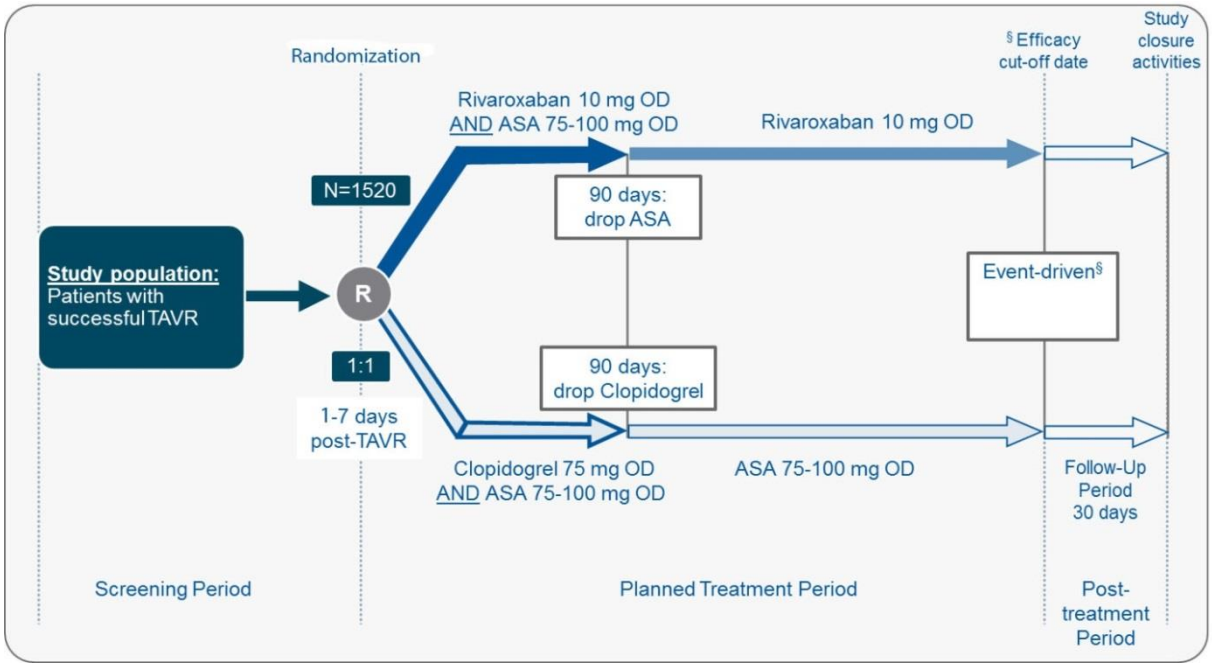
4. STUDY DESIGN

The GALILEO-4D trial will be conducted as a substudy of the multicenter, open-label, randomized, event-driven, active-controlled GALILEO trial. Patients will be 1:1 randomized to an antiplatelet-based strategy *vs.* rivaroxaban-based strategy – the randomization will adopt the same 1:1 randomization of the main GALILEO trial. In total, 300 patients will be randomized in the GALILEO-4D trial.



The 4DCT-scan should be performed 90days ± 15 days after randomization. The 4DCT-scan should preferentially be performed at the same day of Visit #3 *or* some days before Visit#3, but should – if possible – NOT be performed after Visit #3.

Study design of the GALILEO trial:



Successful transcatheter aortic valve replacement (TAVR) as defined in the main GALILEO study protocol.
R, randomization; ASA, acetylsalicylic acid; OD, once-daily.

5. STUDY POPULATION

5.1. Inclusion & exclusion criteria

- **Inclusion criteria**
  1. Patient included in the randomized GALILEO trial
  2. Written informed consent

- **Exclusion criteria**
  1. Severe renal insufficiency (eGFR < 30 ml/min/1.73 m^2) or on dialysis, or post-TAVR unresolved acute kidney injury with renal dysfunction ≥ stage 2
  2. Iodinate contrast media allergy or other conditions that prohibit CT imaging (i.e. multiple myeloma, etc.)

6. STUDY PROCEDURES

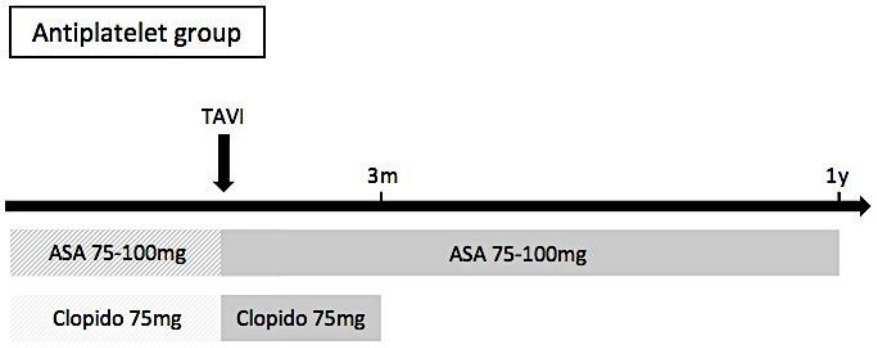
6.1. Patient information

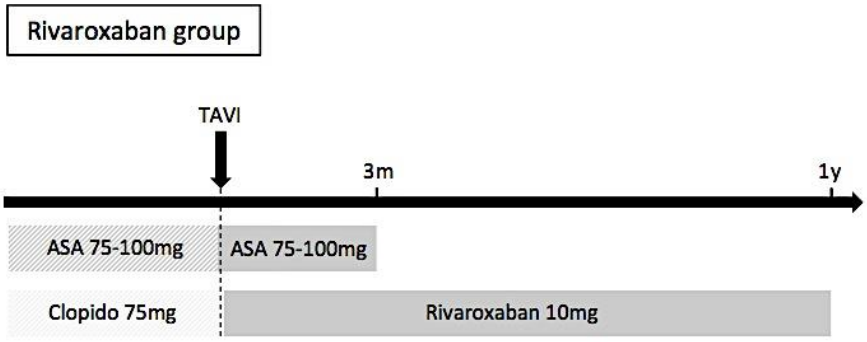
The patient is informed orally and in writing by an investigator about the GALILEO-4D substudy and written informed consent is obtained before study inclusion. Patients will have to give written informed consent for the GALILEO and GALILEO-4D substudy before study entry, preferably in parallel. The patient will also receive a copy of the patient information and, if requested, of the informed consent.

6.2. Randomization

All criteria of the GALILEO-4D trial have to be fulfilled in order to make a patient suitable for randomization in the GALILEO-4D trial. In order to obtain 1:1 randomization in the GALILEO and GALILEO-4D trial, a stratified randomization will be foreseen for those patients included in both studies.

6.3. Antithrombotic/anticoagulant treatment

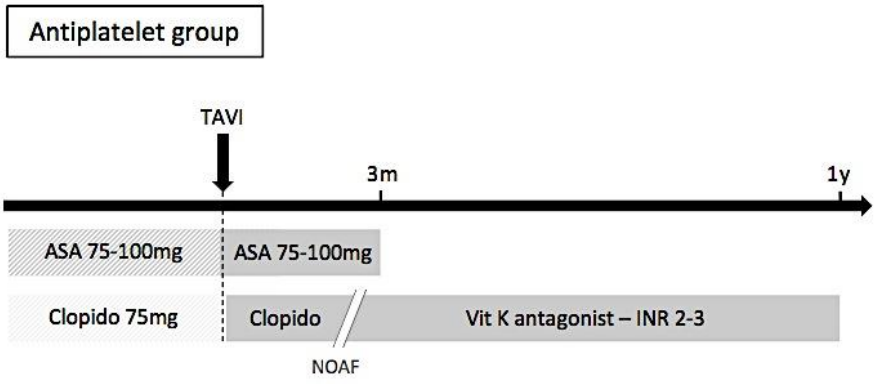


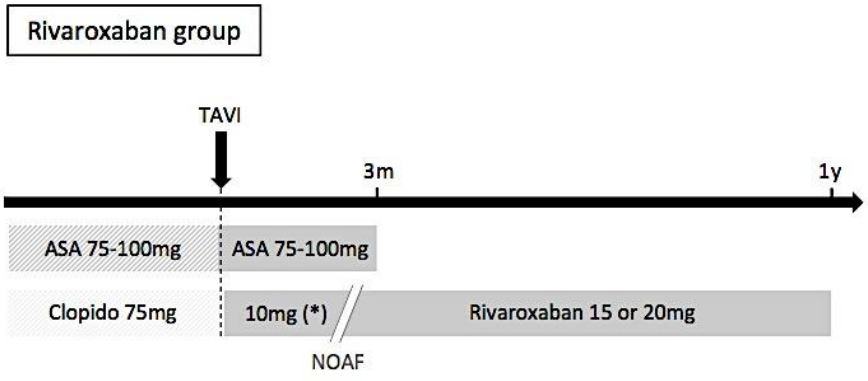


Additional information

- The route of administration of all medication is oral.
- Clopidogrel 75 mg once-daily and ASA 75-100 mg once-daily are to be continued unchanged, or to be started at the time of randomization if not already being taken. In subjects that are clopidogrel naïve at randomization, a loading dose of at least 300 mg clopidogrel should be administered.
- The first dose of rivaroxaban (10mg once-daily) is given either immediately after randomization or within 1-3 days after the last intake of clopidogrel. Rivaroxaban 10 mg once-daily can be taken with or without food; rivaroxaban 20 mg once-daily should always be taken with food. Rivaroxaban is continued until the end-of-treatment period visit of the main GALILEO trial.

➢ ***IN THE EVENT OF NEW-ONSET ATRIAL FIBRILLATION (NOAF):***





Additional information

- In the event of NOAF, the antiplatelet-based strategy will be stopped and a vitamin K antagonist (VKA) with a target INR 2-3 started. ASA 75-100 mg once-daily is to be continued in combination with VKA until 90 days after randomization.
- In the event of NOAF, the dose of rivaroxaban is switched from 10 mg once-daily to 20 or 15 mg once-daily – depending on renal function – for those patients in the rivaroxaban group. Rivaroxaban 20 and 15 mg once-daily should be taken with food. ASA 75-100 mg once-daily is to be continued until 90 days after randomization.

In order to preserve the 1:1 randomization in the main GALILEO trial and avoid excessive and unfounded 'cross-over' from the antiplatelet group to the rivaroxaban group, results of the 4DCT-scan will be kept blinded for the treating physician and patient until the end oft he main GALILEO study.

Only in case of a clinical overt ischemic stroke or non-CNS systemic embolism within three months after randomization, an additional cardiac 4DCT-scan within 8 days of this thrombo-embolic event could be considered. The result of this additional cardiac 4DCT-scan could be made available to the treating physician.

6.4. Adverse event reporting

Adverse Event (AE) reporting will be done via the main GALILEO trial as described in the main GALILEO protocol. As the GALILEO-4D study will be a diagnostic sub-study (involving only a single 4DCT-scan and transthoracic echocardiography), no treatment related Serious Adverse Event (SAE)-reporting should be anticipated.

7. STUDY ENDPOINTS

All endpoints will be assessed at three months after TAVR.

7.1. Primary endpoint

- The rate of patients with at least one prosthetic leaflet with > 50% motion reduction as assessed by cardiac 4DCT-scan (total N = 300).

7.2. Secondary endpoints

- The rate of prosthetic leaflets with > 50% motion reduction as assessed by cardiac 4DCT-scan (total N = 900).
- The rate of patients with at least one prosthetic leaflet with thickening as assessed by cardiac 4DCT-scan (total N = 300).

- The rate of prosthetic leaflets with thickening as assessed by cardiac 4DCT-scan (total N = 900).
- Aortic transvalvular mean pressure gradient and effective orifice area (cm^2) as determined by transthoracic echocardiography.
- Functional NYHA class.
- Death, first thromboembolic event (DTE), and safety endpoints (see GALILEO trial) will be assessed in the main GALILEO study and analyzed in the GALILEO-4D substudy with regards to occurence of the leaflet abnormalities – as exploratory analysis.

Definitions:

- Leaflet thickening: Hypoattentuating leaflet thickening *or* focal hypoattenuating abnormality attached to the prosthetic leaflet *or* diffuse thickening of the prosthetic valve leaflet identifiable on at least two reconstructed planes (typically double-oblique axial and multiplanar reformatted reconstructions).
- Reduced motion: Reduced systolic leaflet excursion is classified as: (I) normal, (II) mildly reduced (<50%), (III) moderate to severely reduced (>50%), and (IV) immobile. Reduced systolic leaflet excursion is considered significant when it is > 50% or immobile. Quantitative assessment of leaflet motion is performed with a blood pool inversion volume rendered cine reconstruction throughout the cardiac cycle evaluating the bioprosthetic leaflets.

The 4DCT CoreLab evaluation will be performed at Rigshospitalet, Copenhagen (Denmark) under supervision of Prof. Dr. Klaus Fuglsang Kofoed and at St. Paul's Hospital, Vancouver, BC (Canada) under supervision of Dr. Jonathon A. Leipsic. The readers of the 4DCT-scan will be blinded from the treatment arm.

8. STATISTICAL ANALYSIS

The primary endpoint of reduced prosthetic leaflet motion is expected to occur in 20% of patients.[6] Equal number of patients are warranted in both treatment groups. A 65% reduction of the GALILEO-4D primary endpoint requires inclusion of 246 patients in order to demonstrate superiority. Taking into account an estimated loss at follow-up of 18% of patients, the total sample size (N) needed to demonstrate superiority will be 300 randomized patients. The primary endpoint will be analysed using an exact Fisher test or a X^2 test, as required.

SAMPLE SIZE CALCULATION (Power 0.8, Alpha 0.05)

- Probability of event in Group A: 0.20
- Probability of event in Group B: 0.07
- Proportion of sample in Group A: 0.50
- Evaluable subjects needed in Group A: 123
- Drop-out: 0.18

N = 300

Estimation of drop-out rate:

- *A 10% loss at follow-up or death at 3 months is expected in this elderly patient population.*
- *In approx. 8% of cases, an inconclusive cardiac 4DCT can be expected.*

9. PARTICIPATING CENTERS

The GALILEO-4D trial is a multicenter, open-label, randomized, active-controlled trial and will be conducted as a substudy of the international GALILEO trial. Some selected centers participating at the GALILEO trial – and having the possibility to perform cardiac 4DCT-scans – will be offered the possibility to include patients in the GALILEO-4D trial. Inclusion will be by competitive enrollment until inclusion of 150 patients in both treatment groups of the GALILEO-4D trial

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10. CLINICALTRIALS.GOV AND DATATILSYNET

The GALILEO-4D trial will be registered at ClinicalTrials.Gov and will be conducted according to guidelines of the Danish Datatilsynet (Danish Data Protection Agency – The act implements the European Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data). The study results will be published regardless of the outcomes and conclusions that can be extracted.

11. ECONOMICS

The study is being economically supported by Bayer AG (Germany) to cover study costs – this financial support will be used primarily for research staff as well as for financial compensation of participating centers for additional study costs (such as 4DCT scan, echocardiography). None of the study investigators or members of Study Committees has a financial interest in the study. None of the supporters will have any conflict of interest with regard to the results of the study. Insurance and any legal requirements of the trial follow local legislation.

12. ETHICAL ASPECTS

There are some ethical issues involved in the treatment and follow-up part of this study. Anti-coagulation treatment in TAVR patients has proven to be safe in previous studies and in our experience with TAVR patients with previously known AF. There might be a slightly increased bleeding risk, however, this bleeding risk is kept to a minimum due to the exclusion of patients with an *a priori* increased bleeding risk (*see* exclusion criteria). We can consider this risk well counterbalanced by the advantage of reducing the risk of reduced valve leaflet motion as well as the risk of stroke. The risk related to the 4DCT-scan is low – patients with a renal insufficiency, iodine contrast allergy and/or contraindications for CT are excluded (*see* exclusion criteria) Concerning the radiation dose of the 4DCT-scan, we can report that patients will receive a radiation dose of 5-20mSievert, depending on weight and heart frequency/rhythym. It can be calculated that lifetime risk to die from cancer, hereby, theoretically increases with maximally 0,06%. Thus, the patients' lifetime risk to die from cancer increases from 25,0% to 25,06%. Furthermore, more than 95% of all study patients are expected to be more than 70 years of age. The patients are informed orally and in writing and are only included in case of written consent. Results of the study are expected to be of value for future patients undergoing TAVR.

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4DCT-scan – technical requirements

It is essential to have optimal CT image quality for accurate assessment of TAVR leaflet morphology and motion. The highest degree of image quality is needed especially during the systolic phase of the cardiac cycle, whereas late-diastolic images are less important. High performance in terms of temporal and spacial resolution of the CT technology used is mandatory. Each participating site are requested to forward pilot data-sets to the Corelab at Rigshospitalet for image quality assessment, prior to study initiation. Accordingly, a list of minimal requirements in terms of CT methodology is tabulated below.

MDCT scanner type: High-end CT scanners with >64 detector technology are required. Any CT vendor will be allowed, provided that the site has comprehensive experience in cardiac CT imaging using the specific CT tomograph. Each site is requested to specify CT-scanner type and number of performed ECG-gated cardiac CT scans yearly.

Patient preparation pre-MDCT: To achieve the highest possible temporal resolution and hemodynamic standardization of valve function - regardless of CT scanner used – all patients will be required to undergo pre-treatment with betablocker or ivabradine for heart-rate control. Target heart rate is less than 65 bpm. Each site is requested to specify if heart-rate control is part of the current routine of the CT unit.

MDCT-contrast: Contrast injection system (single vs dual-phase) and contrast type are according to local preference. Each site is requested to specify injection protocol and contrast type routinely used.

MDCT-acquisition: Arterial phase (LV or descending aortic triggering), retrospective image acquisition with recordings of the entire R-R interval is needed. Both dose-modulation, reducing dose during diastole or without dose-modulation is allowed. Scan-field of view (Z-axis) should be 1 cm above and 1 cm below the TAVR stent frame. In centers, where radiation dose and scanner specifications allow it, a Z-axis 1 cm above the TAVR stent frame and below the caudal boundary of the left ventricle should be recorded. Vendor specific scan protocols will be provided to each individual site. In addition to scan parameters, heart rate and blood pressure during the scan should be recorded.

MDCT-reconstruction: Recorded image data should be reconstructed using appropriate filtering and iterative reconstruction according to a vendor specific protocol provided. Data sets of lowest possible slice thickness (0-5-0-9 mm) at each 5% intervals of the R-R cycle (0-95%) should be reconstructed including the TAVR. In addition, at site where the whole heart may be included in the image, data sets of 2 mm slice thickness at each 5% interval of the R-R cycle should be reconstructed including the heart chambers. These images will be used to assess LV cardiac volumes and specifically LV stroke volume.

MDCT-images: All recorded MDCT image data should be saved in DICOM format and forwarded to the Corelab at Righospitalet.

4DCT-scan – protocol

Scan protocol: Prior to imaging, patients are required to abstain from caffeine intake 16 hours before the scan. Baseline ECG, heart rate and blood pressure are recorded and reviewed before the scan. A single dosage of oral metoprolol (50 to 150 mg) is administered 1.5-2 hours before the scan, according to the heart rate, blood pressure and weight. In patients with a heart rate more than 60 bpm at the time of CT scan, additional metoprolol i.v. should be given for heart rate control. In patients with metoprolol contraindications (allergic asthma or left ventricular ejection fraction below 30%) a single dose of oral ivabradin (15 mg) is given 2 hours prior to the scan.

Patients should be scanned using a 320-row multidetector CT (MDCT) scanner, using a dedicated 4D CT volume image protocol. An image noise standard deviation level of 30 is predefined, which results in a variable kV and mA per patient. The kV is set to 120 by default; if this results in a maximal mA the kV is raised, until a sub-maximal mA is reached. The start- and end-position of the scan is determined by the initial scanogram. Start-position is defined as 20 mm cranial to the metal stent frame of the valve and end-position 16 mm (maximal Z-axis coverage) caudally by retro-spective volume imaging. To minimize radiation exposure, a dose-modulation approach can be used, reducing dose in the 55-100% RR-range (diastole). The contrast images are recorded by one rotation of the gantry at a heart rate of less than 75 bpm, by two rotations at a heart rate of 75 to 100 bpm, and by three rotations at a heart rate above 100 bpm. A total volume of 70-110 ml contrast agent (Visipaque, GE Healthcare) – depending on the weight of the patient – is infused at a rate of 5-6 ml/sec. The scans are initiated by real time bolus tracking in the left ventricle. Images are reconstructed at 0.5 mm slices with 0.25 mm overlap with an FC03 filter and an iterative reconstruction algorithm (AIDR) for valve evaluation at 5% intervals within the 0-95% RR range.

CT Image reading: The valve leaflets will be assessed systematically using 2D and 3D-VR (volume rendered) imaging. The 3D-VR images are generated throughout the cardiac cycle and provide an animated movie of the valve (4D VR-CT), with an emphasis on assessment of systolic leaflet opening. Leaflet motion is defined as normal, mildly reduced (<50% reduction), moderately reduced (50 to 70% reduction), severely reduced (>70% reduction), or immobile (lack of motion in at least one valve leaflet). Hypo-attenuating leaflet lesions are also studied on maximal intensity projection (MIP) 2D CT and correlated to reduced leaflet motion.

Inter-observer variability: 4DCT-scans performed in the SAVORY trial were analyzed by a local site reader (K.K.) and the CT Core Lab (H.J.). There was concordance between both readers in 61 out of 62 patients included in the SAVORY cohort. The presence of reduced leaflet motion on 4D VR-CT was compared with independent observations between different CT software (3mensio and Vitrea) by two different groups of specialists (H.J. and J.F./D.B.) – in 20 consecutive patients, there was a 100% concordance for assessment of leaflet motion (Makkar et al., NEJM 2015).

N.B. In case of questions regarding the 4DCT protocol or need for support in order to set-up the 4DCT protocol at your institution, please contact Prof Dr Klaus Kofoed, Rigshospitalet, Non-Invasive Imaging Specialist, Department of Cardiology, Copenhagen, Denmark.