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INVITED EDITORIAL

Real-world data show the effect of statins in primary prevention

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This editorial refers to 'The effect of statins on mortality and cardiovascular disease in primary care hypertensive patients without other cardiovascular disease or diabetes', by T. Andersson *et al.*, https://doi.org/10.1093/eurjpc/zwad212.

Lipid-lowering therapy with statins is one of the cornerstones of the secondary prevention of atherosclerotic cardiovascular disease, and lower treatment targets have been recommended for both stroke and myocardial infarction in later years. The effect of statin therapy on later cardiovascular disease in the presence of atherosclerosis is undisputed and also recommended as the first-line drug above other lipid-lowering agents. Hence, all major guidelines addressing cardiovascular disease risk reduction recommend the use of statins in secondary prevention. In contrast to this, recommendations regarding statins used in the primary prevention of atherosclerotic cardiovascular disease are not equally unambiguous. This may lead to different approaches towards patients with the same cardiovascular risk.

Hypertension is the leading contributor to disease in adults in the world and also one of the most important risk factors for cardiovascular disease. Hypertension management is pivotal to reduce the risk of later cardiovascular disease, with a focus on early and sustained blood pressure control. Hypertension often co-exists with dyslipidaemia and shares many of the same risk factors as increased low-density lipoprotein cholesterol (LDL-C).

In this issue of *the Journal*, Andersson *et al.*[1] present the result of their study on statins in cardiovascular disease and mortality in primary care patients. In their observational register study of treated hypertensive patients, their aim was to investigate the impact of statin therapy in primary prevention. A total of 13 193 participants were included from the Swedish primary health care quality assurance register QregPV. They were all without known cardiovascular disease or diabetes mellitus, and they were *de novo* statin users. Patients with other indications for statin therapy were excluded, and both registered cardiovascular disease diagnoses and also prescription of drugs commonly used in the treatment of cardiovascular diseases, such as platelet inhibitors and other lipid-lowering agents, were exclusion criteria. Hence, the authors aimed to only include patients prescribed statins for the primary prevention of cardiovascular disease. The study was conducted with equally many controls using a 1:1 propensity score matching. Kaplan–Meier survival analyses were performed with a maximum of 8 years, and Cox regression analyses with 4 years of follow-up were performed with an intention-to-treat approach.

The risk of cardiovascular death was 20% lower in the group treated with statins compared with the control group [hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.65–0.99, $P = 0.05$] during the first 4 years of the study, with a non-significant absolute risk reduction of 0.25%. After the first 4 years of follow-up, the proportional hazard assumptions were no longer met. There was also a significant reduction in all-cause mortality in the statin group (HR 0.72, 95% CI 0.62–0.84, $P < 0.0001$) compared with controls. The between-group differences were attenuated over time. Although no significant effect was seen with regard to myocardial infarction, a subgroup analysis showed 39% lower risk (HR 0.61, 95% 0.44–0.84, $P = 0.003$) in females in the statin group compared with female controls during the first 4 years. The overall results show favourable effects of statins in primary care.

Two randomized controlled trials have been executed in a hypertensive population, in a factorial design with statin add-on to antihypertensive drugs, namely ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)[2] and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial).[3] In ALLHAT, participants with hypertension and at least one additional risk factor for coronary heart disease were randomized to pravastatin 40 mg or usual care. The ALLHAT study had no significant difference in all-cause mortality, its primary outcome, or with regard to the benefit on cardiovascular risk. Unfortunately, ALLHAT suffered from modest LDL-C reduction, low adherence at the end of the trial, and high crossover rates.[4] Therefore, one should not necessarily conclude with no effect of statins in general in hypertensives in a primary prevention setting. However, the results of ALLHAT may indicate more modest results of statins under conditions resembling everyday clinical situations.

In ASCOT, participants were randomized to 10 mg atorvastatin compared with placebo.[3] The study showed the significant benefit of this low-dose statin therapy on cardiovascular mortality in general and also coronary disease and stroke. The ASCOT population may not be directly comparable with the population in the study by Andersson *et al.*, as the ASCOT population had higher cardiovascular risk, and also, 14% had signs of left ventricular hypertrophy on either electro- or echocardiogram, indicating hypertensive end-organ damage. Is it tempting to assume that the presence of subclinical atherosclerotic disease or high cardiovascular risk greatly increases the benefit of statins, compared with the effect in patients with a low 'atherosclerotic

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burden'. Not acknowledged atherosclerosis is not the same as non-existing atherosclerosis, which may explain some of the effects of statins in primary prevention.

In the American and European guidelines for the prevention of cardiovascular disease, pharmacological intervention towards dyslipidaemia is recommended in participants with a high or very high risk of cardiovascular disease.[5,6] This should always be proceeded by adequate lifestyle intervention, including diet and regular physical activity. If targets cannot be reached by this, statin is the first drug of choice. The method used in the study by Andersson *et al.* does not take into account the impact of physical exercise and whether the same effects would have been conveyed through increased physical activity. The participants not prescribed statins may also be those being more prone to attempting physical activity and other lifestyle measures to achieve LDL-C goals. Physical activity is also a first-line intervention in hypertension and should therefore be a part of all of the participants' approach to reduce cardiovascular risk.

The results of the study by Andersson *et al.* provide valuable real-world data. The authors have thoroughly included participants at moderate risk, with hypertension as a known modifiable risk factor for cardiovascular disease, hence pinpointing a common and important situation for the primary care physician. The study shows that the effect of statins on a low-moderate-risk population extends beyond clinical trials. Still, it is worth noting that the participants received suboptimal antihypertensive treatment, with a mean blood pressure of 142/86 mmHg. Although there were no differences between the groups, it would be interesting to see if statins add to the risk reduction in a real-world population optimally treated below today's treatment targets for blood pressure reduction. The results also emphasize that the more promising results found in well-performed randomized clinical trials may be more modest in real-world population studies, findings that directly impact the clinician's decisions in everyday patient meetings.

Adherence to prescribed treatment is a well-known challenge in hypertension management, and the more pills prescribed, the lower the adherence.[7] Patients not taking their prescribed medication leave the physician confused and the patients at risk; indeed, patients have been referred to tertiary care before the lack of adherence has been unveiled as a reason for not reaching treatment targets.[8] Physicians' recommendations to increase the number of prescribed pills must therefore be based on solid evidence taking into account more than mere hazard ratios.

The threshold for using statins in hypertensive patients should not be high. Although Andersson *et al.* show the benefit of statins in the primary prevention of hypertensive patients, can we from these results justify increasing the pill burden of asymptomatic patients based on the relatively modest reduction in absolute risk? At least, we need to acknowledge that the effects of statins in real-world populations may be less pronounced than our strong intention to reduce cardiovascular risk.

Based on the results from the ASCOT trial[3] among others, people with hypertension and clearly elevated cardiovascular risk should be treated with statins. Of note, many hypertensive patients will be classified as having high or very high risk, thus fulfilling the criteria for intensive lipid-lowering therapy. To attain LDL-C goals for cardiovascular prevention in patients with high-risk hypertension, it is recommended to titrate statins to a maximally tolerated dose.[9] High-intensity statin therapy includes atorvastatin ≥40 mg or rosuvastatin ≥20 mg once daily. Ezetimibe should be added if LDL-C control is not achieved (preferably as a single pill combination to improve adherence to treatment),[10] and PCSK9 inhibitors or siRNA may be considered in very-high-risk patients to attain LDL-C targets.

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