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Advertisements Press Council / SwissMedic

Olten, 08.08.2022 - final version

Dear Ladies and Gentlemen

Due to multiple misstatements regarding the facts concerning effects and side effects of cholesterol-lowering drugs and in particular regarding the facts concerning statins in print media and on SRF Puls, I feel compelled to file specific reports with the Swiss Press Council and SwissMedic and ask the institutions / authorities to address my concerns.

The content of the advertisement is listed below. The justifications for the reports are addressed to the Press Council in the form of objections and to SwissMedic in the form of reports.

My explanations are deliberately detailed and extensive as far as possible to ensure that the subject matter is dealt with as professionally as possible.

With kind regards

Michel Romanens

Copy: Ethics Committee Canton Bern

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View

(1) Swiss Press Council:

Complaints:

Subject: https://www.tagesanzeiger.ch/wir-wissen-nicht-wie-gross-der-nutzen-bei-aelteren-menschen-ist-840587827178

This interview by Ms. Frei with Prof. Rodondi gives rise to the following objections:

Violations of the statement of the Press Council:

Violation of Art. 1: Ms. Frei has not adhered to the truth.

Violation of Art. 3: Ms. Frei has concealed important information

Violations of the guidelines of the Press Council:

Violation Guideline 1.1: Truth Search

Violation Guideline 2.2: Pluralism of Opinion

Violation Guideline 2.3: Separation of facts and commentary

Demand:

According to Art. 5 of the Press Council Declaration, statements in the Sunday newspaper that do not correspond to the truth and the facts must be corrected.

(2) SwissMedic:

Message 1

Smarter Medicine Recommendation No. 1, 2021, on discontinuation of statins after cardiovascular events, particularly after myocardial infarction, places such individuals at unnecessary risk and should be sanctioned by authority [1]. Legal Opinion of Prof. Kieser [2].

Message 2

The stream study patient statements contain statements that jeopardize the safety of the individuals involved and misleadingly disinform them [3].

Misinformation: The central misstatement in patient recruitment is that there is too little evidence that statins over 70 are sufficiently effective. It should read: there is less evidence. The existing evidence does not show a reduction in statin effects compared to younger individuals. People who are supposed to participate in the study are thus being lied to.

Incorrect patient information is misleading: When deprescribing statins after 70, LDL rises again to the baseline value. It is false that LDL cholesterol is a negligible risk factor after 70. It is also suppressed that with statins compared to placebo in randomized trials the risk of myocardial infarction is reduced by about 40% and the risk of stroke by about 25%. The clip

was deleted from Youtube by Nicolas Rodondi on 6/23/2022. Therefore, here is the direct link to the video of the stream study: https://www.statin-stream.ch/infos-fuer-teilnehmer/

Message 3

May 2017 on the broadcast of May 8, 2017, our submission (link) and associated report of the Ombudsman's Office. The statements in this broadcast about the risk for cardiovascular events are highly misleading. Prof. Rodondi tells us in this video excerpt from the May 08, 2017 Pulse broadcast that without smoking, patient Harry Roos' cardiovascular risk in 10 years is low at 6% (direct link to video with new time stamp 12:15). This is only the risk for myocardial infarction, the risk for stroke and other diseases common in smokers (PAVK, aortic aneurysm ecc) has been suppressed, and the patient Harry Roos thus feels in false security. Thus a label swindle is operated here. Corresponding legal opinion of Prof. Kieser [4]. Furthermore, the risk of 6% is reached only after years, and the immediate stress of stopping nicotine even increases the cardiovascular risk in the short term, one more reason to use a statin as a protective measure - at least temporarily. The discussion of possible endpoints is also of enormous importance [5,6]: the risk of myocardial infarction must be multiplied by 4 to reflect cardiovascular events (including stroke, PAVK, coronary artery revascularization). ASCVD accounts for slightly more than half of all preventable first-time cardiovascular events and first- and repeat events in contemporary practice. Estimating more comprehensive CVD end points can improve risk discussions with patients and facilitate decision making. Why all these important points were left out of the risk discussion with Harry Roos and Prof Rodondi remains unclear. The explanation could be that it was only a matter of not prescribing a statin. Questions arise about the honesty of the SRF Pulse program of May 08, 2017.

Message 4

The interview article by Ms. Frei with Prof. Rodondi misrepresents the effect of statins and cholesterol-lowering drugs in old age and thus endangers the health of numerous people who take statins. There is a risk that statins and other cholesterol-lowering drugs will be discontinued because of Prof. Rodondi's misleading statements, with corresponding health consequences. SwissMedic is requested to demand a correction from the Sonntagszeitung if the contents are not correctly presented in a second article [7] (in analogy to a dangerous article of the Health Tip).

Background to the ads:

With the medical success of statins, critics have followed. In particular, Prof. Michel de Lorgeril scandalized the use of statins by pointing out that cholesterol is indispensable for the functioning of the body and that lowering cholesterol is therefore life-threatening, as can be seen from a report on French television [8]. Whoever does not like to follow him in his selective

logic, is gladly called an idiot. [9]. In German-speaking Switzerland, reports about controversial cholesterol-lowering drugs led to uncertainty among the population, in particular an earlier report on Swiss television [10] and an article in the Sonntagspresse (Cholesterol-lowering drugs are not for healthy people[11]). But also in the professional training of the University of Basel (MedArt 2011 [12]) Prof. Beat Müller expressed himself negatively about statins: "We make asymptomatic people dependent on tablets or "sick" ...otherwise only "drug dealers" do that and: People, do YOU want to live forever?". So here doctors who follow the guidelines of international medical societies are turned into drug dealers, and the question whether one wants to live forever implies the efficacy of statins, but here the author seems to have meant the costs of statins, costs which should rather be used more wisely elsewhere. This utilitarian attitude finally culminates in the statin report of the Swiss Medical Board, according to which statin costs of 210,000 Swiss francs can be expected for the maintenance of quality of life over one year. However, this statement is based on a calculation error that the VARIFO foundation has uncovered and published several times [13–15]. The SMB report also exaggerated side effects and minimized effects, which led law professor Brigitte Tag to identify criminal law problems in prescribing statins to healthy people. [14,16]. The Swiss Ethics and Medicine Association (VEMS) has published a counterstatement on this issue, which reveals the problematic views on statin issues of the legal expert.[16]. Regarding side effects of statins, the public is misinformed. The USPSTF meta-analysis showed that statins are not problematic with regard to muscle disorders, diabetes, kidney failure, liver damage, cancer, and stunting, in that such problems occurred with equal frequency compared to placebo. [17]which is supported by the Cochrane meta-analysis [18] and CTT meta-analysis [19] was confirmed. The fact that concerted criticism of statins persists despite a scientifically clear situation is medically incomprehensible. The opponents of cholesterol argue as follows: first, the importance of cholesterol for the organism is exaggerated, then it is doubted that atherosclerosis is triggered by cholesterol, advanced stages of arteriosclerosis, which can hardly be influenced by statins, are confused with atherosclerosis, which can be treated and even reversed the earlier the more efficiently. [20–22]then observational studies are mentioned which have long since been disproved, or the controlled randomized trials are presented as falsifications, or selectively those are cited in which cholesterol lowering actually had no effect, e.g. in advanced renal impairment, where atherosclerosis, which is treatable by statins, has been converted into atherosclerosis (essentially by the calcification and stiffening of the arteries by hydroxyapatite). The systematic and aggressive confounding by the cholesterol opponents has resulted in about one-third of cardiologists and about half of primary care physicians believing the cholesterol opponents, at least in part. If the cholesterol opponents were followed consistently, statins would have to be discontinued even after a heart attack, which fits the smarter medicine recommendation that is objected to here.

Despite the scientifically clear evidence that statins should also be used in "healthy people" according to current guidelines, SRF PULS portrays a 65-year-old man (Mr. Roos) on May 08, 2017, who has been a smoker for 45 years and has an LDL of 3.5 mmol/l. This man has an AGLA risk of 14.5% and a risk of death according to SCORE of 7.8%. In this clinically clear situation, statin prevention with a target LDL of 1.8 mmol/l is reasonable, since it can be assumed that the man is not healthy but has advanced atherosclerosis. In the broadcast, the use of statins was recommended by 2 experts (Prof. Lüscher, Prof. Von Eckardstein), a third expert (Prof. Rodondi) said that the man should stop smoking, then his risk would be low (6%). Furthermore, the 6% risk is reached only after years and the immediate stress of nicotine cessation increases cardiovascular risk in the short term, one more reason to use a statin as a protective measure - at least temporarily. The discussion of possible endpoints is also of enormous importance [5,6]: the risk of myocardial infarction must be multiplied by 4 to reflect cardiovascular events (including stroke, PAVK, coronary artery revascularization). ASCVD accounts for slightly more than half of all preventable first-time cardiovascular events and first- and repeat events in contemporary practice. Estimating more comprehensive CVD end points can improve risk discussions with patients and facilitate decision making. Why all these important points were left out of the risk discussion with Harry Roos and Prof Rodondi, remains unclear. The explanation could be that it was only a matter of not prescribing a statin. Questions arise about the honesty of the SRF Pulse program of May 08, 2017. Furthermore, a fourth expert is quoted (Prof. Pascal Meier), who as a Cochrane collaborator was diametrically opposed to the evidence of the own Cochrane Collaboration [18]. SRF-PULS further conflates coronary heart disease (CHD) risk with cardiovascular risk (CVD), according to which CHD may still be moderately elevated, whereas CVD risk, which also includes stroke and bypass or PTCA coronary intervention, may already be high. The AGLA risk must be multiplied by 4 to estimate the CVD risk [5]. Thus, in the above patient (Mr. Roos), instead of 14.5% risk in 10 years for myocardial infarction only, new 58% for cardiovascular disease and an NNT of < 10 in 10 years with achieved target LDL (1.0 mmol/l).

Impact of Statin Criticism In 2016, the effect of hypercritical media coverage of statins was observed and found that, in particular, individuals taking statins for primary and secondary prevention had discontinued them in 12% of cases; the authors expect this to result in 2,000 preventable cardiovascular events over a 10-year period [23]. A second study from Denmark also found an association between negative statin reports and increased incidence of death and myocardial infarction [24] . This implicitly raises the question of the responsibility of the media and the SMB in reporting medical evidence, which is presented in a distorted way. In any case, the VEMS has so far been unable to persuade the SMB to withdraw the statin report. On the part of the media, a responsible commentary recently appeared [25] on a one-sided statin report on the state broadcaster Arte: the big cholesterol bluff [26]. How many

thousands of lives could be saved each year in Switzerland with statins, if GPs would use statins more consistently, is not known.

Against this background, the interview of Martina Frei with Prof. Rodondi fits seamlessly into the renewed narration of the cholesterol lie: On 12/07/2022, I received an email from Ms. Martina Frei requesting more information about my "veto" regarding the stream study. A telephone meeting took place at 3:31 pm for 58 minutes. In this meeting, a detailed briefing was given by Ms. Frei. Subsequently, on 07/17/2022, Ms. Frei published an interview with Prof. Rodondi regarding the stream study. On 07/12/2022, 16:08, Ms. Frei received another link to a paper from the e-journal of the European Heart Society [27], at 16:49 still the following information: "Here is still the compilation of statin effects in the elderly: https://varifo.ch/statin-effekte/. On our page https://varifo.ch all further information is available: https://varifo.ch/smarter-medicine/ with subpages. On carotid imaging and consequent reassessment of risk, our cohort study, including Prof. Th. Szucs, VRP Helsana. https://www.sciencedirect.com/science/article/abs/pii/S0091743521001092". On 07/13/2022, 08:00 more information via email: "I am still sending you the work of Mortensen on "negative risk factors" and how those could be helpful in deprescribing statins [28,29]. This safety barrier is missing in the Stream study, so you can blithely leave people 70 and older with advanced atherosclerosis to their fate unprotected [30]. From my point of view a "no got", red line!

After the interview appeared, another email on 07/18/2022, 11:11: "Here are links to diet and statins, the opposite of Prof. Rodondi's claim: https://www.sciencedirect.com/science/article/abs/pii/S0167527318338191, https://pubmed.ncbi.nlm.nih.gov/12394655/".

Factual situation about the interview:

Ms. Frei received all relevant information in the telephone briefing as well as by e-mail in order to inform herself about the facts regarding cholesterol treatment in elderly persons. The following are the truthful corrections to the statements made in the interview. The information is consistent with the submission to the Cantonal Ethics Committee [31]. The result shows that Ms. Frei published a courtesy and advertising interview for Prof. Rodondi by misappropriating scientific facts known to her and made available by me, which does not truthfully inform persons over 70 and does not separate the facts from the partly false scientific comments of Prof. Rodondi. Ms. Frei is a physician with training in public health and quite capable of publishing critical articles meticulously researched, e.g. especially also medicine-critical on Infosperber. [32]. Ms. Frei was also informed that Prof. Rodondi sometimes changes facts in order not to have to recommend statins to the public. [33,34].

Global evidence base on lipid-lowering agents 65 years and older:

Observational studies of >1.6 million elderly patients show a 46% reduction in all-cause mortality (95%CI: 37%-54%): [35]

Background: Evidence on the use of statins for primary prevention of cardiovascular disease (CVD) in the elderly needs to be expanded and updated to provide further guidance for clinical practice. METHODS: PubMed, EMBASE, Cochrane Library, and Web of Science were searched for eligible observational studies comparing statin use with nonstatin use for primary prevention of CVD in the elderly (age ≥65 years). The primary end points were all-cause mortality, CVD mortality, coronary heart disease (CHD)/myocardial infarction (MI), stroke, and all CV events. Risk estimates for each relevant outcome were synthesized as hazard ratios (HR) with 95% confidence intervals (95% CI) using a random-effects model. Results: Twelve eligible observational studies (n = 1,627,434) were included.
Pooled results suggest that statin use was associated with a significantly reduced risk of all-cause mortality (HR: 0.54, 95% CI: 0.46-0.63), CVD mortality (HR: 0.51, 95% CI: 0.39-0.65), CHD/MI (HR: 0.83, 95% CI: 0.69-1.00), stroke (HR: 0.79, 95% CI: 0.68-0.92), and total cardiovascular events (HR: 0.75, 95% CI: 0.66-0.85). The association with all-cause mortality remained at older ages (≥70 years, HR: 0.56, 95% CI: 0.44-0.71; ≥75 years, HR: 0.70, 95% CI: 0.60-0.80; ≥85 years, HR: 0.85, 95% CI: 0.74-0.97), ≥20% (HR: 0.47, 95% CI: 0.35-0.62) and <20% diabetic (HR: 0.50, 95% CI: 0.40-0.64), and ≥50% (HR: 0.68, 95% CI: 0.59-0.79) and <50% hypertensive (HR: 0.38, 95% CI: 0.16-0.88). Conclusions: Statin use was associated with a 46%, 49%, 17%, 21%, and 25% reduction in the risk of all-cause mortality, CVD mortality, CHD/MI, stroke, and CV events overall in elderly patients, respectively. A significant association was also observed in elderly patients and in individuals aged ≥75 years for primary prevention of cardiovascular disease.

Comment on the Ramos study [36]: this observational study has numerous weaknesses and may need to be revised. In particular, the propensity score matching is unsatisfactory, and the hazard ratios for all-cause mortality derived from it need to be questioned, as has apparently been done in the recent work by Huang [35]. According to Forrest plot B of hazard ratios (Fig. 2) in this paper, the reduction in all-cause mortality thanks to statins in the elderly without the Ramos study remains highly significant. The multivariable hazard ratios (HRs) obtained from Cox hazard regression analysis and the corresponding 95% confidence intervals (95% CIs) for the outcomes of interest were estimated mainly with the DerSimonian-Laird (D-L) random-effects model, because the associated assumptions take into account the presence of heterogeneity within and between studies. To obtain the most comprehensive results, the results of both the fixed-effects and random-effects models were presented in the

Forrest plots. Adjusted relative risk (RR) and odds ratio (OR) in the primary studies were considered approximate HR.

Placebo-controlled randomized trials of approximately 25,000 elderly patients show a 39% reduction in cardiovascular events for myocardial infarction and a 24% reduction for stroke in the short term: [37]

This study investigated whether statins reduce all-cause mortality and cardiovascular events in older people without established cardiovascular disease.

Due to population aging, prevention of cardiovascular disease in the elderly is of great importance. In elderly patients with previous cardiovascular events, the use of statins is recommended in guidelines, whereas the effect of these drugs in elderly people without previous cardiovascular events is still controversial.

Included were randomized trials comparing statins with placebo and examining all-cause mortality, mortality from myocardial infarction, stroke, and new-onset cancer in the elderly (age ≥65 years) without established cardiovascular disease.

Eight studies with 24,674 subjects (42.7% women; mean age, 73.0 years; mean follow-up, 3.5 years) were included in the analysis. Statins significantly reduced the risk of myocardial infarction by 39.4% (relative risk [RR]: 0.606 [95% confidence interval (CI): 0.434 to 0.847]; p = 0.003) and the risk of stroke by 23.8% (RR: 0.762 [95% CI: 0.626 to 0.926]; p = 0.006) compared with placebo. In contrast, the risk of all-cause death (RR: 0.941 [95% CI: 0.856 to 1.035]; p = 0.210) and death from cardiovascular disease (RR: 0.907 [95% CI: 0.686 to 1.199]; p = 0.493) was not significantly reduced. The incidence of new cancers did not differ between statin- and placebo-treated subjects (RR: 0.989 [95% CI: 0.851 to 1.151]; p = 0.890).

In older people at high cardiovascular risk without established cardiovascular disease, statins significantly reduce the incidence of MI and stroke but do not significantly prolong *short-term* survival.

LDL cholesterol is the most important risk factor in old age [38,39]:

Myocardial Infarction: Relative risks for BMI decreased with age and were significantly (P<0.05) associated with the occurrence of myocardial infarction only when measured at ages 50 and 60 years. The relative risks for systolic blood pressure and smoking also decreased with age, but in these cases, a significant association was found in all examinations up to age 77 years. In contrast, the relative risks for LDL cholesterol tended to increase with age and were highly significant even at age 82.

Cerebral Stroke: When the relative risks for the traditional risk factors were calculated separately for measurements at ages 50, 60, 70, 77, and 82 years, they decreased with age for hypertension, fasting glucose, and smoking, and were significant for hypertension in all age groups up to 77 years, whereas glucose and smoking were significant only at ages 50 and 60 years. The influence of HDL and LDL cholesterol, on the other hand, tended to increase over time and was significantly associated with the occurrence of ischemic stroke at ages 77 and 82 years.

Mendelian Randomization Study [39]:

Background: Observational studies in the elderly have shown no or an inverse association between cholesterol levels and mortality. However, in the elderly, plasma levels of low-density lipoprotein (LDL-C) may not reflect lifetime levels because of reverse causality, and risk may be underestimated. In the current study, we used a genetic LDL risk score (GRS) to address this issue. METHODS: Using 51 single nucleotide polymorphisms associated with LDL-C levels, a weighted GRS was generated. The LDL-GRS was calculated in three Dutch cohorts: the Leiden Longevity Study (LLS) (n=3270), the Leiden 85-plus Study (n=316), and the Rotterdam Study (n=4035). We examined the association between LDL-GRS and LDL-C levels, chronological age, familial longevity, and mortality. Results: By age 90 years, individuals with high LDL GRS had higher LDL-C levels in each age stratum (P=0.010 to $P=1.1 \times 10^{-16}$). The frequency of LDL-increasing alleles decreased with age [β=-0.021 (SE=0.01) per year, P=0.018]. In addition, individuals with a genetic predisposition to longevity had significantly lower LDL GRS compared with age-matched individuals in the general population [LLS nonagenarians vs >90 years: β=0.73 (SE¼0.33), P=0.029, LLS offspring vs partners: β=0.66 (SE=0.23), P=0.005]. In the longitudinal analysis, high GRS was associated with increased all-cause mortality in persons older than 90 years, with a 13% increased risk in persons with the highest LDL GRS (P trend=0.043). CONCLUSION: The results of the current study suggest that a genetic predisposition to high LDL-C levels contributes to mortality throughout life, including in the elderly, and that a favorable LDL genetic risk profile is associated with familial longevity.

Studies with publication in the next few years

Staree study with 18,000 subjects, end of study December 2023. [40]:

Intervention: atorvastatin 40 mg versus placebo.

Place of implementation: Australia

Primary outcome measures: (1) to death or development of dementia (measured by cognitive function tests) or development of disability (measured by the KATZ ADL test) or (2) to a serious fatal or nonfatal cardiovascular event.

Secondary outcome measures: Cardiovascular death, fatal and nonfatal myocardial infarction, hospitalizations with reasons for hospitalization and length of stay, new-onset diabetes, fatal and nonfatal cancer, cognitive decline, cost-effectiveness of statin, fatal and nonfatal stroke, approved need for permanent inpatient care, dementia of all causes, frailty/disability.

Inclusion criteria: (1) men and women aged ≥70 years who (2) live independently in the community and (3) are willing and able to give informed consent and accept the study requirements.

Exclusion criteria: (1) history of cardiovascular disease (defined as myocardial infarction, stroke, peripheral vascular disease, angina, transient ischemic attack, coronary artery angioplasty and/or stenting, coronary artery bypass grafting, or heart failure), (2) history of dementia or a 3MS score <78 at screening, (3) history of diabetes, (4) total cholesterol >7.5 mmol/L, (5) moderate or severe chronic kidney disease (persistent proteinuria (urine albumin: Creatinine ratio >30mg/mmol or urine protein: Creatinine ratio >45 mg/mmol)45 and/or eGFR <45ml/min/1.73m^2), (6) Moderate or severe liver disease (persistent elevation of transaminases more than three times the upper limit of the normal laboratory reference range), (7) Severe intercurrent disease likely to result in death within the next 5 years, such as terminal cancer or obstructive airway disease, (8) Current participation in a clinical trial (Note: If yes, this is only a reason for exclusion if the other study involves taking a drug or other intervention), (9) Absolute contraindication to statin therapy, (10) Current use of statin therapy or other lipid-lowering therapy for primary prevention and unwillingness to discontinue therapy, (11) Current long-term or sustained use of the following cytochrome P450 (CYP) 3A4 inhibitors: Amiodarone, boceprevir, cimetidine, cyclosporine, danazol, fosamprenavir, indinavir, lopinavir + ritonavir, erythromycin, fluconazole, itraconazole, ketoconazole.

Preventable study with 20,000 subjects, end of study December 2026. [41]:

Place of implementation: USA

In the PREVENTABLE study, 20,000 community-dwelling adults aged 75 years or older without clinically apparent cardiovascular disease, significant disability, or dementia will be randomized to receive 40 mg of atorvastatin daily or matching placebo and followed for up to 5 years (estimated median 3.8 years). The study will recruit participants from approximately 100 U.S. sites. Community groups and physician practices will be used as partners in recruiting participants. We plan to collaborate with participants, caregivers, and clinicians in all aspects of the study. Participating facilities will be non-Veteran Affairs and Veteran Affairs facilities. Each site will apply a study-specific cohort identification algorithm to its electronic health record to generate a list of eligible participants based on the study's inclusion and exclusion criteria. Cohort identification will exclude individuals with clinically apparent

cardiovascular disease, significant disability, or dementia, as well as other exclusions resulting from data queries, to define a potential cohort. Sites will screen potential participants to confirm eligibility and consent and randomize those interested in participating in the study. Specific to dementia, the qualifying exclusion is a clinical diagnosis in the medical record or a physician's assessment that dementia may be present. Institutions enter contact information, mailing address for study drug, demographic information, height, weight, statin history (if available), Social Security number, and aspects of medical history that cannot be obtained from the electronic medical record. In addition, a brief physical performance assessment (SPPB) and an on-site activities of daily living (ADL) assessment will be conducted at baseline. The SPPB will provide an objective assessment of function to understand the frailty and physical function of the participating population. The baseline lipid panel (core laboratory) and biospecimens will be obtained through the same blood collection (20 ml). Blinded lipid testing will be performed in all participants (n=20,000) at baseline and repeated after 3 months in a random subset (n=2,000). Lipid panels will be sent to the PREVENTABLE Core Lab to ensure blinding of the study. Future testing of lipid panels as part of routine clinical care will be actively discouraged, but other laboratory testing indicated as part of clinical care will be permitted. Baseline SPPB and biorepository labs are not required but are encouraged.

As part of the study operation, follow-up will be conducted by a combination of centralized and decentralized research teams to focus on the patient, facilitate participation, and facilitate access for vulnerable participants. This includes a call center and a nationwide system of decentralized research staff who are trained in the protocol and can meet patients at home or other desired location. Centrally administered baseline and annual assessments include a telephone assessment of cognitive function (TICS-M) and physical function (Patient-reported Outcome Measurement Information System-Physical Function [PROMIS-PF]). After the first year, in-person assessments by trained and certified research staff at a mutually agreed-upon time and a standardized interview with a knowledgeable informant will be conducted if pre-specified thresholds are exceeded. Cardiovascular events will be recorded using a systematic approach to obtaining data from the electronic medical record, Medicare, and the National Death Index. For convenience and compliance, the study pharmacy will ship a 90-day supply of study medications directly to participants. This shipment will begin immediately after randomization and will continue as long as the participant is taking the study drug.

SITE study with 1'230 persons, end of study December 2023 [42]:

Place of implementation: Bordeaux (F)

Statins in primary prevention are associated with a 1.2% reduced absolute risk of cardiovascular events in large randomized trials. However, in patients ≥ 75 years of age, the effect of statins on mortality has not been demonstrated, and large observational studies have shown an increased risk of mortality in people with low cholesterol. In addition, statins are associated with numerous side effects, particularly in the elderly, including myalgia and myositis, diabetes, cognitive impairment, fatigue and loss of energy and physical activity, and treatment interactions. Finally, the cost of statins to French health insurance is €800 million per year (of which about €200 million for people ≥ 75 years).

The risk-benefit ratio of statins in primary prevention in people ≥ 75 years of age has not been clarified, leading to numerous and conflicting expert recommendations because no specific randomized trial has been conducted in this population.

Therefore, in patients ≥ 75 years of age treated with statins in primary prevention, the strategy under study will be to discontinue statin therapy. The comparator strategy will be the group of patients who will continue to take their statin at the same dose.

Patients will be followed up every three months for 36 months in Bordeaux (F) according to general recommendations. Clinical events will be recorded prospectively.

Differences from the stream study

The Staree and Preventable trials are high-quality studies with a randomized study design and a placebo-controlled intervention with statins. In the Staree study, people aged 70 and older are included, but with the expected longer life span, hypercholesterolemia of 7.5 mmol/l or more and the presence of type II diabetes mellitus are exclusion criteria. This should also be the case in the Stream study, because statins are also to be discontinued from the age of 70. The SITE study is structured very similarly to the Stream study, but here, too, people who are already at least 75 years old are included as a precaution. This raises two ethical inclusion problems for the Stream study.

Complaints about the interview with Prof. Rodondi:

Article in the Sunday newspaper from 17.07.2022

Author:	Author:
Martina Frei	Michel Romanens
"We don't know if the cholesterol-lowering drug is doing more harm than good to older people"	The title does not correspond to the truth[31]. There are also different cholesterol-lowering drugs.
Prevention *Tablets that lower cholesterol levels have been among the most commonly prescribed medications for many*	False statement: there is no ambiguity[31].

years. But whether patients benefit from them if they were previously healthy is still unclear, says family physician professor Nicolas Rodondi.	
In Switzerland, about one in eight people takes cholesterol-lowering drugs, and one in three over the age of 75. How great is the benefit of these statins?	
We don't know that about many older people.	False statement: we know [31,35].
How can that be, with so many users?	
We know the benefit in so-called "secondary prevention". This means that someone has already had a stroke or heart attack and wants to prevent it from happening again. Cholesterol-lowering drugs clearly reduce the risk in all age groups. This is true at least up to the age of 82, possibly even beyond, and even if cholesterol levels are only slightly elevated. Therefore, in this situation, cholesterol-lowering drugs should be taken on a long-term basis.	However, the Smarter Medicine movement wants to deny statins from 75 even after heart attack. This is in contradiction to this statement. Accordingly, Smarter Medicine would have to reverse the recommendation. [43–45]→ Complaint to SwissMedic.
And where is there ambiguity?	
In people aged 70 and older who have not yet had a heart attack or stroke, we do not know whether they benefit from a cholesterol-lowering drug or whether it does them more harm than good. What this "primary prevention" with a cholesterol-lowering drug does for them is controversial.	False statement [31]: we know effect and side effects and the predominance of the effect over the side effect from age 65.
But some heart specialists see it differently. Why, despite more than thirty years of use, is there no clearer evidence	

of how much the elderly benefit from statins in primary prevention?	
The pharmaceutical companies select the study participants well. It is much easier and carries a lower risk of adverse effects if they have few concomitant diseases. That's why those aged 70 and older formed only a minority in many studies. Because this question is so important, we are now conducting a study together with all the GP institutes and many hospitals. The aim is to clarify the benefits of statin treatment for people over 70 who have not yet had a heart attack or stroke. The aim is also to investigate your quality of life and the frequency of side effects.	False statements [31]: (1) The number of concomitant diseases is not an established exclusion criterion for inclusion of persons 65 and older in statin studies. (2) Quality of life cannot be clarified because of open-label bias.
In your study, half of the participants will continue to take the statin as before, while the other half will discontinue it. Don't these people risk suffering an avoidable heart attack or stroke - perhaps only after the end of the five-year study?	
We don't know whether the rate of heart attacks and strokes increases if you've been taking the cholesterol-lowering drug for years and suddenly stop taking it. The data on this are inconsistent. That's why we think it makes sense to discontinue these drugs, if at all, only as part of a study. If it became apparent that more problems would occur, then we would immediately pull the ripcord. We permanently compare the course in both groups.	False statement [31]: especially the work of Giral proves the exact opposite [30]. The data on this are consistent [31].
Why should it hurt to take a statin as a preventive measure against heart	

attacks and strokes, even at an older age?	
About 9 percent of all users feel muscle pain or weakness. That's a lot. Older people get side effects even more often. There are patients who can no longer do sports, it's so unpleasant. In addition, the statin sometimes promotes diabetes. In two studies, a bit more seniors also died of cancer. That may have been a coincidence, but such possible harm must be weighed against the possible benefit.	Problematic statement: more cancer cases.
These complaints and diseases are generally more frequent in old age. Aren't cholesterol-lowering drugs unfairly suspected?	
There is certainly the effect that some people feel side effects just after reading the package insert. But this does not explain everything. Statins can exacerbate pre-existing muscle weakness or muscle pain. In addition, the kidneys and liver, through which the active ingredients are broken down or excreted, become weaker with age. And finally, seniors usually take several medications. This can lead to undesirable interactions.	Problematic statement: all statin side effects are known and are adequately treated in clinical practice. This does not require an open-label study.
For years, increasingly lower target values for cholesterol have been recommended in medical guidelines - "a strategy for which sufficient evidence of benefit is lacking, wrote the pharma-critical Arzneimittel-Telegramm 2021. There is also repeated criticism that the authors of such guidelines often have conflicts of interest. To which value	Ms. Frei refers here to https://www.arznei-telegramm.de/html/2021_02/2102013_01.html , which refers to https://www.arznei-telegramm.de/html/2019_07/1907060_01.html . The one-sidedness and overcritical view of the effects of statins can easily be seen in the texts (example: NNT/year is misleading, see https://varifo.ch/deprescribing/: an NNT of

should the bad LDL cholesterol be lowered?	70 in the first year of treatment corresponds to an NNT of 7 in 10 years of treatment) and have already been criticized elsewhere for disinformation. [46–48]. On conflicts of interest, cf. the Cochrane development [49]. It is disconcerting that Ms. Frei cites this source, which is not legitimized in scientific discourse.
It's not so much the value that matters, but the sum of the risk factors: Age, smoking, diabetes, high blood pressure, obesity, family predisposition, heart disease, it all plays together. The target value in someone who has already had a heart attack, for example, is lower than in someone who has an intermediate risk of cardiovascular disease.	
Around one in five people who were prescribed a cholesterol-lowering drug for the first time discontinued treatment again, according to the Helsana Medicines Report 2020. What tips are there if you can't tolerate a statin?	
The first thing to do is to contact your family doctor. A blood test can clarify whether continued use is dangerous. If this is not the case, the dose could be reduced or a different statin could be tried.	
Women suffer from statin side effects more often than men. Why?	
We don't know. Women were underrepresented in the manufacturer-sponsored studies.	Problematic statement: in the Jupiter study [50] 38% were women, in the HOPE-3 study [51] 46% were women.
What other factors promote adverse effects besides gender?	
This is a big problem in primary prevention: there are no studies on this question. So	False statement: there are indeed studies demonstrating additive protection by statins

far, no one has compared what a healthy lifestyle brings compared to statins. Most studies are done by pharmaceutical companies. They have no interest in answering this question. In a study of people who had already had a heart attack, the risk of having another one dropped by about 30 percent if they ate a Mediterranean diet. That's about the same as what can be achieved by taking a statin. So lifestyle could be very effective.	even with a healthy lifestyle, especially Mediterranean diet and fitness [52–61]also concerning biomarkers of cardiovascular risk. [62]. That pharmaceutical companies have no interest in answering these questions is an unproven assertion. That healthy lifestyle can replace statin treatment is wishful thinking. In addition, older statin users live healthier lives [63] and have better outcome data with statins [64]. Also, the positive effects usually clearly outweigh the side effects [65].
Many people have deposits in the arteries You can see this in the ultrasound examination Shouldn't they better take a cholesterol-lowering drug?	
From about 70 years of age, almost all people have vascular deposits. The crucial point is whether the cholesterol-lowering drug prevents vascular occlusions in the heart or in the brain. And here the statins in the studies did not provide any benefit in people over 70 years of age without a pre-existing heart attack or stroke.	False statement: the burden of deposits on the arteries increases the risk of "occlusions" (meaning atherothrombotic events): the more deposits, the higher the risk [66–71]. The atherosclerosis must be treated [72,73]which also reduces the amount of atherosclerosis and decreases the risk of atherothrombosis. [74]. The measurement of the deposits is cost effective [75–77] and reproducible [78]. The statement that cholesterol-lowering drugs (other than statins) do not prevent vascular occlusion (clinical events such as heart attack and stroke) in the absence of a pre-existing heart attack or stroke is false. [31]. Diabetes mellitus type II > 70 require statins [79], it would be malpractice not to treat these individuals. In general, it is recommended to use statins even from 70 years of age if life expectancy is > 2.5 years [27,80]. At most, one could discuss combining high-dose statins

	with a combination of low-dose statin and ezetimibe from 75 years of age onwards [81].

Misappropriated information by Ms. Martina Frei in interview

	Justification Michel Romanens
Discontinuation of statins was associated with a 33% increased risk of admission for a cardiovascular event in 75-year-old primary prevention patients [30]. Fall events (as a marker of frailty) did not occur more frequently with continued statin treatment (table S5 in [30]).	This important study should not be underestimated. In addition, LDL cholesterol is the strongest risk factor for heart attack and stroke until over 80 years of age [38] and lower LDL levels are associated with longevity well into old age. [39].
How Prof. Rodondi tells Harry Roos wrong about his cardiovascular risk in the SRF program Puls. https://tcloud.docfind.ch/index.php/s/YEipeasfXt6LQLk	False statement: "If Mr. Roos did not smoke, his cardiovascular risk would be 6%". May 2017 to the broadcast of May 8, 2017, our submission (link) and related report of the Ombudsman's Office. The statements in this broadcast about the risk for cardiovascular events are highly misleading and were reported to the authority SwissMedic on 09.07.2021. Prof. Rodondi tells in this video excerpt from the Pulse broadcast of 08 May 2017 that without smoking the cardiovascular risk of patient Harry Roos in 10 years is low at 6% (timestamp 02:34: the video was deleted by Youtube at the request of Nicolas Rodondi. Therefore, here is the direct link to the video with new timestamp 12:15). This is only the risk for myocardial infarction, the risk for cerebral stroke was suppressed, and the patient Harry Roos thus feels in false security. → Report to SwissMedic

Mortensen negative risk factors	Mentions [28,29].
Smarter medicine recommendation statins stop from 70 after myocardial infarction	[43–45] The recommendation is incorrect and continues to exist unchanged→ Message SwissMedic
Cost-effectiveness of statins up to 75 according to HTA BAG	This information was also discussed with Ms. Frei and then misappropriated [77].
Misinformation that cholesterol is no longer a risk factor after 70 and therefore does not need to be treated.	**Incorrect patient information is misleading:** When deprescribing statins after 70, LDL rises again to the baseline value. It is false that LDL cholesterol is a negligible risk factor after 70. It is also suppressed that with statins compared to placebo in randomized trials the risk of myocardial infarction is reduced by about 40% and the risk of stroke by about 25%. The clip was deleted from Youtube by Nicolas Rodondi on 6/23/2022. Therefore, here is the direct link to the video of the stream study: https://www.statin-stream.ch/infos-fuer-teilnehmer/. According to the legal opinion of Prof. Kieser, there are also legal problems concerning deprescribing and advertising for it. [2].
No mention of the CEC decision that Prof. Rodondi must respond to Romanens' submission by 08/08/2022.	Despite extensive briefing by me, Ms. Frei did not consult with me after the interview with Prof. Rodondi was available. I would then have informed her about the latest CEC decision [82].
Study design: to study the effects of statins on event rates, prospective, randomized, double-blind superiority trials are needed according to the European Medical Agency. For persons 65 and older, 3 very large publications in the next few years will further substantiate the known situation of the effects of statins in old age [27].	Noninferiority studies must not be conducted with placebo or no therapy at all; an active comparator is always used (1). Placebo controlled trials must be conducted with superiority trials (European Medical Agency) to detect clinically and statistically relevant effects of the active comparator [84].

○ A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE): atorvastatin 40 mg compared in healthy elderly people (≥70 years). [40] ○ Statins In The Elderly (SITE): RCT on statin cessation in people ≥75 years. [42] ○ Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults (PREVENTABLE) (Recruiting expected to start in September 2020). [83] Conducting a non-inferiority study before superiority studies have been published is incorrect.	"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." Only when the results of the three superiority trials are known would a non-inferiority trial be considered. However, this would have to include far more people than the stream study and would have to be conducted in a blinded manner in order to determine side effects of statins without subjective bias.
Strandberg review	Statins should not be discontinued even after 75 years of age; moreover, the side effects are much less severe compared with protection from heart attack and stroke [85].

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