Protocol for a target trial emulation on the risk of MACE when discontinuing statins used for primary prevention

Background

The role of statins as primary prevention (without previous history of cardiovascular disease) in the elderly population (≥75 years) remains uncertain as evidence regarding their benefit is limited. [1, 2] Existing data are predominantly derived from subgroup analyses or post hoc evaluations of randomized controlled trials, where older individuals are typically underrepresented. These meta-analyses suggest that the benefits of statins as primary prevention may be less pronounced in this age group. [1, 2] Ongoing trials—such as the Statin Therapy for Reducing Events in the Elderly (STAREE; NCT02099123) and the Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults (PREVENTABLE; NCT04262206)—seek to address this knowledge gap, however, results are yet to be presented. Consequently, European guidelines recommend considering statin therapy for individuals aged 75 and older at high cardiovascular risk, but this recommendation is based on low-quality evidence. [3]

The use of statins in elderly populations raises critical questions about the goals of preventive pharmacotherapy in this age group. Factors such as competing mortality risks, polypharmacy, and increased susceptibility to side effects underscore the importance of ensuring that preventive treatments contribute to meaningful outcomes, such as improved quality of life or other benefits that outweigh these potential risks. When the risk outweighs the benefits, discontinuation of statins may be appropriate. Discontinuation, defined as the planned or supervised cessation of medication, aims to improve patient outcomes by reducing polypharmacy risks, minimizing adverse events, and aligning treatment with evolving health goals. [4-6] However, the potential benefits of discontinuing statins in the elderly remain unclear due to a scarcity of high-quality data. Some studies assessing statin discontinuation in individuals aged ≥70 years, including those using statins for both primary and secondary prevention, have reported an increased risk of major adverse cardiovascular events (MACE) following cessation of therapy.[7-9] Observational studies often lack the…..

Suggested Aims:

1. *This study aims to assess the 5-year risk of MACE in individuals aged 75 and older who discontinued statin treatment within one year of initiation, compared to those who continued therapy over the same period.*
2. *This study aims to evaluate the 5-year risk of MACE following the discontinuation of long-term statin use for primary prevention in individuals aged 75 and older.*

Considerations:
As mentioned in the Thompson et al study [9], statin discontinuation in the elderly (when sourced from registers) is likely a marker of frailty and generally poor health. In this study, they were not able to use laboratory results. By limiting the study period to where we have available laboratory data on the entire Danish population we could source information on LDL measurements (and other fractions of cholesterol) to mitigate some of the confounding by indication from this study.

Subgroup analyses of persons with and without diabetes. Diabetes is an independent risk factor for CVD, especially in women. Trials performed on persons with T2D (exclusive or subpopulations) have demonstrated significant benefits of statin therapy irrespective of prior history of vascular disease. [10]

We need to find a period of “sustained " use before discontinuation, as this would indicate that adverse events are likely not the reason for discontinuation. - Find ref. for this statement. is this typically true for medication but is it proven to be the case with muscle pain/rhabdomyolysis and statins?

Current guidelines for primary prevention:
Target: LDL-C <2,6 mmol/l
High-risk patients:

Diabetes without risk factors Kidney disease eGFR 60-30	2.6 mmol/l
Diabete3s with albuminuria, eGFR <60 or ≥3 of the following: age >60 years, males, familial disposition, dysregulated hypertension ≥130/80, smoking	1.8 mmol/l
Documented atherosclerotic disease	1.4 mmol/l

How to define discontinuation and sustained use?

Table 1) Summary of the protocol for a target trial and emulation, - aim 1.

This study aims to assess the 5-year risk of MACE in individuals aged 75 and older who discontinued statin treatment within one year of initiation, compared to those who continued therapy over the same period.

Protocol element	Target trial	Target trial emulation
Eligibility criteria	Inclusion 1) First time users of statins for primary prevention (e.g., no history of CVD) 2) 75 years or older at initiation of statins Exclusion 1) Use of stains in the previous 5 years 2) History of manifest CVD (e.g., previous MI, IHD, stroke (including TCI), HF…..)	Inclusion 1) First time users of statins for primary prevention (e.g., no history of CVD) 2) 75 years or older at initiation of statins Exclusion 1) Use of stains in the previous 5 years, from the date of statin initiation 2) History of manifest CVD defined by ICD-10 codes and combination medication user? (e.g., previous MI, IHD, stroke (including TCI), HF…..) 3) Immigration <5 years prior to initiation. 4) At least 5 years of potential follow-up
Treatment strategies	Initiate statin therapy as primary prevention for both arms. The control arm will continue sustained statin use for x years, while the intervention arm discontinues statins after one year of continuous use and does not restart statins therapy for x-1 years. The use of additional lipid-lowering medications is not permitted.	Same as for the target trial.
Assignment procedures	Participants will be randomized at baseline to either continue sustained statin use or discontinue statins after one year. The discontinuation will not be blinded.	
Time zero and follow-up period	Follow-up starts at randomization and ends at outcome occurrence, death, loss to follow-up, re-initiations of statins during the period of discontinuations, initiations of other lipid-lowering medication, or end of study (x years after randomization), whichever comes first.	Same as for the target trial. (Additionally, to administrative censoring, if relevant)
Outcome	Cardiovascular disease including ischemic heart disease (inc. MI), stroke (inc. TCI), “macrovascular atherosclerotic disease” and peripheral atherosclerotic disease. **Or** 3-4P MACE (MI, stroke (inc. TCI), all-cause mortality and HF?)	Same as for the target trial.

Causal contrasts of interest	Per-protocol effect (what if hypothetically all patients complied to their assigned protocol?) Intention-to-treat effect?	Per-protocol effectObservational analogue to the per-protocol effect (as-treated) Observational analogue to the Intention-to-treat effect (as-started)?
Analysis plan		

Table 2) Summary of the protocol for a target trial and emulation, - aim 2.

This study aims to evaluate the 5-year risk of MACE following the discontinuation of long-term statin use for primary prevention in individuals aged 75 and older. inspired by the Thompson et al. study.

Protocol element	**Target trial**	**Target trial emulation**
Eligibility criteria	Inclusion 1. First time users of statins for primary prevention (e.g., no history of CVD) 2. 75 years or older at initiation of statins Exclusion 1. Use of stains in the previous 5 years 2. History of manifest CVD (e.g., previous MI, IHD, stroke (including TCI), HF…..)	Inclusion 1. First time users of statins for primary prevention (e.g., no history of CVD) 2. 75 years or older at initiation of statins Exclusion 1. Use of stains in the previous 5 years, from the date of statin initiation 2. History of manifest CVD defined by ICD-10 codes and combination medication user? (e.g., previous MI, IHD, stroke (including TCI), HF…..) 3. Immigration <5 years prior to initiation. 4. At least 5 years of potential follow-up
Treatment strategies	Initiate statin therapy as primary prevention for both arms. The control arm will continue sustained statin use for x years, while the intervention arm discontinues statins after one year of continuous use and does not restart statins therapy for x-1 years. The use of additional lipid-lowering medications is not permitted.	Same as for the target trial.
Assignment procedures	Participants will be randomized at baseline to either continue sustained statin use or	

	discontinue statins after one year. The discontinuation will not be blinded.	
Time zero and follow-up period	Follow-up starts at randomization and ends at outcome occurrence, death, loss to follow-up, re-initiations of statins during the period of discontinuations, initiations of other lipid-lowering medication, or end of study (x years after randomization), whichever comes first.	Same as for the target trial. (Additionally, to administrative censoring, if relevant)
Outcome	Cardiovascular disease including ischemic heart disease (inc. MI), stroke (inc. TCI), "macrovascular atherosclerotic disease" and peripheral atherosclerotic disease. **Or** 3-4P MACE (MI, stroke (inc. TCI), all-cause mortality and HF?)	Same as for the target trial.
Causal contrasts of interest	Per-protocol effect (what if hypothetically all patients complied to their assigned protocol?) Intention-to-treat effect?	Per-protocol effectObservational analogue to the per-protocol effect (as-treated) Observational analogue to the Intention-to-treat effect (as-started)?
Analysis plan		

Table 3) Table over ICD-10 codes and procedure codes used to define the study outcome:

Disease	**ICD-10**	**Procedures codes**
Heart failure	I110, I50, I130, I132	
Non-MI Ischemic heart disease	I20, I25	
Myocardial Infarction	I21, I23, I24	KFNA00, KFNA10, KFNA20, KFNA96, KFNB00, KFNB20, KFNB96, KFNC10, KFNC20, KFNC30, KFNC40, KFNC50, KFNC60, KFNC96, KFND10, KFND20, KFND96, KFNE00, KFNE10, KFNE20, KFNE96, KFNF00, KFNF10, KFNF20, KFNF30, KFNF96, KFNG00, KFNG00A, KFNG00B, KFNG00C, KFNG00D, KFNG02, KFNG02A, KFNG05, KFNG05A, KFNG10, KFNG12, KFNG30, KFNG40, KFNG96, KFNH20
Macrovascular Atherosclerotic disease (ex. Peripheral atherosclerotic disease)	I70 (excluding I702), I71	

Peripheral atherosclerotic disease (including revascularization)	I739, I702, E105, E115, E125, E135, E145	KPDE, KPEE, KPFE, KPDF, KPEF, KPFF, KPDU74, KPEU74, KPFU74, KPDH, KPEH, KPFH, KPGH (ex KPGH10), KPDN, KPEN, KPFN, KPDU82, KPEU82, KPFU82, KPDP, KPEP, KPFP, KPDU83, KPEU83, KPFU83, KPDW, KPEW, KPFW
Stroke		
Hemorrhagic stroke	I60, I61, I62, I691, I692	
Ischemic stroke	I63, I64, I693, I694, I698	
Transient cerebral ischemia	G45	

References:

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