Discontinuing Statins in Multimorbid Older Adults without Cardiovascular Disease (STREAM) – a randomized non-inferiority clinical trial

Study Type:	Other Clinical Trial
Risk Categorisation:	A
Study Registration:	ClinicalTrials.gov SNCTP (Swiss National Clinical Trials Portal)
Sponsor-Investigator:	Prof. Dr. med. Nicolas Rodondi Department of General Internal Medicine University Hospital Bern (Inselspital) CH-3010 Bern nicolas.rodondi@insel.ch +41 31 632 41 63
Investigated Intervention:	Discontinuing statins compared to continuing statins for primary prevention
Protocol ID	STREAM
Version and Date:	V2.3, 13.06.2022

PROTOCOL SIGNATURE FORM

The sponsor-investigator has approved this study protocol and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Sponsor-Investigator:

Name: Prof. Dr. med. Nicolas Rodondi

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Kantonsspital Aarau, Medizinische Universitätsklinik, Tellstrasse H7, 5001 Aarau

Principal Investigator (name in print): Prof. Dr. med. Philipp Schütz

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Kantonsspital Baden AG, Departement Innere Medizin, Im Ergel 1, 5404 Baden

Principal Investigator (name in print): Prof. Dr. med. Maria Wertli

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Universitätsspital Basel, Klinik für Endokrinologie, Diabetologie und Metabolismus / Klinik für Innere Medizin, Petersgraben 4, 4031 Basel

Principal Investigator (name in print): Prof. Dr. med. Mirjam Christ-Crain

Date: _____ Signature: _____

Principal Investigator (name in print): Prof. Dr. med. Stefano Bassetti

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Ospedale Regionale di Bellinzona e Valli, Medicina interna e RAMI, 6500 Bellinzona

Principal Investigator (name in print): Prof. Dr. med. Luca Gabutti

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Spital Emmental, Medizinische Klinik, Oberburgstrasse 54, 3400 Burgdorf

Principal Investigator (name in print): PD Dr. med. Robert Escher

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): CHUV, Centre Hospitalier Universitaire Vaudois, Service de medicine interne, Av. du Bugnon 46, CH-1011 Lausanne

Principal Investigator (name in print): Dr. med. Marie Méan

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Hôpitaux universitaries de Genève, Service de médecine interne de l'Agé, 3. Chemin du Pont-Bochet, 1226 Thônex

Principal Investigator (name in print): Prof. Dr. med. Dina Zekry

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Hôpitaux Universitaires de Genève, Service de médecine interne générale, Rue Gabrielle-Peret-Gentil, 4, 1211 Genève

Principal Investigator (name in print): PD Dr. med. Sebastian Carballo

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Hôpital de La Tour, Service de médecine interne générale, Avenue Jacob-Daniel Maillard 3, 1217 Meyrin

Principal Investigator (name in print): Prof. Dr. med. Omar Kherad

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Regionalspital Emmental AG Langnau, Dorfbergstrasse 10, 3550 Langnau i.E.

Principal Investigator (name in print): Dr. med. Martin Egger

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Réseau Hospitalier Neuchâtelois, Département de médecine, Maladière 45, 2000 Neuchâtel

Principal Investigator (name in print): Prof. Dr. med. Jacques Donzé

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Geriatrische Klinik St. Gallen AG, Rorschacher Strasse 94, 9000 St. Gallen

Principal Investigator (name in print): PD Dr. med. Thomas Münzer

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Stadtspital Waid und Triemli, Departement Innere Medizin, Standort Triemli, Birmensdorferstrasse 497, 8063 Zürich

Principal Investigator (name in print): Prof. Dr. med. Lars Huber

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address):

Universitätsspital Zürich, Klinik für Altersmedizin, Rämistrasse 100, 8091 Zürich

Stadtspital Zürich Waid, Universitäre Klinik für Altersmedizin, Tièchestrasse 99, 8037 Zürich

Principal Investigator (name in print): Prof. Dr. med. Heike Bischoff-Ferrari

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Hôpital du Valais, Médecine Interne, Av. Grand-Champsec 80, 1951 Sion / Av. de la Fusion 27, 1920 Martigny

Principal Investigator (name in print): Prof. Dr. med. Pierre-Auguste Petignat

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Kantonsspital Graubünden, Departement Innere Medizin, Loestrasse 170, 7000 Chur

Principal Investigator (name in print): Dr. med. Martina Heim (main responsibility)

Date: _____ Signature: _____

Co- Principal Investigator (name in print): Dr. med. Patrick Hofmann

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Spital Limmattal, Urdorferstrasse 100, 8952 Schlieren

Principal Investigator (name in print): Prof. Dr. med. Alain Rudiger

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Klinik Barmelweid AG, 5017 Barmelweid

Principal Investigator (name in print): Dr. med. Mathias Schlögl

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): HFR Fribourg, Hôpital cantonal, Chemin des Pensionnats 2-6, 1752 Villars-sur-Glâne

Principal Investigator (name in print): Dr med. Marco Mancinetti

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): CUTR Sylvana, Chemin de Sylvana 10, 1066 Epalignes

Principal Investigator (name in print): Dr med. Luca Barbarossa

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Luzerner Kantonsspital, Spitalstrasse, 6000 Luzern 16

Principal Investigator (name in print): Dr med. Lukas Burget

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): Centre hospitalier Bienne, Chante-Merle 84, 2501 Bienne

Principal Investigator (name in print): Prof. Dr med. Daniel Genné

Date: _____ Signature: _____

Local Principal Investigator at study site:

I have read and understood this study protocol and agree to conduct this study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines, as well as the local legally applicable requirements.

Site (name and address): LUMC, Leiden the Netherlands, Albinusdreef 2, Leiden, 2333 ZA, Netherlands

Principal Investigator (name in print): Prof. Dr. med. Jacobijn Gussekloo

Date: _____ Signature: _____

TABLE OF CONTENTS

GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR	*Annual Safety Repot*
BASEC	*Business Administration System for Ethical Committees*
CEC	*Clinical Event Committee*
ClinO	*Ordinance on Clinical Trials in Human Research*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
CV	*Cardiovascular*
CVD	*Cardiovascular Disease*
DSMB	*Data and Safety Monitoring Board*
EC	*Ethics Committee*
eCRF	*electronic Case Report Form*
EDC	*Electronic Data Capturing*
GCP	*Good Clinical Practice*
GP	*General Practitioner*
HR	*Hazard Ratio*
HRA	*Human Research Act*
ICH	*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*
ITT	*Intention-To-Treat*
PP	*Per-Protocol*
RCT	*Randomized Controlled Trial*
SAE	*Serious Adverse Event*
TSC	*Trial Steering Committee*

1 STUDY SYNOPSIS

Sponsor-Investigator	Prof. Dr. med. Nicolas Rodondi Department of General Internal Medicine University Hospital Bern (Inselspital) CH-3010 Bern nicolas.rodondi@insel.ch
Study Title	Discontinuing Statins in Multimorbid Older Adults without Cardiovascular Disease – a randomized non-inferiority clinical trial
Short Title / Study ID	STREAM
Protocol Version and Date	V2.3, 13.06.2022
Study Registration	ClinicalTrials.gov SNCTP (Swiss National Clinical Trials Portal)
Study Category and Rationale	According to ClinO, Art. 60 & 61, this clinical trial, assessing deprescribing of statin, comes under “Other Clinical Trial”, Risk Category A.
Background and Rationale	Statins are among the most widely used drugs. While they were found to be effective for primary and secondary prevention of cardiovascular disease (CVD) in middle-aged subjects, their benefits for primary prevention in older people (aged ≥70) without CVD are uncertain, particularly for those with multimorbidity. However, statin side effects and drug interactions are common in a multimorbid elderly population and can negatively impact quality of life and increase adverse drug reaction-related hospitalizations. Therefore, we aim to conduct a statin deprescribing randomized controlled trial (RCT) to provide guidance on the long-term benefits and risks for the ever-growing multimorbid elderly population.
Risk / Benefit Assessment	Potential risks of discontinuing statins might include increased CV events. However, current trials found no benefits of statins after 70 years of age for primary prevention. In the multimorbid elderly, statin side effects and drug interactions are common and discontinuing statin might positively impact quality of life.
Objective(s)	The primary objective is to compare a composite endpoint of major CV events and all-cause death between control and intervention group. Secondary objectives are the comparison of patient-centered outcomes between the two groups.
Endpoint(s)	The primary endpoint is a composite endpoint of major CV events (non-fatal myocardial infarction, non-fatal ischemic stroke) and all-cause death over a follow-up period of 2 years. Secondary endpoints are all-cause death, non-CV death, major CV events, coronary and peripheral artery revascularization, EQ-5D questionnaire, verbal numeric pain rating score, falls, SARC-F questionnaire and Girerd Medication adherence scale.
Study Design	The study is a multicenter, randomized, non-inferiority trial conducted in multiple hospitals in Switzerland. The study is open-labelled, with blinded outcome adjudication. Study subjects are randomly assigned in a 1:1 ratio to either discontinue (intervention arm) or continue (control arm) statin therapy.
Statistical Considerations	We hypothesize that discontinuing statins does not result in shorter event-free survival. The non-inferiority margin is set at 5.2 weeks over a two year observation period. To claim non-inferiority, the lower limit of the difference in two-year restricted mean survival time (RMST) between the treatments must be less than the non-inferiority margin in both intention-to-treat and per-protocol analyses. RMST will be calculated using either Statas strsmst2 or Rs survRM2 package. Besides RMST, the effect will also be reported on the hazard ratio scale. Interim analyses will compare the proportion of events that occur in the two arms after each 50 events. Of the 50 events, if significantly more than half occur in the experimental arm, the DSMB will be called to an adhoc meeting to discuss closing the trial early. Due to safety concerns in the those under 75, we will use a lower stopping boundary to ensure stopping that arm if there is evidence of a safety issue. Should this boundary be breached, the DSMB will have to decide whether to close the strata (not the trial).

Inclusion- / Exclusion Criteria	Inclusion criteria: • ≥70 years of age • Multimorbid with ≥2 coexistent chronic conditions (defined by ICD-10 codes) with an estimated duration of 6 months or more based on clinical decision, besides dyslipidemia treated by statins • Taking a statin for ≥80% of the time during the year before baseline Exclusion criteria: 1. Secondary prevention based on previous large statin trials, defined as: • History of myocardial infarction type 1 (NSTEMI/STEMI) OR • History of unstable angina, defined as ACS symptomatic at rest, crescendo or new-onset angina (CCS 2 or 3) without ECG or cardiac biomarker changes (based on available documents) OR • Stable angina pectoris with a documented ischemia on a stress test or with a significant coronary disease defined as a coronary stenosis >50% OR • History of percutaneous coronary intervention (balloon or stent) or coronary artery bypass graft OR • History of ischemic stroke[1] OR • History of Transient Ischemic Attack, defined as transient neurological deficit without diffusion restriction in MRI OR • History of carotid revascularization (stent or bypass) OR • History of peripheral arterial disease requiring revascularization (stent or bypass; Fontaine IV) 2. Aortic disease that required a vascular repair or aortic aneurysm with a maximum diameter >5.5 cm (men) or >5.2 cm (women) based on available documents 3. Diagnosis of familial hypercholesterolemia based on Dutch lipid score ≥6 based on available documents (LDL-c, Family History, Personal History) (1) 4. Elevated risk of death within 3 months after baseline, defined as: • hospitalized patients planned for palliative care within 24h of admission OR • hospitalized patients with a Palliative Performance Scale (PPS) level <30% (based on situation at least 1 month before hospitalization), this corresponds to an estimated survival of 43% after 3 months (2); OR • patients with an advanced metastatic cancer prognosis of ≤20% survival rate within 1 year after baseline (based on an online tool: https://cancersurvivalrates.com) 5. Participation to a clinical trial with potential impact on the STREAM cardiovascular endpoints (based on clinical judgment)
Number of Participants with Rationale	The target sample size is 1'800 participants, 900 in each group. Assuming an event rate of 34% at 24 months, a 2% dropout rate per year and 85% protocol adherence (based on OPERAM data), 1800 participants should yield 89% power for the ITT analysis and 83% power for the approximated PP analysis at a one sided α of 0.025. Simulations were performed in Stata 15.1 with the *strmst2* package for calculating restricted mean survival time.
Study Intervention	In the intervention group, statin therapy will be stopped from the next scheduled intake after given informed consent onwards. Additional lipid-lowering medication lowering LDL cholesterol (i.e., ezetimibe, PCSK9 inhibitors, future novel lipid-lowering medications with lowering of LDL cholesterol demonstrated in randomized trials) will also be stopped in the intervention group.
Control Intervention	No control intervention is planned. In the control group, statin therapy will be continued as prescribed before the trial.
Study procedures	Study inclusion and baseline assessment is performed on-site. Then, outcomes are assessed at three months and afterwards yearly by phone call. In addition, medical records are reviewed to obtain information from hospitals and GPs about medical events and concomitant treatment during the intervention period. Patients are asked for a separate consent for yearly observational data collection after the intervention period up to 10 years after baseline.
Study Duration and Schedule	The expected recruitment period is 36 months. Study subjects remain in the study for the entire duration of the intervention period. Minimum intervention period duration is 12 months, maximum intervention period duration is expected to be 48 months. After the end of the intervention period, an optional long-term follow-up observation with annual phone calls for a maximum of 10 years from baseline is planned. Planned First-Participant-In: 10/2021 Planned Last-Participant-Out (Intervention period): 10/2026 Planned Last-Participant-Out (Long-term follow-up): 10/2035

[1] This exclusion criterion does not apply to clearly cardio-embolic causes for stroke, (e.g. due to atrial fibrillation)

Investigator(s)	Prof. Dr. med. Nicolas Rodondi (Inselspital) Prof. Dr. med Philipp Schütz (Aarau) Prof. Dr. med. Maria Wertli (Baden) Dr. med. Marie Méan (CHUV) Prof. Dr. med. Luca Gabutti (Bellinzona) Prof. Dr. med. Lars Huber (Triemli Hospital) PD Dr. med. Sebastian Carballo (Geneva, Internal medicine) Prof. Dr. med. Dina Zekry (Geneva, Geriatrics) Prof. Dr. med. Mirjam Christ-Crain and Prof. Dr. med. Stefano Bassetti (Basel) Prof. Dr. med. Jacques Donzé (Neuchâtel) Prof. Dr. med. Heike Bischoff-Ferrari (University Hospital Zurich and Stadtspital Zürich Waid) Prof. Dr. med. Omar Kherad (Meyrin) PD Dr. med. Robert Escher (Burgdorf) Dr. med. Martin Egger (Langnau) Lorenz Landolt (Langnau) PD Dr. med. Thomas Münzer (St. Gallen) Prof. Dr. med. Pierre-Auguste Petignat (Martigny, Sion) Dr. med. Martina Heim and Dr. med. Patrick Hofmann (Graubünden) Prof. Dr. med. Alain Rudiger (Hospital Limmattal) Dr. med. Mathias Schlögl (Clinic Barmelweid) Dr. med. Marco Mancinetti (Cantonal Hospital Fribourg) Dr. med Luca Barbarossa (CUTR Sylvana) Dr. Med. Lukas Burget (Cantonal Hospital Lucerne) Prof. Dr. med. Daniel Genné (Centre hospitalier Bienne) Prof. Dr. med. Jacobijn Gussekloo (LUMC, Netherlands)
Study Center(s)	The study will be started at the University Hospital Bern (Inselspital), Switzerland. Then, it is aimed to conduct the study in multiple hospitals in Switzerland. Participating core sites: - Department of General Internal Medicine, Inselspital, Bern University Hospital, Bern - Cantonal Hospital Aarau - Cantonal Hospital Baden - Centre Hospitalier Universitaire Vaudois (CHUV) - Ospedale Regionale di Bellinzone e Valli - Triemli Hospital, Zurich - Department of Internal Medicine, Geneva University Hospitals - Department of Geriatrics, Geneva University Hospitals - University Hospital of Basel - Hospital of Neuchâtel - University Hospital of Zurich - Stadtspital Zürich Waid - La Tour Hospital, Meyrin - LUMC, Netherlands Participating auxiliary sites: - Hospital Emmental, Burgdorf, Medizinische Klinik - Regional Hospital Emmental, Langnau - Geriatric Clinic St. Gallen - Hôpital du Valais, Internal Medicine - Cantonal Hospital Graubünden - Hospital Limmattal - Clinic Barmelweid - Cantonal Hospital Fribourg - CUTR Sylvana - Cantonal Hospital Lucerne - Centre hospitalier Bienne
Data privacy	For each enrolled trial participant, an eCRF is maintained, using a dedicated electronic data capturing (EDC) system (Webspirit®). Study-related data of the participants are collected in a coded manner. At each study site, the principal investigators safeguard the confidentiality of participating patients' data and maintain appropriate medical and research records for this trial. No patient information containing identifying data will leave the study site, except for contact information that is entered in a separate built-in module in the database and only accessible by specifically-assigned users. Biological material will be appropriately stored in

	the biobank of the University Hospital Bern, a restricted area only accessible to the authorised personnel.
Ethical consideration	The authorization from the local ECs is collected prior to the commencement of the trial, and all protocol changes or unexpected problems concerning human participants will be reported during the trial.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

Statins are among the most widely used drugs (3). While they were found to be effective for primary and secondary prevention of cardiovascular disease (CVD) in middle-aged subjects (4-6), their benefits for primary prevention in older people (aged ≥70) without cardiovascular disease (CVD) are uncertain, particularly for those with multimorbidity (7).

At present, there is no clear benefit of statins in 70+ on all-cause mortality and CVD in primary prevention. First, no evidence of statin benefit for primary prevention was shown in Randomized Controlled Trials (RCTs). In the PROSPER trial among 5804 older adults aged 70-82 years, there was no benefit of statins on CVD in primary prevention (8). In the ALLHAT-LLT trial, there was even a nonsignificant increase in mortality rate in the pravastatin group (24.5%) compared with the UC group (18.5%) (HR=1.34; 95% CI, 0.98-1.84; P=.07) for adults 75 years and older, and no significant between-group difference in the 65-74 years age group (for all-cause mortality, HR 1.08, 95%CI 0.85-1.37; for CHD rate, HR 0.94, 95%CI 0.58-1.51) (9). In subgroups of 70+ participants, a 2019 meta-analysis of RCTs found no statistically significant benefit of statins in primary prevention of CV events in participants without established CVD aged 70 to 75 years (rate ratio (RR) per 1mmol/l reduction in LDL=0.84, 95% CI 0.70 to 1.01) and ≥75 years (RR per 1mmol/l reduction in LDL=0.92, 95% CI 0.73 to 1.16) (10), although results might have been impacted by the unusual adjustment per 1mmol/l (not so randomized) and the unusual inclusion of revascularization in the combined endpoint (11). Second, the majority of older individuals suffer from multimorbidity (defined as ≥2 chronic conditions) (12-15), and most large RCTs do not include such multimorbid elderly (16). To this day, no RCT examining the benefits of statins in primary prevention has exclusively recruited multimorbid 70+ participants (17), and 70+ participants are under-represented in most RCTs, including those examining statin benefits for prevention (8, 9, 18-23). However, statin side effects and drug interactions are common in a multimorbid elderly population and can negatively impact quality of life and increase adverse drug reaction-related hospitalizations. The proportion of patients developing myalgia on statins has been shown to be as high as 5-20% in observational studies (24, 25), as older age and polypharmacy are known risk factors for developing muscle problems under statins (26). Furthermore, multimorbid elderly patients with polypharmacy are more likely to experience side effects with statins (e.g. elevated liver enzymes, diabetes, myopathy, rhabdomyolysis) and drug-drug interactions (e.g. antibiotics, antifungals), with the potential consequences of drug toxicity, reduced physical activity, sarcopenia and falls (27, 28). In practice, statins are often discontinued in multimorbid elderly without CVD after side effects (29). Third, LDL and total cholesterol levels do not predict CV risk in 70+ individuals without pre-existing CVD, as shown in a study aiming at improving coronary heart disease (CHD) risk prediction (hazard ratio (HR) of CHD events per LDL-Cholesterol per 10mg/L 1.01, 95% CI 0.98 to 1.04) (30). Fourth, the use of the AGLA Risk Score – the tool most used in Switzerland to evaluate CV risk – is not validated in 70+ individuals, as this tool is based on the PROCAM trial, which only included men aged 36 to 65 years (31). Therefore, the use of this tool in 70+ individuals represent an extrapolation but no definitive CV risk evaluation. In summary, the net clinical benefit of statins for primary prevention in multimorbid 70+ elderly remains unclear, and the effect of multimorbidity might shift the evidence towards favoring no statin treatment.

While there is little data to support prescribing of statins for primary prevention in elderly multimorbid persons, there is even less data as to whether it is safe to discontinue statins in these

individuals. Recent guidelines on the topic are conflicting. AHA/ACC Cholesterol Guidelines from 2018 mentioned that it may be reasonable to stop statin therapy when: *"functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statins"* (32), while 2019 ESC/EAS Guidelines for the management of dyslipidaemias stated that *"the use of statin therapy declines with increasing age*" (33). Moreover, a 2018 multidisciplinary expert panel invited by the US National Institute of Aging (NIA) and the National Heart, Lung and Blood Institute (NHLBI) concluded that *"existing data cannot address uncertainties about the benefits and harms of statins for primary cardiovascular prevention in adults aged 75 and older, especially those with comorbidities, frailty, and cognitive impairment"* (34). Those are however expert opinions, not based on data from large RCTs on discontinuing statins. The impact of discontinuing statins has not been evaluated in RCTs so far, except in a single RCT including participants with a short life expectancy (<1 year) that found no difference in CV events and mortality between the groups, but a slightly better quality of life among those who discontinued statins (35). In a retrospective cohort study, elderly participants who discontinued statins for primary prevention were more often admitted to the hospital for a CV event. However, several CVD confounding factors were not measured, all-cause death was not examined, and reasons for statin-discontinuation were not reported (36).

Inappropriate medication prescribing encompasses not only under-treatment but also over-treatment, which is common and particularly problematic in the multimorbid elderly with polypharmacy (37). Therefore, the decision to discontinue a medication should be given the same importance as the assessment to start one and should be based on evidence obtained from RCTs. According to a survey of US Medicare beneficiaries ≥65 years, deprescribing (if medically justified) would be well received (38). In fact, 92% said they would stop taking one or more of their drugs if their doctor deemed this possible, and 67% wanted to decrease the number of daily drugs (38). When geriatric experts were asked to prioritize candidate drugs for deprescribing, statins ranked third after benzodiazepines and atypical antipsychotics (39). Similar findings are available for Switzerland: as national coordinators for Switzerland, we participated in a multi-national study that conducted a survey among 2,250 General Practitioners (GPs) from 30 countries. Eighty percent of GPs advised discontinuing statins in the oldest-old (i.e. 80+) who suffered from statin-related side effects and frailty, but did not have established CVD (29). In another ongoing survey, 80% of 300 multimorbid elderly were willing to deprescribe (unpublished data). Yet, RCT data on safety of discontinuing statins are lacking.

Given the uncertainty of statin benefits for CVD primary prevention in the multimorbid elderly and the lack of evidence that statins may be safely discontinued (40), we aim to conduct a statin deprescribing RCT to provide guidance on the long-term benefits and risks for the ever-growing multimorbid elderly population, who has been systematically neglected in RCTs (16, 17, 34).

Coronary artery calcium (CAC) measurement is rapidly increasing in clinical use and is recommended for risk re-classification in some guidelines.(33, 41-43) In addition, traditional risk prediction models perform poorly in multimorbid older adults, and addition of CAC and biomarkers might improve prediction in this population. Older patients in primary prevention with subclinical atherosclerosis or elevated biomarkers associated with CVD risk might benefit from continuing statins to prevent CVD, but this hypothesis has not been tested in RCTs and evidence remains also unclear in most guidelines. To address these questions, in a subsample of the present RCT, we aim to measure CAC and biomarkers at baseline.

According to ClinO, Art. 60 & 61, this clinical trial, assessing deprescribing of statin, comes under "Other Clinical Trial", Risk Category A.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and study objectives

The overall aim of this study is to assess the safety of discontinuing statin therapy compared to continuing statin therapy in multimorbid elderly adults without clinical cardiovascular disease.

The primary objective is to compare a composite endpoint of major CV events and all-cause death between control and intervention group. We hypothesize that discontinuing statins does not result in shorter event-free survival. The non-inferiority margin is set at 5.2 weeks over a two year observation period (as justified under 5.1).

Secondary objectives are the comparison of all-cause death (including CV and non-CV deaths) and patient-centered outcomes between the two groups.

In the subsample of subjects undergoing assessment of subclinical atherosclerosis using CAC scoring and biomarker measurements, the primary aim is to determine if the risk of a composite outcome of CV events and all-cause mortality after statin discontinuation differs among those with higher burden of subclinical atherosclerosis, as funded by the Swiss National Science Foundation. We hypothesize that in participants with greater degrees of subclinical atherosclerosis, statin discontinuation might be associated with a higher risk of CV events and mortality, compared to statin continuation. Secondary objective in the subsample is to determine if the risk of CV events and mortality after statin discontinuation differs according to the baseline levels of previously validated blood biomarkers.

3.2 Primary and secondary endpoints

Schedule of assessment

Study Period	Screening & Baseline	Intervention period				After intervention period	
Time	0	3 months	12 months	24, 36, 48 months	End of intervention	+ 1 month from end of intervention	Yearly after end of intervention[4]
Time window		+/- 4 weeks	+/- 12 weeks	+/- 12 weeks	+/- 12 weeks	- 8 weeks	+/- 12 weeks
Visit type	On-site / Call*	Call	Call	Call	Call	GP practice	Call
Patient Information	X						
In- /Exclusion Criteria	X						
Informed Consent	X						
Randomization	X						
Start intervention	X						
Demographic data and contact information	X						
Mediterranean diet adherence questionnaire	X						
PASE questionnaire	X						
Physical variables[1]	X						
Biological variables[1]	X						
FRAIL-scale	X						
6-CIT	X						
Medical history	X						
Statin and other lipid-lowering drug intake	X	X	X	X	X		X
Current medication	X	X	X	X	X		X
CV event		X	X	X	X		X
Death		X	X	X	X		X
EQ-5D (5) – incl. CEA	X	X	X	X	X		X
VNPRS (verbal numeric pain rating score)	X	X					
Falls [3]	X	X	X				
SARC-F questionnaire	X		X	X	X		X
Girerd adherence scale	X		X	X	X		
Lipid level			X[2]			X[5]	
Blood sample for biobank	X[7]		X[6]				
SAEs	X	X	X	X	X		
Coronary artery calcium scoring in cardiac CT	X[7]				X[8]		

[1] collected retrospectively from medical records up to one year before baseline
[2] taken from a sub-sample at GP practices (if the corresponding consent is available), results remain blinded until end of intervention visit
[3] self-reported from baseline to 12 months
[4]up to 10 years after baseline, if patient consent to data collection after end of intervention visit
[5] if available at GP practices
[6] taken from a sub-sample at GP practices (if the corresponding consent is available)
[7] performed in a sub-sample at selected participating sites (if the corresponding consent is available), results remain blinded until end of intervention visit
[8] potentially performed in the sub-sample that underwent baseline cardiac CT scanning (funding pending)
*Baseline can be performed by phone if wished by patient

Primary endpoint (see schedule of assessment for time of acquisition):

The primary endpoint is a composite endpoint of major non-fatal CV events (non-fatal myocardial infarction, non-fatal ischemic stroke) and all-cause death over a follow-up period of 2 years. All-cause death (and not CV death only) is chosen to account for a possible shift from CV to other causes of death (such patterns were seen in two statin RCTs (8, 9)). The composite endpoint was selected to assess the net clinical benefit in this population with expected high mortality.

Secondary endpoints (see schedule of assessment for time of acquisition):

- Composite endpoint of all-cause death and major non-fatal CV events (non-fatal myocardial infarction, non-fatal ischemic stroke)
- Major CV events (CV death, non-fatal myocardial infarction and non-fatal ischemic stroke) as composite and components thereof
- Total CV events (CV death, non-fatal myocardial infarction, hospitalization for unstable angina, non-fatal ischemic stroke (including TIA) and arterial revascularization (coronary and peripheral urgent and non-urgent revascularization)
- Total composite events (all-cause death, non-fatal myocardial infarction, hospitalization for unstable angina, non-fatal ischemic stroke (including TIA) and arterial revascularization (coronary and peripheral urgent and non-urgent revascularization)
- All-cause death
- Non-CV death
- EQ-5D questionnaire: for general quality of life and possible future cost-effectiveness (44)
- Verbal numeric pain rating score (VNPRS): statin associated muscle symptoms (45, 46)
- Falls
- SARC-F questionnaire: muscle function and sarcopenia (47, 48)
- Girerd Medication adherence scale: general medication adherence

Safety endpoints:

Safety endpoints are collected as primary/secondary endpoints.

Other endpoints (see schedule of assessment for time of acquisition):

- Statin and other lipid-lowering drug intake
- Current medication: Drugs against high blood pressure, antiplatelet drugs, blood thinners, and drugs against diabetes
- After 12 months, blood samples are collected from a consecutive sub-sample of 100 subjects per group who remained in the assigned group (i.e., no change in treatment allocation recorded and no CV event). The lipid levels, collected for indirect assessment of statin intake of these blood samples, will remain blinded until the end of the trial. In this sub-sample, an additional blood sample is stored in the biobank of the University Hospital Bern for further, not yet specified, analyzes. The blood sampling is only done if the subject has given his/her separate consent for blood sampling. In addition, the biobank storage is only done if the subject has given his/her consent to the further use of samples.
- Additional lipid level measurements are collected at the end of the intervention period from GPs, if available.
- At the end of the intervention phase, repeat cardiac CT scan will be potentially performed in participants who underwent a baseline cardiac CT scan, depending on future funding. The CT scans are only done if the subject has given his/her consent for this procedure. The outcome will be annualized change of Agatston score with adjustment for baseline value.

Baseline factors

- Demographic data
- Physical variables: weight, size, BMI, systolic arterial blood pressure, diastolic arterial blood pressure
- Biological variables: lipid levels, creatinine, albumin, blood glucose; in subgroup with cardiac CT scan: lipoprotein(a), high-sensitivity C-reactive protein, NT-proBNP, troponin
- Medical history: Cardiovascular (family) history, cardiovascular surgery, cancer history, diabetes history
- Current medication: Drugs against high blood pressure, to regulate heart rate / rhythm or for heart failure, Antiplatelet drugs, blood thinners and drugs against diabetes
- Physical activity (Physical Activity Scale for the Elderly (PASE)) (49, 50)
- Nutrition status (Validated 14-items questionnaire of Mediterranean diet adherence) (51, 52)
- Questionnaire for frailty (FRAIL-Scale) (53, 54)
- Cognition (6-CIT) (55, 56)
- A subgroup of subjects at sites that participate to this part of the trial will undergo a baseline native ECG-gated CT scan of the entire heart on a multi-slice helical CT scanner. At the end of the intervention period, the images from the CT scans will be centrally assessed at the Department of Cardiology in the Inselspital (University Hospital of Bern) and used for semi-automated CAC scoring using the Agatston method.(57, 58)

3.3 Study design

The study is a multicenter, randomized, non-inferiority trial conducted in multiple hospitals in Switzerland. Study sites have been grouped into core and auxiliary sites according to their recruitment capacity. All sites with a recruitment goal of ≤ 90 participants over the entire recruitment period are called auxiliary sites, sites with more than 90 participants are core sites.

Study subjects are randomly assigned in a 1:1 ratio to either discontinue (intervention arm) or continue (control arm) statin therapy.

The study is open-labelled, with blinded outcome adjudication. Identification of potential outcome events is performed centrally by partially blinded study team members over the phone and by collecting medical records. Partially blinded means that the study team members assess the participant's outcome events over the phone without knowing the group assignment. However, they will know the group assignment retrospectively when assessing medication compliance. Then, a blinded clinical event committee (CEC) classifies suspected events for the primary and secondary clinical outcomes (see 8.1 for details).

The mains risks of this study design are:
a) Potential co-medication and co-interventions that could influence endpoints (see also chapter 4.5 for details). This is addressed by 1.) documenting these co-medications and co-interventions at each follow-up and 2.) accounting for co-medication and co-interventions in the statistical analysis.
b) Cross-over from one group to the other. This is addressed by 1.) distributing flyers to participants, GPs, and pharmacists, explaining the rationale of the trial and the group allocation 2.) documenting medication adherence, 3.) repeatedly advising GPs that lipid levels of the intervention group participants should not be measured during the trial, and 4.) performing a statistical Per-Protocol (PP) analysis that accounts for cross-over appropriately.

3.4. Study intervention

In the intervention group, statin therapy will be stopped from the next scheduled intake after given informed consent onwards. Additional lipid-lowering medication lowering LDL cholesterol (i.e., ezetimibe, PCSK9 inhibitors, future novel lipid-lowering medications with lowering of LDL

cholesterol demonstrated in randomized trials) will also be stopped in the intervention group. The participant's GP and pharmacist (if applicable) will be informed about the study.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

See chapter 2 for justification of study population and chapter 5.1. for sample size calculation. The target sample size is 1'800 participants. This study also enrolls vulnerable patients that cannot themselves provide informed consent (see 4.2).

Inclusion criteria:

- ≥70 years of age
- Multimorbid with ≥2 coexistent chronic conditions (defined by ICD-10 codes) with an estimated duration of 6 months or more based on clinical decision, besides dyslipidemia treated by statins
- Taking a statin for ≥80% of the time during the year before baseline

Exclusion criteria:

1. Secondary prevention based on previous large statin trials, defined as:
   - History of myocardial infarction type 1[2] (NSTEMI/STEMI) OR
   - History of unstable angina, defined as ACS symptomatic at rest, crescendo or new-onset angina (CCS 2 or 3) without ECG or cardiac biomarker changes (based on available documents) OR
   - Stable angina pectoris with a documented ischemia on a stress test or with a significant coronary disease defined as a coronary stenosis >50% OR
   - History of percutaneous coronary intervention (balloon or stent) or coronary artery bypass graft OR
   - History of ischemic stroke OR[1]
   - History of Transient Ischemic Attack, defined as transient neurological deficit without diffusion restriction in MRI OR
   - History of carotid revascularization (stent or bypass) OR
   - History of peripheral arterial disease requiring revascularization (stent or bypass; Fontaine IV)
2. Aortic disease that required a vascular repair or aortic aneurysm with a maximum diameter >5.5 cm (men) or >5.2 cm (women) based on available documents
3. Diagnosis of familial hypercholesterolemia based on Dutch lipid score ≥6 based on available documents (LDL-c, Family History, Personal History) (1)
4. Elevated risk of death within 3 months after baseline, defined as:
   - hospitalized patients planned for palliative care within 24h of admission OR
   - hospitalized patients with a Palliative Performance Scale (PPS) level <30% (based on situation at least 1 month before hospitalization), this corresponds to an estimated survival of 43% after 3 months (2); OR
   - patients with an advanced metastatic cancer prognosis of ≤20% survival rate within 1 year after baseline (based on an online tool: https://cancersurvivalrates.com)
5. Participation to a clinical trial with potential impact on the STREAM cardiovascular endpoints (based on clinical judgment)

The following additional exclusion criteria apply only for the performance of cardiac CT scans (subsample of 500 subjects):

[1] This exclusion criterion does not apply to clearly cardio-embolic causes for stroke, (e.g. due to atrial fibrillation)
[2] patients with a history of type 2 myocardial infarction are eligible for the trial unless there is a significant coronary disease defined as a coronary stenosis >50% or a history of revascularization with PCI (balloon or stent) or CABG.

1. Body measures exceeding the CT scanner limits (morbid obesity exceeding weight and diameter limits)
2. Cardiac implants with metallic interference, such as pacemaker and mechanical heart valves
3. Orthopedic hardware in the mid or lower thoracic spine
4. Inability to hold breath for 10 seconds

4.2 Recruitment, screening and informed consent procedure

The participating study centers screen their electronic patient records in line with the local regulations on data protection for patients fulfilling the eligibility criteria. Also, GP practices and, depending on the recruitment rate, retirement and nursing homes, patient associations (e.g. Pro Senectute, Spitex), and pharmacies, will be contacted and asked to screen and inform their patients about the possibility to participate in the study. In addition, potentially eligible participants from our previous OPERAM study (59) will be contacted and informed about the possibility to participate in the study. Depending on the recruitment rate, also public advertisement, e.g., in local hospitals and GP practices, magazines, newspapers or public transport might be an option. Each patient fulfilling all eligibility criteria is invited to participate. For screened patients who do not consent to participate, age, gender, eligibility criteria assessment and the reason for not consenting is collected systematically in the eCRF, (without any identifying information) to assess the degree of potential selection bias in the study enrollment process.
The screening and baseline visit is performed at a study site. The informed consent procedure is either performed by a study nurse in a hospital (supervised by a medical doctor) or by a GP. The study nurses are supervised locally by study physicians, who are involved in case of questions that require the expertise of a physician. In addition, study nurses have phone access to the study physicians at the main trial site (Bern). The study nurse/GP explains to each potential participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and any discomfort it may entail. Each candidate is informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment. Each candidate has the opportunity to ask questions to a medical doctor if the study nurse performs the inclusion procedure.

Study nurses who are responsible for the informed consent procedure must have a GCP certificate and receive tailored training for their study specific tasks. GPs without GCP certification are provided with a tailored GCP training specific for their limited task within the study, which includes training on patient information and consenting, and on adverse event detection, documentation, and reporting. Since GP practices are distributed all over Switzerland, this training will be provided through video and a written transcript of the key points of the video.

The candidate is informed that his or her medical records are examined by authorised individuals other than their treating physician and that their treating physician(s) and/or pharmacist(s) will be informed about the study participation. They are informed that institutions that provided or will provide medical care for the candidate (such as GP practices, pharmacies, hospitals, retirement or nursing homes) can be contacted during the conduct of the study to obtain medical information. They are also informed that the community of residence can be contacted to obtain a death certificate or information on change of residence.

Each candidate is provided with a participant information sheet and a consent form describing the study and providing sufficient information for the candidate to make an informed decision about his or her participation in the study. Since the study inclusion is under no time pressure, the candidates are given as much time as they deem necessary to consider participating in the study. The consent of a participant is obtained before the participant is submitted to any study procedure.

The consent form is signed and dated by the study nurse/GP at the same time as the participant signs. A copy of the participant information sheet and signed informed consent form is given to the study participant. The consent form is retained as part of the study records. The informed consent process is documented in the patient file of the hospital/GP practice.

For the enrolment of mentally impaired participants, we rely on the procedure of the OPERAM study (59), which has proven itself in the clinical practice and has been approved by the Swiss Ethics Committee (EC) (BASEC Nr. 2016-01200): as the enrolment of a patient with mental impairment (dementia, confusion) is usually limited by the physical absence of the legal representative in hospitals, the informed consent can be given orally in the presence of at least one witness. The witness should be formally independent of the study team. The oral consent can be given by the patient, provided that he/she is able to consent orally and to understand the study participation. If the patient is unable to give his or her consent orally, oral consent can also be obtained over the phone from a legal representative. Written consent from the legal representative is obtained as soon as possible thereafter. Also, in this procedure, patients/legal representatives are given adequate time to consider their decision whether or not to accept participation. This procedure is intended to avoid selection bias of this vulnerable group of patients with mental impairment that is often excluded from clinical trials.

4.3 Study procedures

The expected recruitment period is 36 months. Study subjects remain in the study for the entire duration of the intervention period. Minimum intervention period duration is 12 months, maximum intervention period duration is expected to be 48 months. Mean intervention period is expected to be 24 months.

Outcomes are assessed at each study follow-up. Study personnel contacts the subject, and and/or GPs by phone and will review medical records to obtain information from hospitals and GPs about medical events and concomitant treatment during follow-up. If a subject is unavailable and cannot be reached, or if the subject is mentally not capable to perform the phone interview, a family member and/or a friend not living in the same household will be contacted. For subjects who die during the intervention period, the cause of death based on medical reports, death certificates, and autopsy reports (if available) will be recorded.

After the end of the intervention period, the subjects or, if unavailable, GPs, family members/friends are contacted annually by phone for a follow-up visit for a maximum of 10 years from baseline. The follow-ups after the intervention period are optional, depending on the time and financial resources of the study team. Upon inclusion, patients are asked for a separate consent for data collection after the intervention period.

See chapter 3.2 “Schedule of assessments” for a detailed description of the study procedures.

4.4 Withdrawal and discontinuation

Withdrawal from intervention

For the intervention group (statin discontinuation): If a participant suffers a CV event during the intervention period, restarting a statin is up to the discretion of the treating physician. If a subject would like to restart their statin without CV event (e.g., because of an external lipid measurement), we advise GPs not to restart a statin or other lipid lowering medication, since the evidence for a statin therapy in primary prevention in elderly patients is unclear and currently no clearly defined LDL target for this patient group exist based on trial data. However, the final decision is up to the discretion of the treating physician.

For the control group (statin continuation): If a subject would like to stop their statin (e.g., because of side effects), stopping a statin is up to the discretion of the treating physician and of the patient. Since the currently limited evidence does not show very clear difference in muscle symptom scores between statin and placebo (60), we advise GPs not to prompt statin discontinuation in subjects with muscle symptoms without criteria for myositis (CK> 10 ULN).

The treating physician and the participant are asked to inform the study team about any change regarding lipid lowering medication.

If a subject withdraws from the assigned intervention, follow-up will continue until the end of the trial.

Change in drug dose

Statin doses are monitored during the study. Change in drug dose is at the discretion of the treating physician.

Discontinuation of study

A study participant must be withdrawn from the study if he or she withdraws consent for further study participation. A study participant who discontinues study participation prematurely is defined as dropout if the participant has already been randomized.

No replacement of participants discontinuing study intervention or study participation is foreseen. Any samples and data collected until study withdrawal will remain coded for the analysis. It is not possible to anonymize the collected study data upon withdrawal.

4.5 Concomitant care

There are no restrictions on concomitant care during the trial except for the following therapies in the intervention group:

- ezetimibe therapy
- PCSK-9 inhibitors
- any other LDL cholesterol-lowering medication

GPs and pharmacists are advised to avoid these therapies unless there are justified clinical reasons.

5 STATISTICS AND METHODOLOGY

5.1. Non-inferiority margin and sample size calculation

The sample size calculation is based on a non-inferiority design where we test whether discontinuing statins does not result in reduced event-free survival time (primary endpoint) up to a certain degree (non-inferiority margin). The primary effect measure will be the difference of the Restricted Mean event-free Time over 24 months between the two arms (61, 62).

We defined the non-inferiority margin on the absolute scale of integrated risk difference and fixed it at 5% over 24 months of follow-up (63). This can be interpreted as follows: we want to exclude a loss in event-free time of more than 2 ½ weeks per year (or about 1.5 days per month) over a two year observation period (5.2 weeks overall). This difference is considered by the Steering Committee clinically irrelevant (=non-inferiority) given the multimorbid study population with a high event and death risk.

Based on data from our OPERAM trial (59), we calculated the probability of dying from non-cardiac causes at 12 months as 11.6% and the probability for non-fatal and fatal CV events as 9.1%. Simulations with 10,000 runs were used to calculate the sample size. A Weibull distribution was used to simulate event-free survival data (64). Parameters were chosen to account for a flattening of event probabilities over time. Based on the available OPERAM data, the primary event probabilities in the control group at landmark timepoints were as follows: 22% at 12 months, 34% at 24 months, 43% at 36 months; a drop-out rate of 2% over 1 year was observed (59). Sample size calculations were done in Stata (release 15.1) using the *survsim* package for the simulations and the *strmst2* package for calculating Restricted Mean Event-free Time (65). With 1,800 participants, we will achieve a power of 89% in the Intention-To-Treat (ITT) and 83% in the approximated PP analysis set at a one-sided α level=0.025. We performed several sensitivity

analyses assuming higher and lower event rates as well as non-proportional hazards, and power was >80% in all scenarios. The planned interim analysis (see 5.5) will have no relevant influence on the type I and II error rate and therefore, sample size is not adjusted (66).

For the subgroup analysis on the effect on LDL cholesterol, we based the sample size calculation on data for over 75 years old patients from the Cholesterol Treatment Trialists' Collaboration (67). Based on an assumed mean LDL cholesterol concentration of 3.2 mmol/L and a standard deviation of 0.8 mmol/L for the statin stop group, a between-group difference in LDL cholesterol of 0.3 mmol/L can be detected at 80% power with a two-sided alpha of 0.05. As previously described, in the case of continuous outcomes, a trial with ~100 participants per treatment arm is considered a large trial, where baseline variables can be expected to be evenly distributed between treatment arms (68).

For the subgroup of patients undergoing cardiac CT scans and measurement of biomarkers at baseline, we based the sample size calculation on a superiority design where we test whether the treatment effect differs by baseline CAC. Based on an assumed CAC distribution from data in the MESA cohort for asymptomatic men and women over 75 years (69), an assumed increased risk per 1-standard deviation change of baseline CAC score on a logarithmic scale (70), 7% of participants with a CAC score of 0 (71), primary outcome event rate at 36 months as in the STREAM trial, and assumption of no treatment effect, we determined that a fixed sample size of 500 participants provides 80% power (with one-sided alpha of 0.05) to detect an interaction term odds ratio as small as 1.9, corresponding to a traditional relative risk estimate of 1.37 at an assumed event prevalence of 43%, since ORs are overinflated when the outcome is common.(72) The power for analyses using biomarkers on a continuous scale will be similar as or even higher than for CAC score, e.g. for NT-proBNP the simulation showed 80% power to detect a relative risk of 1.3 at a fixed sample size of 500 participants.

5.2 Randomization

Participants are randomized (in a 1:1 ratio) to either discontinuing statin vs. continuing statin, with stratification according to age (categorized into two groups: cut off <75/≥75 years of age), statin intensity (categorized into high, moderate and low intensity, according to the 2018 AHA/ACC guidelines (32)), and time under statin before inclusion, (categorized into two groups: cut off: ≤6/>6 years, as 6 years is the longest follow-up in statin trials published in the CTT metaanalysis; beyond 6 years evidences on elderly under statin is based on simulations) using computer-generated randomly permuted blocks of varying size (67, 73).

Study arm allocation is done using a web-based system which also contains the electronic case report form (eCRF) (Webspirit, hosted by CTU Bern). The randomization list is generated by an independent statistician and only system administrators who are otherwise not involved in trial conduct will have access to them to ensure concealment of allocation.

5.3 Statistical methods for primary and secondary outcomes

The primary statistical analysis of the trial will be done at CTU Bern based on well-established standard operating procedures, using an appropriate statistical software. Details are specified in a statistical analysis plan, to be written at the start of enrolment and to be finalized before 25% of patients are enrolled. The plan determines all necessary data preparation steps (e.g. additional validations, generation of new variables), definitions (e.g. analysis sets), and statistical analyses (e.g. models, outputs such as tables and graphs).
The primary outcome of the trial is analyzed with a flexible parametric survival model with all stratification factors as covariates. The difference in Restricted Mean Event-free Time over 2 years will be the effect measure (61, 74). Two years was chosen as this is the average follow-up time in the trial and a clinically useful timeframe given the elderly patient population with higher mortality. Two analyses sets are used for the primary analysis as described below. Non-inferiority will be declared, if for both ITT and PP analysis sets, the one-sided 97.5% confidence interval does not cross the non-inferiority margin. We acknowledge that any choice for the non-inferiority

margin is to some extent subjective and a margin that is universally agreeable is not achievable especially in this heterogeneous patient population (75, 76). Therefore, we will also present results for various margins with the respective uncertainty (77). Components of the primary outcome and other time-to-event outcomes are analyzed with the same methods as the primary outcome. Effects on time-to-event outcomes may also be presented as hazard ratios. Continuous outcomes will be analyzed using linear regression with baseline values and stratification factors as covariates and mean difference as effect measure. Given the potentially high mortality rate we will also explore joint modelling of continuous outcomes and death (78).

ITT and PP analyses will be performed. The ITT analysis set consists of all randomized patients in the allocated group regardless of any protocol violations. For the PP analysis set, we will first carefully define criteria for protocol adherence and post-randomization factors that might cause confounding/selection bias before trial start to allow for appropriate data collection.(79) For this, we will consider pre- and post-randomization factors that are predictive of adherence, amount of statin intake that constitutes adherence to each arm, cross-overs, other CV active medication, and intercurrent events. PP analyses will be done using g-Methods adapted to estimate Restricted Mean Event-free Time (80).

A separate statistical analysis plan will be developed for the analysis of CAC scores and baseline blood biomarkers in the subsample of subjects undergoing these procedures. The primary analysis will be an ITT analysis using Cox proportional hazards regression modelling to assess the effect modification of continuous CAC score on a linear scale on the relationship between treatment and the primary outcome, taking event time into account. Further analyses will test non-linear relationships and/or include biomarkers instead of CAC score.

Any deviation from the original statistical analysis plan will be described and justified in the final trial report. Full details to the statistical analysis will be described in a statistical analysis plan.

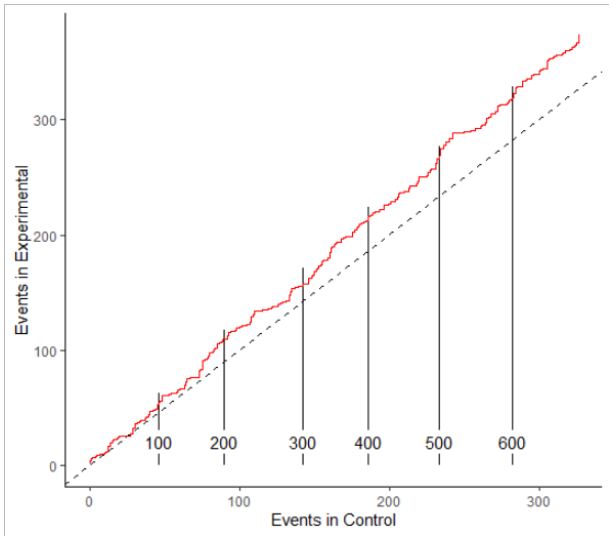
5.4 Statistical methods for additional analyses

We perform subgroup analyses according to statin intensity and time on statin before baseline, sex, age, and degree of frailty, accompanied by appropriate tests for interaction. All subgroup analyses will be described in the statistical analysis plan.

5.5 Safety Interim Analysis

Formal interim analyses are performed to assess intervention safety (discontinuing statins). The main safety concern is increased risk of CV events in the experimental arm, therefore, the primary endpoint is monitored. We will take an event driven approach by conducting an analysis after a certain amount of events (in both arms combined) have accumulated and monitoring the proportion of events in the experimental arm. A one-sided boundary, calculated based on exact binomial tests with a pre-defined alpha that optimizes the stopping probability under different conditions, is used for decision-making. If there is evidence that the proportion of events in the experimental arm is higher than 50%, i.e. the boundary is crossed, the DSMB will be informed and an ad hoc meeting of the DSMB will be called to discuss possible termination of the trial for safety reasons. As there are concerns about those under 75, interim analyses will be performed separately for the two age groups, with lower boundaries used for younger group (making it more likely to stop the trial in this arm). Interim analyses will be performed after every 50th event in the older group and after the 50th event in the younger group (with only one look).

The following figure gives a fictional example for a trial with ca 700 events and interim analyses at each 100th event (indicated by the black lines). As the red line remains beneath the black lines, the trial could continue. This approach does not increase the type 1 error rate. The frequency of safety interim analyses and other details will be included in the statistical analysis plan.



5.6 Data and Safety Monitoring Board (DSMB) and Trial Steering Committee (TSC)

Safety is descriptively monitored throughout the trial by an independent DSMB. The DSMB members are unblinded and independent of the study team. Roles and responsibilities of the DSMB are described in a DSMB charter. Each DSMB member evaluates interim safety results. Based on these results, the DSMB recommends continuing, amending, or terminating the trial. The DSMB will meet after 600 and 1,200 participants have been recruited and ad hoc, when indicated as described in chapter 5.5.

The TSC consists of the sponsor-investigator and some experts in the fields of clinical trial management, statistics, geriatrics, statin intake, endocrinology, cardiology, and patient involvement. In addition, the principal investigators of the main participating trial sites are members of a General Assembly. The TSC will decide on the implementation of the recommendations of the DSMB following a DSMB review of the trial. The final decision to amend or terminate the trial lies with the TCS.

5.7 Handling of missing data and drop-outs

Depending on the extent of cross-overs and intercurrent events at the end of the trial, further analyses will model them, taking into account possible post-randomization confounding by using causal inference methods (81).

Very little missing data for either primary or secondary outcomes or important baseline covariates are anticipated. Generally, missing data on secondary outcomes will be handled with multiple imputation.

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP guidelines, the Swiss Human Research Act (HRA) as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect.

In this study, the follow-up assessment is carried out centrally by the team of the sponsor-investigator, without involvement of the local study sites. For this reason, the SAE assessment is only made by the sponsor-investigator (or delegate), also for patients who were included at a local site. The sponsor-investigator (or delegate) makes a causality assessment of the event to the trial intervention, (see table below). Any event assessed as possibly, probably, or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	The adverse event is clearly related to the trial intervention. Clear-cut temporal association and no other possible cause.
Probably	The adverse event is likely related to the trial intervention. Clear-cut temporal association; a potential alternative aetiology is not apparent.
Possibly	The adverse event may be related to the trial intervention. Less clear temporal association; other aetiologies also possible.
Unlikely	The adverse event is doubtfully related to the trial intervention. Temporal association between the AE and the trial intervention and the nature of the event is such that the trial intervention is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).
Not related	The adverse event is clearly not related to the trial intervention. The AE is completely independent of trial treatment and/or evidence exists that the event is definitely related to another aetiology.

The sponsor-investigator (or delegate) makes an intensity assessment of the event. The intensity assessment is performed in accordance with “Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0” terminology, using a grading scale from 1 to 5.

Reporting of SAEs (see ClinO, Art. 63)

If it cannot be excluded that the SAE is attributable to the intervention under investigation, the SAE is documented in a standardized manner and reported immediately (within a maximum of 24 hours) by the study team member who performs the follow-up assessment to the sponsor-investigator (or delegate). The period for documenting and reporting SAEs in this study is the study intervention period.

The sponsor-investigator (or delegate) reports these SAEs to the EC via BASEC within 15 days. If the SAE occurs at one of the study sites, the coordinating Investigator reports the events to the EC concerned, within 15 days.

Follow up of (Serious) Adverse Events

Reported ongoing SAEs are followed-up until resolution or stabilisation, even if the subject has already completed the study.

Notification of safety and protective measures (see ClinO, Art. 62, b)

If immediate safety and protective measures must be taken during the conduct of the study, the sponsor-investigator (or delegate) notifies the EC of these measures, and of the circumstances necessitating them, within 7 days.

6.3 (Periodic) safety reporting

An annual safety report (ASR) over all study sites is submitted once a year to the local EC by the sponsor-investigator (or delegate) (ClinO, Art. 62, d). The sponsor-investigator (or delegate) distributes the ASR to all local principal investigators.

6.4 Radiation

The CAC scan is a native CT scan only performed over the region of the heart, and the typical average radiation dose of a CAC scan is very low at 0.5-1.0 mSv (82), posing minimal risk for the subjects. For comparison, the worldwide average annual effective radiation dose from natural sources is about 3.1 mSv per person.(83) Total radiation dose for two CAC scans over the entire study duration will be max. 1.0 to 2.0 mSV.
If the permitted dose guidance value is exceeded at any time, the investigator notifies the Ethics Committee via BASEC within 7 working days of it becoming known.

6.5 Pregnancy

Not applicable.

6.6 Amendments

Substantial changes to the study setup and study organization, the protocol, and relevant study documents are submitted to the EC for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and well-being of human subjects may proceed without prior approval of the EC. Such deviations will be documented and reported to the EC as soon as possible.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

6.7 (Premature) termination of study

The TSC may terminate the study prematurely according to the following circumstances:

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive), or
- Early evidence of harm of the experimental intervention based on safety interim analyses and respective recommendations by the DSMB.

Upon regular study termination, the EC is notified via BASEC within 90 days (ClinO, Art. 62, c).

Upon premature study termination or study interruption, the EC is notified via BASEC within 15 days (ClinO, Art. 62, c).

See chapter 8.4 for a detailed description of retention and archiving of study data and biological material.

6.8 Insurance

Insurance is provided by the Sponsor/University Hospital Bern (Inselspital). In the event of study-related damage or injuries, the insurance provides compensation, except for claims that arise from misconduct or gross negligence.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

This trial is conducted respecting the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines as well as the regulatory and legal national applicable requirements. The authorization from the local ECs is collected prior to the commencement of the trial, and all protocol changes or unexpected problems concerning human participants will be reported during the trial.

7.2 Risk-benefit assessment

Potential risks of discontinuing statins might include increased CV events. However, current trials found no benefits of statins after 70 years of age for primary prevention, as shown in chapter 2 of this protocol. Furthermore, a published statin deprescribing RCT showed no increase in CV events by patients with limited life expectancy (35) but even included patients in secondary prevention. Guidelines regarding prescribing statin for primary prevention in the elderly are contradictory, some even suggesting stopping statins in case of functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy (32, 34).

In the multimorbid elderly, the potential benefits of statins for CVD primary prevention might be outweighed by potential harm and side effects. Statin side effects and drug interactions are common in this population. The proportion of patients developing muscle pain on statins has been shown to be as high as 5-20% in observational studies (24, 25). Thus, discontinuing statin might positively impact quality of life.

Benefits and harms of statins in the multimorbid elderly without CVD is considered a major issue as recently recognized by a US NIA/NHLBI workshop which highlighted the need for pragmatic RCTs to address this critical knowledge gap (34). Continuing therapy that is not directly beneficial to patients' health is ethically debatable and needs to be investigated in clinical studies.

CAC score is recommended in some but not all practice guidelines for the CV risk assessment and reclassification in selected low- intermediate risk asymptomatic individuals.(33, 84) The predictive value of CAC scores is currently unknown in multimorbid older adults; even if shown to be predictive, there is currently no evidence from RCTs that an intervention (e.g. statin treatment) lowers CAC-related increased risk. The CAC score is a study specific measurement performed outside of a clinical indication; and deferred CAC score reporting to participants and physicians is favored for the following reasons: 1) There is clear equipoise surrounding the management of ASCVD risk in adults >70 years of age without clinically evident ASCVD; 2) There is uncertainty about the interpretation of risk as a function of CAC scores above age 70, including uncertain value of conventional score categories (i.e. CAC >100 as a marker of high risk, in a population where the 75th percentile is expected to be 400-1200) (85) and uncertain value of the traditional Agatston score (CAC density increases with age and results in higher CAC scores, yet increased CAC density is known to be a marker of stable, lower risk plaque (86)); 3) There is currently no compelling evidence to support the use of statins based on CAC scores to improve outcomes including death, cognition, and disability – the most important outcomes to multimorbid adults age >70; and 4) Reporting CAC scores during the study intervention period could influence participant behavior and might drive downstream testing (i.e. stress tests and cardiac catheterizations) that could lead to harm in patients without symptoms of cardiovascular disease.(87) Thus, CAC score reporting during the intervention phase of STREAM may influence the pharmacologic treatment (including statin therapy or intensity) and result in imbalanced cardiovascular testing, which would compromise the information obtained from the main trial.

The CAC CT scan area also comprises non-cardiac body parts, and incidental findings may be noted on these scans. A retrospective analysis of 966 patients that underwent cardiac CT scans found non-cardiac incidental findings in 41.5% of patients, with 12 (1.2%) patients with clinically significant findings (e.g., suspect pulmonary nodule, pulmonary infiltrates, thrombus) and 68

(7%) with indeterminate findings (predominantly pulmonary nodules).(88) After a mean 18.4 months follow-up, none of the indeterminate findings became clinically significant, and incidental findings did not independently predict non-cardiac death. While such incidental findings may lead to additional diagnostic tests with associated morbidity and costs, at the same time there are potential benefits of detecting these findings; balancing these risks and benefits is challenging and depends on patient preference.(89, 90) Therefore, the informed consent for the CT scan will include an option to opt out of a notification about the results of the assessment of the non-cardiac structures. In addition, the informed consent form will specify that only critical safety findings that may warrant further intervention will be immediately reported to the participant and their clinician. Minor incidental findings which are non-actionable (such as small lung nodules) will not be reported as per Fleischner Society criteria, thus limiting unnecessary anxiety and testing in this older population.(91) Mid-size lung nodules (0.8-2.9 cm, expected prevalence 2-4%) will be subsequently reported after thorough case review by an experienced radiologist applying Fleischer Society High-Risk criteria. CAC scores, placed into context with the overall STREAM results, will be returned at the conclusion of the trial.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Quality visits

For quality assurance, the sponsor, the EC, or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

Outcome ascertainment

Outcome ascertainment is performed centrally by partially blinded study team members. Partially blinded means that the study team members assess the participant's outcome events over the phone without knowing the group assignment. However, they will know the group assignment retrospectively when assessing medication compliance.

Clinical event committee (CEC)

A clinical event committee (CEC) performs blinded outcome adjudication of clinical events. The CEC is blinded to group allocation (information on statins, other lipid-lowering drugs, and lipid levels are removed from documents to review to maintain blinding). Suspected events for the primary and secondary clinical outcomes (deaths and CV events) are transmitted to the CEC for final classification.

Roles and responsibilities of the CEC are described in a CEC charter.

Data and Safety Monitoring Board (DSMB)

See chapter 5.6

8.2 Data recording and source data

Data management system and data recording

For each enrolled trial participant, an eCRF is maintained, using a dedicated electronic data capturing (EDC) system (Webspirit®). The EDC system is activated for the trial only after successfully passing a formal test procedure. All data entered in the CRFs are stored on a Linux server in a dedicated PostgreSQL database.

Responsibility for hosting the EDC system and the database lies with CTU Bern. The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server and back-up tapes. A role concept with personal

passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.

All data entered into the CRFs are transferred to the database using Transport Layer Security (TLS) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail).

A multi-level back-up system is implemented. Back-ups of the whole system including the database are run internally several times per day and on external tapes once a day. The back-up tapes are stored in a secure place in a different building.

Study-related data of the participants are collected in a coded manner. The names of the participants will not be disclosed. A unique code will be attributed to each participant registered.

A separate database containing contact information from the patient, the patient's next of kin and the patient's GP is set-up in a separate built-in module in the Webspirit® system. It ensures that patients and their proxies can be contacted during the telephone follow-ups carried out centrally by the study nurses at the Inselspital, Bern University Hospital. This database can only be accessed by specifically-assigned users with appropriate and dedicated user rights.

The scan images of the subsample of subjects undergoing cardiac CT scans will be locally assessed for incidental findings, before encrypted transmission via secure transfer (PACS) to the central study site in Bern for central (core lab) assessment of the CAC score. These images can only be accessed by specifically-assigned users with appropriate and dedicated user rights.

Source data

Source documents for each study participant include original study related documents, medical treatment records, and medical history records and must be available at the study sites.

All data captured in the eCRF should be itemized on a source data location list, which is stored in the Investigator Site File at each study site. This list should clearly indicate the source data location corresponding to each eCRF entry. If certain data are directly entered into the eCRF (and are thus considered as source data) this must be specified on the source data location list accordingly.

8.3 Confidentiality

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. At each study site, the principal investigators safeguard the confidentiality of participating patients' data and maintain appropriate medical and research records for this trial. No patient information containing identifying data will leave the study site, except for contact information that is entered in a separate built-in module in the database and only accessible by specifically-assigned users (see 8.2). Signed informed consent forms and patient enrolment logs are kept strictly confidential to enable patient identification at the site. The records are kept in compliance with ICH-GCP guidelines and meet regulatory and institutional requirements for the protection of confidentiality of subjects. The principal investigators, sub-investigators, and study nurses or coordinators have access to the records.

Direct access to source documents and other study related records at the participating study sites are permitted for purposes of monitoring, audits and inspections. The monitoring institution (CTU Bern), CEC, and the CA will have access to all information necessary to accomplish their tasks.
Biological material from this study will be attributed to each participant with its unique participant number. Biological material will be appropriately stored in the biobank of the University Hospital Bern, a restricted area only accessible to the authorised personnel. Storage and destruction will be performed according to the local SOPs.

8.4 Retention and destruction of study data and biological material

At interim and final analyses, data files are extracted from the database into statistical packages to be analyzed. After database lock at the end of the study, the status of the database is recorded

in special archive tables, including subject identification codes.

At the end of the study, the sponsor will archive the Trial Master File, the extracted data, the meta data, and interim/final reports for at least 10 years. The local principal investigators will archive their Investigator Site Files at the local trial site for at least 10 years.

The biological material will be kept in a biobank of the University Hospital Bern, until further use will be specified.

If the patient has consented to the further use of data and samples, the data and samples collected for this study can be used indefinitely for further research projects that have not yet been specified.

9 MONITORING AND REGISTRATION

On-site as well as central data monitoring are part of the quality control activities implemented for this study. Monitoring activities are performed by CTU Bern and are defined in a separate monitoring plan.

All involved parties keep participant data strictly confidential.

The study is registered in the Clinical Trials Registry Platform of the National Institute of Health (NIH) – ClinicalTrials.gov and in the Swiss National Clinical Trials Portal (SNCTP via BASEC).

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

The trial is funded by the Swiss National Science Foundation (SNF) by the Investigator Initiated Clinical Trials (IICT) program. The baseline cardiac CT scans and baseline biomarker analyses are funded by SNF project funding as well as by the Swiss Heart Foundation.

The publication policy and data sharing policy between the Sponsor and the trial sites will be defined in sub-center contracts.

There are no conflicts of interest to declare.

10 REFERENCES

1. National Institute for Health and Clinical Excellence. Identification and Management of Familial Hypercholesterolaemia (FH). Identification and Management of Familial Hypercholesterolaemia (FH). National Institute for Health and Clinical Excellence: Guidance. London2008, updated 2017.
2. Babcock M, Gould Kuntz J, Kowalsky D, Calitri N, Kenny AM. The Palliative Performance Scale Predicts Three- and Six-Month Survival in Older Adult Patients Admitted to the Hospital through the Emergency Department. J Palliat Med. 2016;19(10):1087-91.
3. Ioannidis JP. More than a billion people taking statins?: Potential implications of the new cardiovascular guidelines. Jama. 2014;311(5):463-4.
4. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. Journal of the American College of Cardiology. 2008;51(1):37-45.
5. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2016;316(19):2008-24.
6. Adhyaru BB, Jacobson TA. Safety and efficacy of statin therapy. Nature reviews Cardiology. 2018;15(12):757-69.
7. Byrne P, Cullinan J, Smith SM. Statins for primary prevention of cardiovascular disease. Bmj. 2019;367:l5674.
8. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360(9346):1623-30.
9. Han BH, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, et al. Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial. JAMA internal medicine. 2017;177(7):955-65.
10. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393(10170):407-15.
11. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, et al. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). J Am Coll Cardiol. 2015;66(15):1643-53.
12. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. Annals of family medicine. 2012;10(2):142-51.
13. Le Reste JY, Nabbe P, Manceau B, Lygidakis C, Doerr C, Lingner H, et al. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. Journal of the American Medical Directors Association. 2013;14(5):319-25.
14. Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. European journal of public health. 2019;29(1):182-9.
15. World Health Organization. World Report on Ageing and Health: World Health Organization; 2015.
16. Jadad AR, To MJ, Emara M, Jones J. Consideration of multiple chronic diseases in randomized controlled trials. Jama. 2011;306(24):2670-2.
17. Skolnik N. Reexamining Recommendations for Treatment of Hypercholesterolemia in Older Adults. Jama. 2019.

18. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. The New England journal of medicine. 1995;333(20):1301-7.
19. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. Jama. 1998;279(20):1615-22.
20. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361(9364):1149-58.
21. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-96.
22. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368(9542):1155-63.
23. Lonn E, Bosch J, Pogue J, Avezum A, Chazova I, Dans A, et al. Novel Approaches in Primary Cardiovascular Disease Prevention: The HOPE-3 Trial Rationale, Design, and Participants' Baseline Characteristics. The Canadian journal of cardiology. 2016;32(3):311-8.
24. Nichols GA, Koro CE. Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. Clinical therapeutics. 2007;29(8):1761-70.
25. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovascular drugs and therapy. 2005;19(6):403-14.
26. Joy TR, Hegele RA. Narrative review: statin-related myopathy. Annals of internal medicine. 2009;150(12):858-68.
27. Bellosta S, Corsini A. Statin drug interactions and related adverse reactions: an update. Expert opinion on drug safety. 2018;17(1):25-37.
28. Ruscica M, Macchi C, Pavanello C, Corsini A, Sahebkar A, Sirtori CR. Appropriateness of statin prescription in the elderly. European journal of internal medicine. 2018;50:33-40.
29. van der Ploeg MA, Streit S, Achterberg WP, Beers E, Bohnen AM, Burman RA, et al. Patient Characteristics and General Practitioners' Advice to Stop Statins in Oldest-Old Patients: a Survey Study Across 30 Countries. Journal of general internal medicine. 2019.
30. Rodondi N, Locatelli I, Aujesky D, Butler J, Vittinghoff E, Simonsick E, et al. Framingham risk score and alternatives for prediction of coronary heart disease in older adults. PloS one. 2012;7(3):e34287.
31. Cullen P, Schulte H, Assmann G. The Münster Heart Study (PROCAM): total mortality in middle-aged men is increased at low total and LDL cholesterol concentrations in smokers but not in nonsmokers. Circulation. 1997;96(7):2128-36.
32. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082-e143.

33. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88.
34. Singh S, Zieman S, Go AS, Fortmann SP, Wenger NK, Fleg JL, et al. Statins for Primary Prevention in Older Adults-Moving Toward Evidence-Based Decision-Making. Journal of the American Geriatrics Society. 2018.
35. Kutner JS, Blatchford PJ, Taylor DH, Jr., Ritchie CS, Bull JH, Fairclough DL, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA internal medicine. 2015;175(5):691-700.
36. Giral P, Neumann A, Weill A, Coste J. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. European heart journal. 2019.
37. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and ageing. 2015;44(2):213-8.
38. Reeve E, Wolff JL, Skehan M, Bayliss EA, Hilmer SN, Boyd CM. Assessment of Attitudes Toward Deprescribing in Older Medicare Beneficiaries in the United States. JAMA internal medicine. 2018.
39. Farrell B, Tsang C, Raman-Wilms L, Irving H, Conklin J, Pottie K. What are priorities for deprescribing for elderly patients? Capturing the voice of practitioners: a modified delphi process. PloS one. 2015;10(4):e0122246.
40. Rossello X, Pocock SJ, Julian DG. Long-Term Use of Cardiovascular Drugs: Challenges for Research and for Patient Care. Journal of the American College of Cardiology. 2015;66(11):1273-85.
41. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal. 2016;37(29):2315-81.
42. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25).
43. Arnett Donna K, Blumenthal Roger S, Albert Michelle A, Buroker Andrew B, Goldberger Zachary D, Hahn Ellen J, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596-e646.
44. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health policy. 1990;16(3):199-208.
45. Schofield P. The Assessment of Pain in Older People: UK National Guidelines. Age and ageing. 2018;47(suppl_1):i1-i22.
46. Collett B, O'Mahoney S, Schofield P, Closs SJ, Potter J, Guideline Development G. The assessment of pain in older people. Clin Med (Lond). 2007;7(5):496-500.
47. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. Journal of the American Medical Directors Association. 2013;14(8):531-2.

48. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. Journal of cachexia, sarcopenia and muscle. 2016;7(1):28-36.
49. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol. 1993;46(2):153-62.
50. Harada ND, Chiu V, King AC, Stewart AL. An evaluation of three self-report physical activity instruments for older adults. Med Sci Sports Exerc. 2001;33(6):962-70.
51. Zazpe I, Sanchez-Tainta A, Estruch R, Lamuela-Raventos RM, Schroder H, Salas-Salvado J, et al. A large randomized individual and group intervention conducted by registered dietitians increased adherence to Mediterranean-type diets: the PREDIMED study. J Am Diet Assoc. 2008;108(7):1134-44; discussion 45.
52. Hebestreit K, Yahiaoui-Doktor M, Engel C, Vetter W, Siniatchkin M, Erickson N, et al. Validation of the German version of the Mediterranean Diet Adherence Screener (MEDAS) questionnaire. BMC Cancer. 2017;17(1):341.
53. Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. Journal of the American Medical Directors Association. 2008;9(2):71-2.
54. Woo J, Yu R, Wong M, Yeung F, Wong M, Lum C. Frailty Screening in the Community Using the FRAIL Scale. Journal of the American Medical Directors Association. 2015;16(5):412-9.
55. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry. 1983;140(6):734-9.
56. Tuijl JP, Scholte EM, de Craen AJ, van der Mast RC. Screening for cognitive impairment in older general hospital patients: comparison of the Six-Item Cognitive Impairment Test with the Mini-Mental State Examination. Int J Geriatr Psychiatry. 2012;27(7):755-62.
57. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15(4):827-32.
58. Neves PO, Andrade J, Monção H. Coronary artery calcium score: current status. Radiol Bras. 2017;50(3):182-9.
59. Adam L, Moutzouri E, Baumgartner C, Loewe AL, Feller M, M'Rabet-Bensalah K, et al. Rationale and design of OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial. BMJ open. 2019;9(6):e026769.
60. Herrett E, Williamson E, Brack K, Beaumont D, Perkins A, Thayne A, et al. Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. Bmj. 2021;372:n135.
61. Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Statistics in medicine. 2011;30(19):2409-21.
62. Royston P. Estimating the treatment effect in a clinical trial using difference in restricted mean survival time. Stata J. 2015;15(4):1098-117.
63. Manner DH, Battioui C, Hantel S, Beasley BN, Wei LJ, Geiger MJ, et al. Restricted mean survival time for the analysis of cardiovascular outcome trials assessing non-inferiority: Case studies from antihyperglycemic drug development. American heart journal. 2019;215:178-86.
64. Crowther MJ, Lambert PC. Simulating biologically plausible complex survival data. Statistics in medicine. 2013;32(23):4118-34.
65. Cronin A TL, Uno H,. strmst2 and strmst2pw: New commands to compare survival curves using the restricted mean survival time. Stata J. 2016;16:702-16.

66. Lachin JM. A review of methods for futility stopping based on conditional power. Statistics in medicine. 2005;24(18):2747-64.
67. Cholesterol Treatment Trialists C. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393(10170):407-15.
68. Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. Bmj. 2010;341:c3515.
69. Pletcher MJ, Tice JA, Pignone M, McCulloch C, Callister TQ, Browner WS. What does my patient's coronary artery calcium score mean? Combining information from the coronary artery calcium score with information from conventional risk factors to estimate coronary heart disease risk. BMC Medicine. 2004;2(1):31.
70. Folsom AR. Coronary Artery Calcification Compared With Carotid Intima-Media Thickness in the Prediction of Cardiovascular Disease IncidenceThe Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008;168(12):1333.
71. Yano Y, O'Donnell CJ, Kuller L, Kavousi M, Erbel R, Ning H, et al. Association of Coronary Artery Calcium Score vs Age With Cardiovascular Risk in Older Adults: An Analysis of Pooled Population-Based Studies. JAMA Cardiol. 2017;2(9):986.
72. Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ. 1998;316(7136):989-91.
73. Yourman LC, Cenzer IS, Boscardin WJ, Nguyen BT, Smith AK, Schonberg MA, et al. Evaluation of Time to Benefit of Statins for the Primary Prevention of Cardiovascular Events in Adults Aged 50 to 75 Years: A Meta-analysis. JAMA internal medicine. 2021;181(2):179-85.
74. Royston P. Estimating the treatment effect in a clinical trial using difference in restricted mean survival time Stata J 2015;15:1098-117.
75. Gladstone BP, Vach W. Choice of non-inferiority (NI) margins does not protect against degradation of treatment effects on an average--an observational study of registered and published NI trials. PloS one. 2014;9(7):e103616.
76. Snapinn S, Jiang Q. Remaining Challenges in Assessing Non-Inferiority. Therapeutic innovation & regulatory science. 2014;48(1):62-7.
77. Shakespeare TP, Gebski VJ, Veness MJ, Simes J. Improving interpretation of clinical studies by use of confidence levels, clinical significance curves, and risk-benefit contours. Lancet. 2001;357(9265):1349-53.
78. Crowther MJ, Abrams KR, Lambert PC. Flexible parametric joint modelling of longitudinal and survival data. Statistics in medicine. 2012;31(30):4456-71.
79. Dodd S, White IR, Williamson P. A framework for the design, conduct and interpretation of randomised controlled trials in the presence of treatment changes. Trials. 2017;18(1):498.
80. Robins JM, Hernán MA. Estimation of the causal effects of time-varying exposures. In: Longitudinal data analysis New York: Chapman and Hall/CRC Press; 2008. 553-99. p.
81. Danaei G, Rodriguez LA, Cantero OF, Logan R, Hernan MA. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. Statistical methods in medical research. 2013;22(1):70-96.
82. Sandfort V, Bluemke DA. CT calcium scoring. History, current status and outlook. Diagnostic and Interventional Imaging. 2017;98(1):3-10.
83. Radiation UNSCotEoA. UNSCEAR 2008 report Vol. I: Sources of ionizing radiation. New York: United Nations. 2010.
84. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromesThe Task

Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal. 2020;41(3):407-77.
85. The Multi-Ethnic Study of Atherosclerosis. CAC Score Reference Values.
86. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA. 2014;311(3):271-8.
87. Gupta A, Lau E, Varshney R, Hulten EA, Cheezum M, Bittencourt MS, et al. The Identification of Calcified Coronary Plaque Is Associated With Initiation and Continuation of Pharmacological and Lifestyle Preventive Therapies: A Systematic Review and Meta-Analysis. JACC Cardiovascular imaging. 2017;10(8):833-42.
88. MacHaalany J, Yam Y, Ruddy TD, Abraham A, Chen L, Beanlands RS, et al. Potential Clinical and Economic Consequences of Noncardiac Incidental Findings on Cardiac Computed Tomography. J Am Coll Cardiol. 2009;54(16):1533-41.
89. Hlatky MA, Iribarren C. The Dilemma of Incidental Findings on Cardiac Computed Tomography∗∗Editorials published in the Journal of the American College of Cardiologyreflect the views of the authors and do not necessarily represent the views of JACCor the American College of Cardiology. J Am Coll Cardiol. 2009;54(16):1542-3.
90. Oren O, Blankstein R, Bhatt DL. Incidental Imaging Findings in Clinical Trials. JAMA. 2020;323(7):603.
91. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284(1):228-43.