# Deprescribing lipid therapy in the elderly study lead by the Insel-hospital should be stopped immediately

**Introduction**

There is an ongoing debate about the beneficial effects of lipid-lowering drugs in elderly patients aged 65, 70, or 75 years or more. In double-blinded randomised trials with statins and ezetimibe, primary care elderly patients are under-represented, but the trend is going towards benefit. Atherosclerosis is a main cause of myocardial infarction and stroke, as reviewed recently for the presence and extent of carotid atherosclerosis and coronary calcifications (1) and there are no data, that the risk for death and non-fatal cardiovascular events attributed to atherosclerosis are attenuated, once a patient has reached his 75th birthday. As the absolute risk increases with age, even small benefits from statins or ezetimibe should translate into major reduction in the occurrence of all-cause death, myocardial infarction and stroke in patients aged 70 or 75 years or more (2). In a publication of the National Working Group of Atherosclerosis (AGLA), it was recommended, not to use statins in primary care patients aged 75 years or more (3). This AGLA recommendation was referenced with a study published by Ramos et al (4) and this recommendation is in contradiction with the lipid guidelines of the European Society of Cardiology 2019 (5) and possibly in contradiction with several randomized and observational studies in the very elderly.

**What we know from the literature**

The placebo-controlled randomized STAREE trial using 40 mg of Atorvastatin versus Placebo in 18'000 patients aged at least 70 years will produce more direct evidence from Australia by the end of 2022 regarding the primary outcome measure (6). A recent health technology report of the Swiss Federal Office of Health found statins to be cost-effective for an AGLA risk of 10% or more in primary

care subjects aged 65, 70 or 75 years (7). The effects of deprescribing of statins have been studied in the EILAT trial (8,9). The EILAT study included primary care patients aged 65 years or more and reported 347 events in 1255 persons adherent to statins (28%) and reported 4105 events in 7328 patients not adherent to statins (56%). The analysis included 19 518 older adults followed during 10 years (median = 9.7 y). All-cause mortality rates were 34% lower among those who had adhered to statin treatment, compared with those who had not (hazard ratio [HR] = 0.66; 95% confidence interval [CI] = 0.56-0.79). Adherence to statins 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 among beyond age 75 and was evident for both women and men. We also performed a meta-analysis on ASCVD risk lowering effects with statins or ezetimibe using data from 5 trials that included CTT (10), EILAT (8), EWTOPIA (11), Jupiter (12), and HOPE-3 (12). Hazard ratio for fixed effects was 0.602 (95% CI: 0.561 to 0.647, p <0.001) and hazard ratio for random effects was 0.699 (95% CI: 0.506 to 0.964, p=0.029) (13) regarding ASCVD events. Regarding fixed effects on all-cause mortality, the result of statin intervention showed also significant effects (hazard ratio 0.69, p<0.001). Gencer published a random effects meta-analysis in patients 75 years or older for ASCVD events and found for statins a hazard ratio of 0.82 (p=0.0005) per 1 mmol/l LDL reduction, for ezetimibe or PCSK9-inhibitors of 0.67 (p=0.03) and for all drugs 0.74 (p=0.002).

**The STREAM Trial - why it should be stopped**

*Study description*

The STREAM trial, a study lead by Prof. Rodondi randomises patients aged 70 or more with additional co-morbidities such as hypertension or diabetes II to stop lipid lowering therapies (e.g. statins or ezetimibe) in primary care (14). This cohort study is a non-inferiority trial with planned inclusion of 1'800 persons over an average observation time of 2 years. The primary outcome measure is all-cause death and non-fatal myocardial infarction or stroke. Secondary outcome measures include questionnaires about quality of life, muscle pain, falls, and medication adherence. The STREAM study is open-label and therefore not blinded for therapy and doctors participating with their patients are required not to control for LDL values during the study period.

*Expected harm:*

From the EILAT study it can be inferred that the absolute risk reduction is 28% in those adherent to statin therapy over 10 years, resulting in a number-needed-to-treat (NNT) of 4. The annual absolute risk reduction is therefore 2.8% or 5.6% over two years with an NNT of 18. In the STREAM study we therefore expect 162 preventable events in those stopping statins. Because all patients had a statin indication before inclusion in the STREAM Study, it should be inferred that all patients entering the STREAM study had at least an AGLA risk of 10%.

*Problems with STREAM study design*

The non-inferiority approach should not be recommended, because the non-inferiority margins are frequently wrong (15) or do not follow the Extension of the CONSORT 2010 Statement (16). Because of the open-label character of the study, all secondary outcome measures, especially muscle pain and quality of life are biased towards an effect unfavourable for statins (17,18). Stopping statins has been tested by Kutner in patients with life-expectancy below one year (19). The study has eventually been approved by a Swiss ethical committee, but details about this process should be reviewed in detail. Because the bulk of evidence of lipid lowering drugs in the elderly points to an effect regarding avoidance of death and ASCVD, the chosen study design is not appropriate.

The stream trial is an ongoing effort of the smarter-medicine framework in Switzerland, as discussed in detail elsewhere (20), which also recommended to stop statins in patients aged 75 years or more after a myocardial infarction. In the STREAM trials, this is an exclusion criterion. Therefore, the STREAM trial exclusion criteria contradict the smarter-medicine recommendation. Further, the deprescribing community does not recommend stopping statins (21,22).

**The STREAM Trial: how it should be stopped**

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