Cardiovascular risk after deprescribing statins. A base-case risk, cost-effectiveness, and investigator file analysis of the STREAM Trial

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Responsibility:

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Introduction

The Stream Trial [1] is a non-inferiority trial where it is hypothesized that in patients taking statins, deprescribing of statins is non-inferior to ongoing statin therapy in patients aged at least 70 years, and avoids unnecessary discomfort and side-effects.

Authors of the Stream Trail have not presented power calculations, that are available publically, where 1 800 patients are to be included and follow-up time is 4 years. It may be argued that deprescribing statins may cause significant increases in cardiovascular events and may therefore be unethical. But obviously, authors expect no significant harms regarding cardiovascular risk. Further, authors perform a sub-study, where they assess coronary calcifications, but results will be kept blinded until the end of the trial.

Aim

In order to test the safety of the Stream Trial, we use accepted methods of risk assessment in a base-case. We aim to show that the Stream Trial may only be ethically acceptable, if a patient has no coronary calcification, but is unethical if the patient has unknown amounts of coronary calcifications or an Agatston Score of 300.

Methods

1. We create a base-case of a male smoker, 60 years of age, systolic blood pressure 130 mm Hg, Cholesterol 6.0 mmol/l, HDL 1.0 mmol/l, and LDL 3.8 mmol/l. We calculate SCORE2/-OP risk [2], [3] with no statin medication and with statin medication, assuming that LDL is lowered to 1.8 mmol/l and total Cholesterol is therefore lowered to 4.0 mmol/l. Then we calculate the SCORE2/-OP risk for age 70, age 72, age 74 and for age 75, again with the same numbers and with or without statin use. The temporal change in 10-year ASCVD risk over a period of 2, 4 and 5 years reflects success or failure in controlling major cardiovascular risk factors and indicates the risk of future ASCVD events. The Δ10-year ASCVD risk/year can be used as an indicator of primary prevention and guide the application of preventive measures [4]. Further, we calculate posttest risk using the Bayes Theorem for zero coronary calcifications (CAC=0) assuming a sensitivity of 93% and a specificity of 34% and using the results of SCORE2/-OP as prior probabilities (prevalence) and we calculate posttest risk using the Bayes Theorem for coronary calcifications with an Agatston Score of 300 (CAC=300) assuming a sensitivity of 54% and a specificity of 86% and using the results of SCORE2/-OP as prior probabilities (prevalence)[5]. The difference between statin uses or no statin use is calculated for 1 800 patients with the variables of the base-case and from this, the number of avoidable events in statin users is assessed. Further, a cost-effectiveness analysis (CEA) for the 1 800 patients being either dead from cardiovascular

events or having had a non-fatal cardiovascular event is performed for the period 72 to 82 years of age. Treatment costs of a non-fatal event in the first year is 24 000 Fr. and is 8 000 Fr. for subsequent years [6], which, over 7 years, results in total medical costs of 73 000 Fr. Treatment cost with statins including fees for laboratory monitoring for statin treated patients aged 70 is 470 Fr. per patient per year [7]; these treatment costs were calculated for 5 years (all 1 800 patients treated). Further, the value of a statistical life year (VSLY) is estimated at 3 times the BIP per year [8], which is expected to reach 87 951 USD in the year 2023, which results after conversion to Swiss Francs (0.9 Fr = 1 USD) in a VSLY of 237 468 Fr. Finally, we use the CHI Test to assess the statistical significance of the difference in events with (on-treatment assumption) and without statin use.

2. We analyze the investigator file in order to compare our results and to draw attention to eventually present selective reporting. Further we analyze the patient information file for the eventual presence of selective or falsified reporting that might violate rules of the Nuremberg Code.

Results

Base-case calculations

Based upon our model assumptions, Statin use is associated with an absolute risk reduction (ARR) of 2.7% in non-deprescribed statin users with unknown amounts of CAC after 2 years of treatment. In 900 patients, after 2 years of statin withdrawal, ASCVD risk increases to 17.3% without statins, with statins to 14,6%. This creates a disease burden of 4 fatal and 24 non-fatal events and 44 lost life years with a lost value of 10.3 Mio CHF. The return on investment (ROI) is 10.3 Mio. CHF and the event reduction with statins is not statistically significant (p=0.1076). In patients with CAC, ARR is 4,9% with 80 lost life years, a ROI of 120.0 Mio CHF and a statically relevant increase of morbidity and mortality (p=0.0357). In patients without CAC, absolute risk reduction is 0.4% with 7 lost life years, a ROI of 0.1 Mio. CHF and a non-significant ASCVD reduction (p=0.6259). The sensitivity analysis with 4 or 5 instead of 2 years statin deprescribing did change the results significantly in patients with unknown CAC (see Appendix).

Table 1: Difference in outcome and return on investment without deprescribing statins over 2 years. Calculations are based on SCORE2/-OP risk estimates.

Stream Base Case Scenarios Effects of statin deprescription per treatment arm	Patients 900	VSLY 237 468	Years 10	Deprescribing with CAC CAC= 300			Deprescribing, no CAC CAC = 0		
Age	**60**	**70**	**72**	**60**	**70**	**72**	**60**	**70**	**72**
Sex (1=male)	1	1	1	1	1	1	1	1	1
Smoke (1=active smoker)	1	1	1	1	1	1	1	1	1
BP	130	130	130	130	130	130	130	130	130
Chol	6	4	6	6	4	6	6	4	6
HDL	1	1	1	1	1	1	1	1	1
LDL	3,8	1,8	3,8	3,8	1,8	3,8	3,8	1,8	3,8
SCORE2/-OP	9,6	15,6	17,3	29,0	41,7	44,6	2,1	3,7	4,1
SCORE2/-OP with Statin	7,8	13,8	14,6	24,5	37,8	39,7	1,7	3,1	3,7
RRR	18,75	11,54	15,61	15,52	9,35	10,99	19,05	16,22	9,76
ARR	1,8	1,8	2,7	4,5	3,9	4,9	0,4	0,6	0,4
NNT	56	56		22	26		250	167	
NNH Statin Stop			37			20			250
No events	884	884	876	860	865	856	896	895	896
Events	16	16	24	41	35	44	4	5	4
Non Fatal Events	13	13	20	33	29	36	3	4	3
Fatal Events	3	3	4	7	6	8	1	1	1
Life years lost			44			80			7
VSLY Fr			237468			237468			237468
ROI in Mio SFr over 7 years with Statin			10,5			19,0			1,6
Event Treatment Cost first of 7 years			25000			25000			25000
Event Treatment Cost year 2-7			48000			48000			48000
Cost of survived non-fatal event 7 years			73000			73000			73000
Cost total of non-fatal event 7 years			1,5			2,6			0,2
Statin and Lab costs 470/y/pp			1,69			1,69			1,69
ROI Total Mio Fr. with Statin			10,3			20,0			0,1
CHI 2 (for N=1800)			**2,589**			**4,41**			**0,238**
p=			**0,1076**			**0,0357**			**0,6259**

In 1800 Patients	https://kardiolab.ch/riskcalc_JSI.html		
Events no Statin	156	401	37
No Events, no Statin	744	499	863
Events with Statin	131	357	33
No events, with Statin	769	543	867

Analysis of the Investigator File (v2-3)

A) Statement on statin effects (page 31 of the investigator file):

Statin benefits for primary prevention in older people (aged >70) without cardiovascular disease (CVD) are uncertain, particularly for those with multimorbidity [9], PROSPER trial among 5804 older adults aged 70-82 years, there was no benefit of statins on CVD in primary prevention [10], in the ALLHAT-LLT trial [11], there was even a nonsignificant increase in mortality rate 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 [12], most large RCTs do not include multimorbid elderly, statin side effects and drug interactions are common in a multimorbid elderly population and can negatively impact quality of life LDL and total Cholesterol levels do not predict CV risk in 70+ individuals without pre-existing CVD.

Available information on statin effects in the literature:

Several important studies from the literature regarding the effects of statins in 70+ patients have not been reported in this investigator file. One of the investigators of the STREAM Study, Prof. Bischoff, already back in 2016 reported on the positive effects of statins in 65+: Evidence on Statins in Age 65 to 82 is an absolute risk reduction in 5 years of about 5%[1]. The key messages of here presentation:

1. age 65 to 82: statins reduce the risk of major CV events by about 5% within 5 years; important: incidence is high - about 23-25%!
2. age: effect 65 to 82 well proven in all subgroups. Data RCTs with people age > 82 are missing!
3. long-term studies show 29% risk reduction of new dementia disease with statin use. Discussed mechanism: inhibition of cholesterol plaque deposition.
4. statins for patients 65+: - Very good evidence in primary and secondary prevention of major CV events; - Baseline measures include diet and exercise (statins do not replace healthy lifestyle).

We have listed all studies regarding positive effects of statins in the elderly elsewhere[2]: in brief, in 2020, Gencer's meta-analysis showed the effect (impact) of statins and other lipid-lowering agents per 1 mmol/l LDL reduction in persons older than 75 years[3]. The relative risk reduction of statins per 1 mmol/l LDL reduction is 18% with "random effect metaanalysis" and for LDL reduction with non-statins (PCSK-9 inhibitors and ezetimibe) 33%, in combination resulted in an effect of 26%. It should be noted here that usually more than 1.0 mmol/l LDL reduction is achieved with statins. Especially with the combination statin+ezetimibe, LDL reductions of 2.0 mmol/l can be easily achieved even from 65 years of age. This doubles the effect from 18% to 36%. This very good news was discussed

[1] https://www.usz.ch/app/uploads/2021/01/Statine-im-Alter-65-plus_Juni16.pdf
[2] https://varifo.ch/statin-effekte/
[3] https://linkinghub.elsevier.com/retrieve/pii/S0140673620323321

further elsewhere in 2018[4]. A 2017 meta-analysis by Ridker showed within age subgroups of the JUPITER (Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and HOPE-3 (Heart Outcomes Prevention Evaluation) primary prevention trials that evaluated the effects of rosuvastatin on the combined end point of nonfatal MI infarction, nonfatal stroke, or cardiovascular death [5]. In 2013, another meta-analysis by Savarese showed a significant reduction in heart and brain strokes in 24,674 people over age 65, with 39% fewer heart attacks and 24% fewer brain strokes over a median observation period of 3.5 years[6]. It is acknowledged today, that statin intolerance is related to a nocebo effect [13], which is strongly promoted in the STREAM trial (self-fulfilling prophecy study design). A consensus report recommends statins in patients aged 40-75 years without diabetes and ASCVD risk of >7.5%[13].

Analysis of the patient information file on statin effects

Der Nutzen einer Statin-Therapie bei älteren Patienten ohne bestehende Herz-Gefäss103 Erkrankungen ist nicht nachgewiesen. Ein Risiko beim Stoppen der Statin-Therapie ist 104 das Auftreten von Herz-Gefäss-Erkrankungen (Herzinfarkt), wenn die Patienten kürzlich 105 einen Herzinfarkt erlitten haben. Bei Patienten ohne Herzinfarkt oder Schlaganfall trat 106 dieses Risiko jedoch nicht auf.

English translation: The benefit of statin therapy in elderly patients without existing cardiovascular disease has not been established. One risk in stopping statin therapy is the occurrence of cardiovascular disease (myocardial infarction) if the patients have recently suffered a myocardial infarction However, this risk did not occur in patients without myocardial infarction or stroke.

Critique of investigators on statin effects in 70+:

Investigator file: selective reporting about the beneficial effects of statins in 70+.

Patient information: wrong information about protective effects in 70+

B) ASCVD Risk assessment in 70+:

Investigator file:

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. Therefore, the use of this tool in 70+ individuals represent an extrapolation but no definitive CV risk evaluation.

Available information:

SCORE2-OP was published in 2021 and includes ASCVD risk prediction up to 89 years [3].

Critique on ASCVD Risk assessment in 70+:

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[4] https://varifo.ch/wp-content/uploads/2022/06/Mortensen-Falk-2018-Primary-Prevention-With-Statins-in-the-Elderly.pdf

[5] https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.117.028271?papetoc=

[6] https://www.jacc.org/doi/10.1016/j.jacc.2013.07.069

Investigator file: selective reporting.

Patient information: no reporting on SCORE2-OP and the ensuing risk of withholding statins in 70+.

C) Deprescribing of statins no evidence on risk

Investigator file:

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".

Available information:

The risk of stopping statins was observed in several large population-based observations from Italy[7], in the Eilat study[8], the Orkaby study[9], an Asian study[10] and in the Giral study[11] with excessive fatal and non-fatal risk increases for ASCVD when statins were stopped in the elderly, even if 75+. Also, the USPSTF recommended not to stop statins in the elderly in 2022[12]. Further, the Federal Office of Health retains that statins up to age 75 are cost-effective with a return on investment (negative QALY)[13]. Deprescribing of statins in patients aged 70+ should be avoided [13], but diabetes is not an exclusion criterion in the STREAM trial.

Critique in deprescribing information

Investigator file: the statement about little evidence of statin deprescribing evidence is neither referenced nor correct. All the available literature about the risks of deprescribing statins in 70+ has not been reported. This is a massive case of selective reporting.

Patient information: patients are not informed about the risks of deprescribing.

D) Coronary Calcium

Investigator file:

Statement 1: 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

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[7] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2780952
[8] https://agsjournals.onlinelibrary.wiley.com/doi/10.1111/jgs.16060
[9] https://jamanetwork.com/journals/jama/fullarticle/2767861
[10] https://www.internationaljournalofcardiology.com/article/S0167-5273(22)01718-1/fulltext
[11] https://academic.oup.com/eurheartj/article/40/43/3516/5540819
[12] https://jamanetwork.com/journals/jama/fullarticle/2795521
[13] https://varifo.ch/bag-hta-statine/ for all the details

most guidelines. To address these questions, in a subsample of the present RCT, we aim to measure CAC and biomarkers at baseline.

Statement 2: 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.

Statement 3: 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 75‘^ 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)) (reference numbers are from the investigator file)

Available information:

Coronary calcifications maintain a strong prognostic effect in the elderly as reported by Raggi in 2008 [14]: Abstract: “We sought to study the prognostic utility of coronary artery calcium (CAC) in the elderly. The prognostic significance of CAC in the elderly is not well known. All-cause mortality was assessed in 35,388 patients (3,570 were 70+ years old at screening, and 50% were women) after a mean follow-up of 5.8 years. In older patients, risk factors and CAC were more prevalent. Overall survival was 97.9% at the end of follow-up. Mortality increased with each age decile with a relative hazard of 1.09 (95% confidence interval: 1.08 to 1.10, $p < 0.0001$), and rates were greater for men than women (hazard ratio: 1.53; 95% confidence interval: 1.32 to 1.77, $p < 0.0001$). Increasing CAC scores were associated with decreasing survival across all age deciles ($p < 0.0001$). Survival for a <40-year and ≥80-year-old man with a CAC score ≥ 400 was 88% and 19% (95% and 44% for a woman, $p < 0.0001$), respectively. Among the 20,562 patients with no CAC, annual mortality rates ranged from 0.3% to 2.2% for patients age 40 to 49 years or ≥70 years ($p < 0.0001$). The use of CAC allowed us to reclassify more than 40% of the patients 70+ years old more often by excluding risk (i.e., CAC <400) in those with >3 risk factors. Conclusions: Despite their limited life expectancy, the use of CAC discriminates mortality risk in the elderly. Furthermore, the use of CAC allows physicians to reclassify risk in the elderly.” Risk prediction models improve with the information from CAC in the elderly, as shown in the Rotterdam study in 2010 [15]. A consensus report recommends statins in patients with a CAC score of 1 or more in patients with ASCVD risk of >7.5%[13].

Regarding the investigators speculations about higher density CAC (statement 3) and eventual loss of prognostic significance in the elderly, based upon a secondary analysis of the MESA trial, even patients aged 75+ showed maintained ASCVD outcome not significantly different from younger age groups [16]. A state-of-the-art paper described methodologies beyond Agatston scores, e.g. calcified volume or density scores, but stated that such refinements are only relevant for ASCVD risk prediction in those with intermediate CAC scores of 100-299. In the elderly with frequently CAC scores of 300 and more, such refinements are not necessary because of the already high risk approaching secondary prevention risk levels [17].

Critique regarding CAC

Investigator file: the statement 1 about reclassification effects and risk of CAC in the elderly are neither referenced nor correct. False reporting. The statement 2 is in contradiction to statement 1 and is not referenced. The statement 3 is not an appropriate discussion about the problem of Agatston scores. Patients with CAC>300 have very high risk for ASCVD events irrespective of age or plaque density.

Patient information: statement 1: no reporting of CAC risks and reclassification abilities for ASCVD in 70+. Statement 2: patients are not informed about the authors expectation of *increased mortality* in those with CAC and statin discontinuation. This is a violation of the Nuremberg Code 5: "No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects."[14]

E) Muscle effects of Statins

Investigator File

Statement 1: 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).

Statement 2: 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).

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14 https://en.wikipedia.org/wiki/Nuremberg_Code#:~:text=The%20degree%20of%20risk%20to,injury%2C%20disability%2C%20or%20death.

Available evidence:

In a large study it was shown that statin side effects including muscle pain is generally *less* frequently in 75+ than in <75[15]. A large body of scientific evidence has shown that muscle pain or weakness due to statins is highly overestimated by clinicians [18]–[27].

Critique regarding muscle symptoms

Investigator file: there is an obvious discrepancy regarding muscle side effect reported by the authors. While the hole study is about reduction of side effects of statins in the elderly, the most frequent side-effect is not properly discussed.

Patient information: there is no information about the potential of decreased muscle symptoms in the elderly with increasing age. Underreporting of information.

F) Expected risks

Investigator File

Statement 1: 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.

Statement 2: Based on data from our OPERAM trial (59), we calculated the probability of dying from noncardiac causes at 12 months as 11.6% and the probability for non-fatal and fatal CV events as 9.1%.

Statement 3: 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 cointerventions 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.

Available evidence:

An ASCVD risk of 9,1% per year corresponds to a 10-year risk of 91%. This is an excessively high risk that may be present only in diabetic renal failure in a man who smokes, has a blood pressure of 180 mm Hg and a total cholesterol of 10 mmol/l.

Critique regarding risk and margins

Investigator file: the non-inferiority margin at two years is 5% for the primary outcome. Assuming a relative risk reduction of statins of 30% (corresponding to about 1.5 mmol/l LDL reduction), an

[15] https://www.ahajournals.org/doi/full/10.1161/JAHA.118.008546

absolute risk reduction of 5.5% occurs (p=0.0063) in 2 years. Therefore, the non-inferiority margin is not correct. The main risks of the STREAM trial are not addressed properly (statement 3). LDL cholesterol should be measured in statin deprescribed patients in order to detect non-treatment adherence.

Patient information: patients are not correctly informed about the absolute risk increase of 5.5% in 2 years when stopping statins (number needed to harm: 18).

Discussion

Base-case analysis

Based upon accepted risk assessment in Switzerland (SCORE2/-OP), our principal finding when deprescribing statins for 2 years is a number-needed-to-harm (NNH) of 37 and is a NNH of 20 in those with CAC>300 (NNH 250 with CAC=0). At five years, NNH is 26, 15 and 91, respectively. From these calculations it becomes clear, that deprescribing statins at age 70 in the base-case is prohibitive. The study patient information, that statins beyond age 70 have no proven medical effect on cardiovascular events is in contradiction to current medical evidence, which states that in the elderly we have *less* direct evidence of statin effects than in younger patients.

If we value lost life years according to World Health Organization standards as referenced by Schleiniger in 2006 [8], continued statin medication is associated with a return on investment of 10,3 Mio CHF, is 20,0 Mio CHF in those with CAC>300 and is 0.1 Mio CHF in those with CAC=0. Therefore, cost-effectiveness analysis based upon the value of lost statical life years (VSLY) is highly positive for a continued statin treatment. The Federal Office of Health also found return of investment of high significance in patients up to 75 years using QALY assumptions[16].

It has been shown that negative risk factors, e.g., CAC=0, result in a diagnostic likelihood ratio of 0.41, when estimated risk was derived from the pooled cohort equation [28]. Our posttest risk calculator shows a down grading of cardiovascular risk with CAC=0 from 9.6% to 2.1% in non-statin user, which results in a diagnostic likelihood ratio of 0.46 (for statin user: 0.46). Therefore, posttest risk calculation is appropriate.

Investigator file and patient information file analysis

We performed a comparison of the information available from the investigator file and the patient information file and available information from the literature regarding effects of statins in 70+, available tools for ASCVD risk assessment, risk of statin deprescribing, coronary calcifications, muscle side effects of statins, and expected risks of the STREAM trial. The comparison showed consequent selective reporting in the investigator file and consequent misinformation of patients. Especially bothersome are the violation of the Nuremberg Code 5.

There is a very problematic safety calculation regarding the non-inferiority margin of 5% at 2 years. The problem here is the behavior of the patients after 2 years: should they restart statins or avoid them? In patients having a limited life expectancy of e.g., 2 years, deprescribing statins is reasonable and study authors make also reference to such studies, where there was no harm in such patients [29]–[32]. In the STREAM study there is no inclusion criterium for low life expectancy and no exclusion criterium for life expectancy over 2 years. A reasonable[17] cutoff for this non-inferiority trial

[16] https://docfind.ch/H0032CHOL_Corrected%20HTA%20Report%20Statins.pdf

[17] https://fmhub.org/wp-content/uploads/2021/08/HyperlipidemiaDrugs-for-Cardiovascular.pdf

would be an NNT of 50 at 10 years, which corresponds to an absolute risk reduction of 2% in 10 years or, by linear inference to an absolute risk reduction of 0.4% in 2 years. Authors have chosen a cutoff of 5%, which is 12.5 lower than the correct level of non-inferiority. Setting non-inferiority margins is a highly debatable undertaking and should be performed with very low margins in order to account for established treatment effects from superiority trials [33].

The order of study authors to avoid cholesterol tests in statin deprescribed patients is highly problematic, because the effect of LDL lowering on outcome is obscured and does not allow to calculate a dose-response relationship of deprescribing statins. Results will remain foggy and uninterpretable.

Based on available information, there are 3 scenarios, for which the STREAM trial may be appropriate:

1. Patients without coronary calcifications (CAC=0).
2. Patients with life-expectancy of about 2 years (already proven that deprescribing does not cause harm)
3. Doctors fully informed, who despite the caveats would deliberately stop their statins at age 70 (according to the Nuremberg recommendation).

Misleading statin effect studies cited in the investigator file

The study authors cite a number of studies as justification for uncertainty that, on closer examination, do not support the presumed uncertainty.

1. Economist Paula Byrne, conducts a selective analysis because of a large body of missing study data, which is intended to substantiate the presumed doubts about the efficacy of primary care prevention [34]. In fact, however, the statin effects are still statistically significantly better than placebo. In order to remove these positive effects, age groups are formed according to an inadmissible subgroup analysis, where the statin effects are then no longer significant for the individual age groups. This procedure is unscientific, and the question arises as to why the study authors refer to this Byrne study at all.
2. The Shepherd study (PROSPER) showed significant beneficial effects of statins [35] for 5804 individuals aged 70 years and older treated with 40 mg pravastatin for 3.2 years (p=0.014 for the primary endpoint of fatal and non-fatal myocardial infarction, NNT 47 for 3.2 years and NNT 15 linearly extrapolated to 10 years). Pravastatin was well tolerated by this patient population taking a wide range of concomitant medications, and there was no evidence of adverse effects on liver function or muscle enzymes. The lack of effect on prevention of cerebral strokes was attributed to the study duration being too short. However, about 25% of the subjects in the Prosper study were on secondary prevention because of previous myocardial infarction or stroke.

3. The ALLHAT statin study is a post-hoc analysis with massive confounding by crossover in treatment: subjects in the verum group were taking no statins at 6 years in 22% of cases and in the placebo group 29% were taking a statin at 6 years. In this study, in which 63% of patients were >60 years of age, atorvastatin (10 mg) significantly reduced nonfatal myocardial infarctions and fatal CHD by 36% (HR = 0.64; 95% CI 0.50-0.83). Interestingly, a follow-up analysis after approximately 8 years showed long-term benefits in all-cause mortality (-14%) and non-CV deaths (-15%); the latter apparently due to reduced deaths from infections and respiratory diseases.
4. In the review by Ruscica [36] is not at all concerned with the question of whether statins should be used in the elderly - since they are effective - but with the question of dosage. However, Ruscica states that, in general, the oldest age groups (>85 years) are unlikely to be considered for cholesterol lowering in primary prevention. In particular, severely frail elderly patients should not be treated for primary prevention and, unless absolutely necessary, should be treated for secondary prevention
5. The study by Milly shows no new effect data and addresses the issue of deprescribing statins from age 80 in 30 countries [37].
6. Kutner study reports that at end of life, discontinuation of statins is safe [38].

Thus, in the investigator file, the stream authors present either studies with missing significance (Paula Byrne) or studies that prove the positive effects of statins from the age of 65 or reviews on the deprescribing of statins from the age of 80. In addition, numerous other studies, which are listed below, are negligently concealed. Thus, the Stream authors cannot substantiate the claimed uncertainty in any way.

Evidence of the efficacy of LDL lowering in reducing the risk of myocardial infarction and stroke in primary prevention is well established, especially for individuals >75 years of age [39], [40]. We refer here to the comments of the AGLA. In addition, we have also summarized the following study situation online (https://varifo.ch/statin-effekte/).

The meta-analysis by **Gencer** [41] shows the effect (impact) of statins and other lipid-lowering agents in persons older than 75 years per 1 mmol/l LDL reduction. The relative risk reduction of statins per 1 mmol/l LDL reduction is 18% with "random effect metaanalysis" and for LDL reduction with non-statins (PCSK-9 inhibitors and ezetimibe) 33%, in combination resulted in an effect of 26%. It should be noted here that usually more than 1.0 mmol/l LDL reduction is achieved with statins. Especially with the combination of statin plus ezetimibe, LDL reductions of 2.0 mmol/l can be easily achieved even from 65 years of age. This doubles the effect from 18% to 36%.

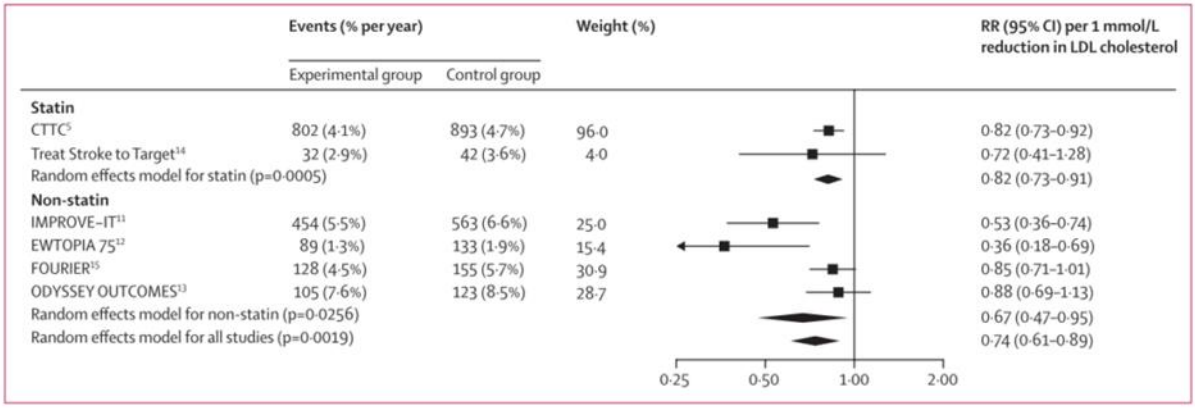
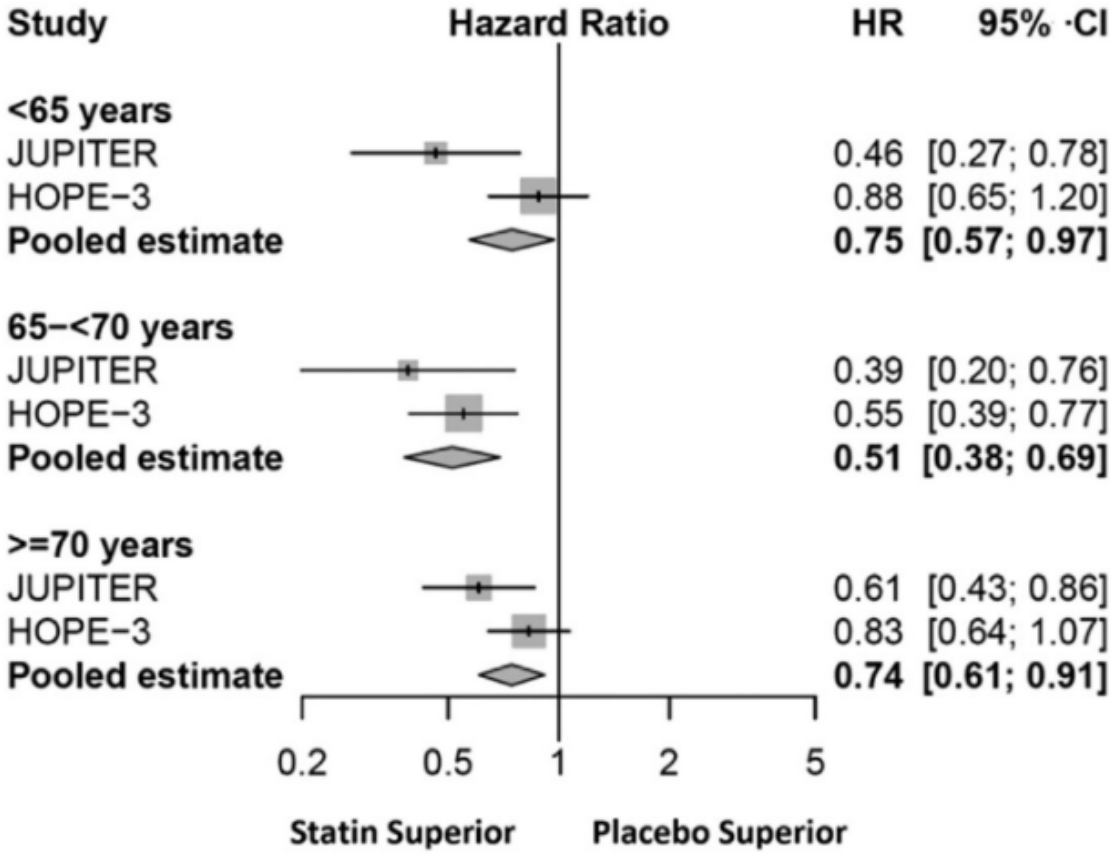


Figure 1: **Effect of LDL cholesterol lowering on the risk of major vascular events with statin and non-statin treatment in older patients**
Older patients were aged 75 years or older. RRs per 1 mmol/L reduction in LDL cholesterol were generated from a random effects model. In the ODYSSEY OUTCOMES trial, the event numbers were provided at 4 years, whereas the RR is for the entire duration of trial. CTTC=Cholesterol Treatment Trialists' Collaboration. EWTOPIA 75=Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerosclerotic Disease in 75 or Older. FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients with Elevated Risk. IMPROVE-IT=Improved Reduction of Outcomes: Vytorin Efficacy International Trial. ODYSSEY OUTCOMES=Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab. RR=risk ratio.

Data from six articles were included in the systematic review and meta-analysis, which included 24 studies from the Cholesterol Treatment Trialists' Collaboration meta-analysis and five individual studies. Of 244,090 patients from 29 trials, 21,492 (8.8%) were at least 75 years of age, including 11,750 (54.7%) from statin trials, 6,209 (28.9%) from ezetimibe trials, and 3,533 (16.4%) from PCSK9 inhibitor trials. Median follow-up ranged from 2.2 to 6.0 years. Lowering LDL cholesterol significantly reduced the risk of major vascular events (n = 3519) in elderly patients by 26% per 1 mmol/l reduction in LDL cholesterol (RR 0.74 [95% CI 0.61-0.89]; p = 0.0019.)), with no statistically significant difference from risk reduction in patients younger than 75 years (0 85 [0 78-0 92]; P interaction = 0 37). In elderly patients, RRs were not statistically different for statin (0 82 [0 73-0 91]) and non-statin treatment (0 67 [0 47-0 95]; P interaction = 0 64). The effect of lowering LDL cholesterol in elderly patients was observed for each component of the combination, including cardiovascular death (0 85 [0 74-0 98]), myocardial infarction (0 80 [0 71-0 90]), stroke (0 73 [0 61-0 87]), and coronary revascularization (0 80 [0 66-0 96]). The authors of this study concluded the following: In patients 75 years of age and older, lipid lowering was as effective in reducing cardiovascular events as in patients younger than 75 years. These findings should strengthen guideline recommendations for the use of lipid-lowering therapies, including non-statin treatments, in elderly patients.

A meta-analysis by **Ridker** within age subgroups of the primary prevention trials JUPITER (Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and HOPE-3 (Heart Outcomes Prevention Evaluation), which evaluated the effects of rosuvastatin on the combined end point of nonfatal MI infarction, nonfatal stroke, or cardiovascular death, also showed significant effects of statin treatment in individuals 70 or more years of age [42].



A meta-analysis by **Savarese** [43], [44] showed a significant reduction with statins in ischemic heart attacks and brain strokes in 24,674 persons over 65 years of age, with 39% fewer heart attacks and 24% fewer brain strokes over a mean follow-up period of 3.5 years.

Zhou published a study on healthy individuals who were either taking statins or not [45]. Of the 18,096 >70-year-old participants included (mean age 74.2 years, 56.0% women), 5,629 were taking statins at baseline. Over a median follow-up period of 4.7 years, statin use at baseline was not associated with disability-free survival or risk of all-cause mortality or dementia. However, it was associated with a lower risk of physical disability and all cardiovascular outcomes. Persistent disability in daily living was reduced by 25% ($p=0.02$), 32% fewer heart and brain strokes occurred ($p<0.001$), cardiovascular mortality was significantly reduced by 29%, 44% fewer heart attacks and 25% fewer brain strokes were found, and statins also did not produce an increased risk of dementia in another study by Zhou (https://www.jacc.org/doi/10.1016/j.jacc.2021.04.075).

The risks of statin cessation were examined in an Italian study [46]. This retrospective, population-based cohort study included 29,047 residents of the Lombardy region of Italy aged 65 years or older who received continuous treatment with statins, antihypertensive, antidiabetic, and antiplatelet agents from October 1, 2013, to January 31, 2015, follow-up to June 30, 2018. Data were collected using the Lombardy Region Health Care Utilization Database in Italy. Data analysis was performed

from March to November 2020. EXPOSURES: Cohort members were followed up to identify those who discontinued statins. In this group, those who maintained other therapies during the first 6 months after statin discontinuation were matched 1:1 with patients who did not discontinue statins or other medications. MAIN RESULTS AND MEASUREMENTS: Patient pairs who discontinued and maintained statins were followed up from initial discontinuation through June 30, 2018, to estimate hazard ratios (HRs) and 95% CIs for fatal and nonfatal outcomes associated with statin discontinuation. RESULTS: The full cohort included 29,047 patients exposed to polypharmacy (mean age [SD] 76.5 [6.5] years; 18,257 [62.9%] men). Of them, 5819 (20.0%) discontinued statins while maintaining other medications, and 4010 (68.9%) of them were matched with a comparator drug. In the discontinuation group, the mean (SD) age was 76.5 (6.4) years, 2405 (60.0%) were men, and 506 (12.6%) had multisource comorbidity scores of 4 or 5. In the maintenance group, the mean (SD) age was 76.1 (6.3) years, 2474 (61.7%) were men, and 482 (12.0%) had multisource comorbidity scores of 4 or 5. HR, 1.24; 95% CI, 1.07-1.43) and all cardiovascular outcomes (HR, 1.14; 95% CI, 1.03-1.26), deaths from any cause (HR, 1.15; 95% CI, 1.02-1.30), and emergency admissions for any cause (HR, 1.12; 95% CI, 1.05-1.19). CONCLUSIONS AND RELEVANCE: In this study of patients receiving polypharmacy, discontinuation of statins while maintaining other drug therapies was associated with an increase in long-term risk of fatal and nonfatal cardiovascular outcomes, and all-cause mortality was also significantly increased.

The **Eilat study** examines the effects of discontinuing statins [47]. The EILAT trial included primary care patients aged 65 years and older and reported 347 events in 1255 individuals taking statins (28%) and reported 4105 events in 7328 patients not taking statins (56%). The analysis included 19,518 older adults followed for 10 years (median = 9.7 years). All-cause mortality rates were 34% lower in those who had adhered to statin treatment than in those who had not (hazard ratio [HR] = 0.66; 95% confidence interval [CI] = 0.56-0.79). Statin adherence was also associated with fewer atherosclerotic cardiovascular disease events (HR = 0.80; 95% CI = 0.71-0.81). The benefit of statin use did not diminish in those older than 75 years and was evident for both women and men.

Dr. Philippe Giral observed the effect the statin stop in people over 75 years of age [48]. Statin discontinuation was associated with a 33% increased risk of admission for cardiovascular events in 75-year-old primary prevention patients. Future studies, including randomized trials, are needed to confirm these findings and to help update and clarify guidelines on the use of statins for primary prevention in the elderly.

Orkaby studied statin effects on mortality from age 75 onward [49]. Results: Of 326,981 eligible veterans (mean [SD] age, 81.1 [4.1] years; 97% men; 91% white), 57,178 (17.5%) newly started statins during the study period. During a median follow-up of 6.8 (SD, 3.9) years, a total of 206902 deaths occurred, including 53296 cardiovascular deaths, with 78.7 and 98.2 deaths/1000 person-

years among statin users and nonusers, respectively (weighted incidence rate difference.) [IRD]/1000 person-years, -19.5 [95% CI, -20.4 to -18.5]). There were 22.6 and 25.7 cardiovascular deaths per 1000 person-years among statin users and nonusers, respectively (weighted IRD/1000 person-years, -3.1 [95% CI, -3.6 to -2.6]). For the composite ASCVD outcome, there were 123379 events, with 66.3 and 70.4 events/1000 person-years among statin users and nonusers, respectively (weighted IRD/1000 person-years, -4.1 [95% CI, -5.1 to -3.0]). After applying the propensity score overlap weighting, the hazard ratios were 0.75 (95% CI, 0.74-0.76) for all-cause mortality, 0.80 (95% CI, 0.78-0.81) for cardiovascular mortality, and 0.92 (95% CI, 0.91). -0.94) for a composite of ASCVD events when comparing statin users with nonusers. **Conclusions and Relevance:** Among U.S. veterans 75 years and older who were free of ASCVD at baseline, new statin use was significantly associated with a lower risk of all-cause mortality and cardiovascular mortality. Further research, including randomized clinical trials, is needed to determine the role of statin therapy more definitively in older adults for primary prevention of ASCVD.

As mentioned earlier, concerning cost-effectiveness, the Federal Office of Public Health has had a report prepared [50], [51]. All correspondence and results can be traced back to us. According to the final version of the HTA report, the costs per QALY concern negative results, thus a "return on investment" in healthy persons up to 75 years. Since persons 75 years and older are often at high risk for cardiovascular (ASCVD) events (about 5% per year), there is no reason to assume that the positive cost-effective effects would suddenly disappear from the age of 75. The FOPH study also shows that the Swiss Medical Board's narrative review of the cost-effectiveness of statins produced erroneous results [7], [52]–[55].

Table 5: HTA report about Statins, BAG Nov 2020, regarding cost-efficiency of statins according to level of AGLA risk.

This is an analysis of cost-effectiveness, HTA BAG Nov 2020

The HTA report has been corrected based upon my intervention. The correction factor of the HTA report for AGLAcvd is 1.80, therefore 80% underestimation of risk with AGLAchd.

In slide 3, we found a correction factor of 1.69, which is therefore very similar to the HTA report and suggests, that AGLAcvd is 69% higher than reported by AGLAchd.

This fact shows, that it is inadmissible that AGLA sells CHD for CVD. This is wrong.

The cost-efficacy of Statins is maintained for all patients up from an AGLA risk of at least 5%, probably 3% (< 100 000 / QALY).

This is similar to our calculations published with Prof. Szucs (we found a threshold of 7%). AGLA never fought publicly against the SMB Statin report. This cannot be tolerated.

Age	AGLA risk					
	1%	5%	10%	15%	20%	25%
Males						
40	39,514	4,518	1,088	-105	-748	-1,154
45	59,300	5,798	925	-466	-1,134	-1,542
50	88,152	8,291	890	-913	-1,652	-2,055
55	114,080	12,185	1,318	-1,297	-2,268	-2,714
60	157,037	18,288	2,694	-1,317	-2,832	-3,472
65	204,759	26,356	5,466	-580	-2,999	-4,115
70	274,366	38,398	10,214	1,565	-2,243	-4,208
75	381,012	59,023	19,420	6,692	677	-2,658
Females						
40	14,133	2,757	471	-722	-1,214	-1,573
45	21,095	3,023	383	-702	-1,320	-1,985
50	35,175	3,114	108	-1,009	-1,653	-2,075
55	61,885	4,348	-370	-1,584	-2,176	-2,563
60	91,027	7,992	-400	-2,322	-2,993	-3,327
65	139,794	15,349	1,200	-2,500	-3,811	-4,345
70	217,042	28,403	5,726	-907	-3,668	-4,963
75	344,412	51,832	16,038	4,660	-634	-3,512

A major issue reflects the AGLA correction factor of 0.7, which was derived from our observation in 100 patients having had a coronary calcium score in the year 2000 (https://cardiovascmed.ch/article/doi/cvm.2005.01103).

Thus, there is widespread certainty about the beneficial statin effects from 65, 70, and 75 years of age, but less direct evidence from randomized, placebo-controlled trials, which is why the Staree trial

is being conducted in Australia [56]. The Staree trial is studying 18,000 people aged 70 years or older. The efficacy of atorvastatin 40 mg versus placebo is double-blinded. The study continues to enrol individuals through the end of 2022 and the study will conclude in December 2023. The primary endpoint is death or dementia. Secondary endpoints (12 total) include myocardial infarction, stroke, dementia, and frailty. Included are all independently living individuals 70 years of age and older; excluded are individuals with known cardiovascular disease (myocardial infarction, stroke, PTCA, PAD, CABG), dementia, type II diabetes mellitus, cholesterol > 7.5 mmol/l, renal insufficiency, liver disease, life expectancy less than 5 years, participation in other studies, absolute contraindication to statins, current use of statins or refusal to discontinue statins, use of certain medications (long-term use of cytochrome P450 (CYP) 3A4 inhibitors.

Problematic STREAM Study design

The Stream Study [1] was designed with the following rationale: "Statins are among the most commonly used drugs. While they have been shown to be effective (efficacious) for primary and secondary prevention of cardiovascular disease (CVD) in middle-aged subjects, their utility (benefit) for primary prevention in older adults (aged ≥ 70 years) without CVD is uncertain, particularly in patients with multimorbidity. The aim of this randomized controlled trial (RCT) is to provide guidance on the benefits and risks of statin discontinuation in multimorbid older adults. "

The authors provide the following rationale for the stream study: "Background: to date, no RCT examining the benefits of statins in primary prevention has exclusively recruited multimorbid participants aged 70 years and older (70+), and participants over 70 are underrepresented in most RCTs, including those examining the benefits of statins in primary prevention. However, side effects of statins and drug interactions are common in populations of multimorbid older adults and may negatively impact quality of life. Observational studies have shown that the proportion of patients who develop myalgia on statins is 5-20%; older age and polypharmacy are known risk factors for developing muscle problems on statins. In addition, multimorbid older adults with polypharmacy are more likely to experience statin side effects (e.g., elevated liver enzymes, diabetes, myopathy, rhabdomyolysis) and drug interactions (e.g., antibiotics, antifungals), with the potential consequences of drug toxicity and decreased physical activity, sarcopenia, and falls. In practice, statins are often discontinued in multimorbid older adults without cardiovascular disease after adverse events. The net clinical benefit of statins for primary prevention in multimorbid older adults over 70 remains unclear, and the effect of multimorbidity may shift the evidence to favour no statin treatment, but no large RCT examined this issue."

Study Design: "The study is a multicentre, randomized, non-inferiority trial conducted at multiple centres in Switzerland. Study participants are randomly assigned in a 1:1 ratio to either interruption (intervention arm) or continuation (control arm) of statin therapy. The study is open-label, with

blinded outcome assessment. After inclusion, study participants are followed up by telephone initially at 3 months and then annually for an average of 24 months (min. follow-up period 12 months, max. follow-up period 48 months). Outcomes will be assessed at each study follow-up. "
Primary endpoints: "death from all causes and serious nonfatal cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke) within 24 months. The primary end point is a composite end point of all-cause death and serious nonfatal cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke). All-cause death (rather than just cardiovascular death) is chosen to account for a possible shift from cardiovascular causes of death to other causes of death. The composite end point was selected to assess net clinical benefit in this population with expected high mortality. The clinical events committee, which classifies suspected events for the primary and secondary clinical end points, is blinded. The primary analysis period is 24 months, and data collection will be conducted for up to 48 months."
Secondary endpoints: "Composite end point of death from any cause and serious nonfatal cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke) within 48 months. Composite endpoint of death from any cause and serious nonfatal cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke). Death from any cause [time frame: up to 48 months]. All deaths (from any cause). Non-CV death [time frame: up to 48 months]: All deaths except deaths due to major CV events. Major CV events [time frame: up to 48 months]. CV death, nonfatal myocardial infarction, and nonfatal ischemic stroke. Total CV events [time frame: up to 48 months]: CV death, nonfatal myocardial infarction, hospitalization for unstable angina, nonfatal ischemic stroke (including TIA), and arterial revascularization (coronary and peripheral urgent and nonurgent revascularization): Total composite events up to 48 months: death from any cause, nonfatal myocardial infarction, hospitalization for unstable angina, nonfatal ischemic stroke (including TIA), and arterial revascularization (coronary and peripheral urgent and nonurgent revascularization). EQ-5D questionnaire [time frames: 3, 12 (primary analysis), 24, 36, 48 months]. EQ-5D is the name of the instrument and not an acronym. General quality of life assessment. The possible range of scores is from 0 to 1.0, with higher scores indicating better quality of life. Verbal numeric pain rating score (VNPRS) 3 months. To assess statin-associated muscle symptoms. The VNPRS is an 11-point scale scored from 0-10, with higher scores indicating higher pain severity. Self-reported falls 12 months. Self-reported falls, each participant collects and lists all falls during the first 12 months after randomization. Circumstances and medical consequences of each fall are collected. Aggregated as fall rate (falls per person per year). Strength, assistance with walking, getting up from a chair, climbing stairs, and falls (SARC-F questionnaire) 12 (primary analysis), 24, 36, 48 months. 5-point questionnaire, scores range from 0 to 10, with higher scores indicating a higher degree of sarcopenia.

Girerd Medication Adherence Scale 12 (primary analysis), 24, 36, 48 months 6-point questionnaire, score ranges from 0 to 6, higher scores indicate poorer medication adherence."
Inclusion criteria: "Written informed consent. ≥70 years of age, multimorbid with ≥2 coexisting chronic conditions (defined by ICD-10 codes) with an estimated duration of 6 months or more based on clinical decision, apart from dyslipidemia treated with statins. Taking a statin for ≥80% of the time during the year before enrolment."
Exclusion criteria: "Cardiovascular secondary prevention based on previous large statin studies, defined as: History of type 1 myocardial infarction (NSTEMI/STEMI), or history of unstable angina defined as symptomatic ACS at rest, crescendo, or new-onset angina (CCS 2 or 3) without ECG or cardiac biomarker changes (based on available documents), or stable angina with documented ischemia on exercise testing or with significant coronary disease defined as coronary stenosis > 50%, or history of percutaneous coronary intervention (balloon or stent) or coronary artery bypass grafting, or history of stroke, or history of transient ischemic attack, defined as transient neurologic deficit without diffusion restriction on MRI, or history of carotid revascularization (stent or bypass), or history of peripheral arterial disease requiring revascularization (stent or bypass; Fontaine IV) or aortic disease requiring vascular repair or aortic aneurysm with a maximum diameter of >5.5 cm (men) or >5.2 cm (women) based on available documents, diagnosis of familial hypercholesterolemia based on Dutch Lipid Score ≥6 based on available documents (LDL cholesterol, family history, personal history), increased risk of death within 3 months of study entry defined as: Hospitalized patients scheduled for palliative care within 24 hours of admission or hospitalized patients with a Palliative Performance Scale (PPS) level <30% (based on situation at least 1 month prior to hospitalization), corresponding to an estimated survival rate of 43% at 3 months; or patients with an advanced metastatic cancer prognosis of ≤20% survival within 1 year of baseline (based on: https://cancersurvivalrates.com)"
The safety and health of affected study participants are at risk in the Stream Study. Medical evidence on the effectiveness of lipid therapy, especially with statins, has also been established for persons 70 years of age and older. The authors' mention of uncertainty in statin effects in persons 70 years of age and older is a misstatement. There is less certainty than in persons younger than 70 years, but no uncertainty. Moreover, the Federal Office of Public Health has established the cost-effectiveness of statins up to age 75.
Criticisms of the stream study authors regarding the study design:
Justification: The efficacy of statins is admitted but described as uncertain at age 70 and older; it should read, less certain. Instead of effect, the term benefit is used without justification for this change in terminology.

Background: The mentioned reasons do not justify a further study. Already in clinical practice all limitations of statin treatment are considered.

Study design: this is incorrectly chosen. A non-inferiority study cannot exclude a missing effect, for this the study design of the Staree study is used with approx. 80'000 patient observation years (stream: approx. 1800). Non-inferiority studies are always conducted with an active comparator for ethical reasons, since the effect of the comparator drug is proven. [57]. Placebo studies or even discontinuation of effective drugs is therefore not permitted in non-inferiority trials. The European Medicines Agency clearly defines: "The objective of a non-inferiority trial is sometimes stated as being to demonstrate that the test product is not inferior to the comparator. However, only a superiority trial can demonstrate this. " [58].

Primary endpoints: the study design does not allow to investigate the effect of statins. The years of observation are chosen far too low.

Secondary endpoints: the open-label study design does not allow conclusions on most secondary endpoints, especially quality of life, pain assessment, strength, drug adherence. For this, e.g., N-1 studies are needed [59].

Inclusion Criteria: Multimorbidity increases the risk for the presence of preclinical atherosclerosis and the risk for fatal and nonfatal heart and stroke, eg. concerning combinations with diabetes mellitus type II, inflammatory rheumatic diseases, renal insufficiency, nicotine or e-cigarette habit, elevated CRP, obesity, arthrosis and other diseases with physical inactivity, arterial hypertension, Dutch Lipid Score 3 to 5, familial hypercholesterolemia is possible (e.g., positive family history and LDL 5.0 mmol/l = 5 points).

Exclusion criteria: In the Staree study, diabetes mellitus type II, renal insufficiency, or cholesterol > 7.5 mmol/l are exclusion criteria. The Stream study, due to the multimorbidity criterion, includes numerous individuals with high cardiovascular risk including cholesterol > 7.5 mmol/l. Therefore, further exclusion criteria are required, e.g., presence of subclinical atherosclerosis on imaging [60]in agreement with Mortensen [61]. Also, there is no recommendation worldwide to discontinue or not to use statins after 70 years of age. The reason for this is the number of expected years of life. If this is more than 5 years, there is a consensus to use statins. [62].

Informed consent form (ICF).

Based on the scientific misrepresentation of statin efficacy in persons 70 years of age and older by the authors of the Stream study, it must be assumed that the information in the ICF is incorrect or that facts are distorted in such a way that the risk to the study participants is under-recognized or not recognized at all by them.

The Stream study of the Bern Institute of Family Medicine invites physicians to ask patients aged 70 and older who have been prescribed a cholesterol-lowering statin whether they would be willing to

discontinue it for study purposes. If they agree, a computer program will randomly decide which half of them will continue to receive the prescribed drug and which will not. After 12 to 45 months, the aim is to see whether more heart attacks and strokes actually occur in the group that has discontinued the treatment.

The Bern Institute of Family Medicine informs study participants about the risks of participating in the study as follows: "Cholesterol levels will increase. However, it has not been proven that elevated cholesterol is a risk factor for heart attack/stroke in 70+ individuals who have never experienced such a disease. " This is a false statement based on the available evidence [63].

And further: "A heart attack/stroke can occur despite statin/low cholesterol. "With such a statement, the positive effect is deliberately talked down. Such misleading statements exploit the uncertainties of senior citizens, a further violation of the Nuremberg Code:

- Point one of the Nuremberg Code states: "The voluntary consent of the subject is absolutely necessary. This means that the subject must be capable, in the legal sense, of giving consent; that he must be able, uninfluenced by force, fraud, trickery, pressure, pretense, or any other form of persuasion or coercion, to exercise his judgment; that he must have sufficient knowledge and understanding of the field in question in its details to be able to make an understanding and informed decision. "

The study admits risks on its website (https://www.statin-stream.ch/infos-fuer-teilnehmer/): "However, it cannot be excluded that stopping statin therapy could increase the risk of heart attack or stroke ..." In the discussion with the patients like it an example film (https://www.youtube.com/watch?v=UYBw1LapqS0&t=1s) shows, however, then one-sidedly one informs and suggestively one asks, with which the seniors could be manipulated. Therefore, the question arises whether treating physicians are allowed to conduct these conversations or whether, against the above background, this should not be reserved for scientific employees, since the conversations themselves are part of the study:

- Point eight of the Nuremberg Code states: "The experiment may only be carried out by scientifically qualified persons. The greatest skill and caution shall be required at all stages of the experiment by those conducting or performing the experiment. "

Conclusion

Based on our base-case analysis, cost-effectiveness calculations, the investigator file and patient information file analysis of the STREAM Trial, only patients with a 1) life-expectancy of 2 years or less, 2) informed doctors who despite the evidence are willing to deprescribe their statins against all evidence, and 3) patients without coronary calcifications should be included in the study.

The investigator file and patient information file are inaccurate. Due to selective reporting, underreporting, false reporting, or non-reporting of available scientific evidence it can be assumed that this allowed authors to achieve ethical approval for the STREAM trial and funding by the national fund.

The study most likely does not allow to increase knowledge about deprescribing statins in various subsets of patients and most questions addressed by the STREAM trial have already been answered or will be answered soon [64].

The study design should be corrected and the study should be stopped, until safety measures have been undertaken to exclude statistically significant excess risk for fatal or non-fatal cardiovascular events. Patients should be informed about our report regarding excess risk of deprescribing statins and associated losses of return on investment. Results from Ca-Scoring should be unblinded immediately and those with CAC>100 should immediately restart their statin medication.
Finally, patients should be informed about financial interests of referring physicians, not included in the patient information files (v2-2-22mar2022-waidspital-clean.pdf).

Appendix

Sensitivity Analysis (4- and 5-years duration of the Stream Trial)

Table 2: Difference in outcome and return on investment without deprescribing statins over 4 years. Calculations are based on SCORE2/-OP risk estimates.

Stream Base Case Scenarios	Patients	VSLY	Years	Deprescribing with CAC			Deprescribing, no CAC		
Effects of statin deprescription per treatment arm	900	237 468	8	CAC= 300			CAC = 0		
Age	**60**	**70**	**74**	**60**	**70**	**74**	**60**	**70**	**74**
Sex (1=male)	1	1	1	1	1	1	1	1	1
Smoke (1=active smoker)	1	1	1	1	1	1	1	1	1
BP	130	130	130	130	130	130	130	130	130
Chol	6	4	6	6	4	6	6	4	6
HDL	1	1	1	1	1	1	1	1	1
LDL	3,8	1,8	3,8	3,8	1,8	3,8	3,8	1,8	3,8
SCORE2/-OP	9,6	15,6	19,0	29	41,7	40,3	2,1	3,7	4,6
SCORE2/-OP with Statin	7,8	13,8	15,6	24,5	37,8	34,7	1,7	3,1	3,7
RRR	18,75	11,54	17,89	15,52	9,35	13,90	19,05	16,22	19,57
ARR	1,8	1,8	3,4	4,5	3,9	5,6	0,4	0,6	0,9
NNT	56	56		22	26		250	167	111
NNH Statin Stop			29			18			111
No events	884	884	869	860	865	850	896	895	892
Events	16	16	31	41	35	50	4	5	8
Non Fatal Events	13	13	25	33	29	41	3	4	7
Fatal Events	3	3	6	7	6	9	1	1	1
Life years lost			45			73			12
VSLY Fr			237468			237468			237468
ROI in Mio SFr over 7 years with Statin			10,6			17,4			2,8
Event Treatment Cost first of 7 years			25000			25000			25000
Event Treatment Cost year 2-7			48000			48000			48000
Cost of survived non-fatal event 7 years			73000			73000			73000
Cost total of non-fatal event 7 years			1,8			3,0			0,5
Statin and Lab costs 470/y/pp			1,69			1,69			1,69
ROI Total Mio Fr. with Statin			10,7			18,7			1,6
CHI 2 (for N=1800)			**3,7**			**6,162**			**0.901**
p=			**0,0533**			**0,0131**			**0,3432**

In 1800 Patients	https://kardiolab.ch/riskcalc_JSI.html		
Events no Statin	171	363	41
No Events, no Statin	729	537	859
Events with Statin	140	312	33
No events, with Statin	760	588	867

Table 3: Difference in outcome and return on investment without deprescribing statins over 5 years. Calculations are based on SCORE2/-OP risk estimates.

Stream Base Case Scenarios Effects of statin deprescription per treatment arm	Patients 900	VSLY 237 468	Years 7	Deprescribing with CAC CAC= 300			Deprescribing, no CAC CAC = 0		
Age	**60**	**70**	**75**	**60**	**70**	**75**	**60**	**70**	**75**
Sex (1=male)	1	1	1	1	1	1	1	1	1
Smoke (1=active smoker)	1	1	1	1	1	1	1	1	1
BP	130	130	130	130	130	130	130	130	130
Chol	6	4	6	6	4	6	6	4	6
HDL	1	1	1	1	1	1	1	1	1
LDL	3,8	1,8	3,8	3,8	1,8	3,8	3,8	1,8	3,8
SCORE2/-OP	9,6	15,6	19,9	29	41,7	49	2,1	3,7	4,9
SCORE2/-OP with Statin	7,8	13,8	16,1	24,5	37,8	42,5	1,7	3,1	3,8
RRR	18,75	11,54	19,10	15,52	9,35	13,27	19,05	16,22	22,45
ARR	1,8	1,8	3,8	4,5	3,9	6,5	0,4	0,6	1,1
NNT	56	56		22	26		250	167	91
NNH Statin Stop			26			15			91
No events	884	884	866	860	865	842	896	895	890
Events	16	16	34	41	35	59	4	5	10
Non Fatal Events	13	13	28	33	29	48	3	4	8
Fatal Events	3	3	6	7	6	11	1	1	2
Life years lost			44			74			13
VSLY Fr			237468			237468			237468
ROI in Mio SFr over 7 years with Statin			10,3			17,7			3,0
Event Treatment Cost first of 7 years			25000			25000			25000
Event Treatment Cost year 2-7			48000			48000			48000
Cost of survived non-fatal event 7 years			73000			73000			73000
Cost total of non-fatal event 7 years			2,0			3,5			0,6
Statin and Lab costs 470/y/pp			2,12			2,12			2,12
ROI Total Mio Fr. with Statin			10,3			19,1			1,5
CHI 2 (for N=1800)			**4,3**			**7,641**			**1,339**
p=			**0,037**			**0,0057**			**0,2471**

In 1800 Patients	https://kardiolab.ch/riskcalc_JSI.html		
Events no Statin	179	441	44
No Events, no Statin	721	459	856
Events with Statin	145	383	34
No events, with Statin	755	518	866

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