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EDITORIAL COMMENTARY

Statin discontinuation: an underestimated risk?

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ABSTRACT

Statin treatment is essential for the prevention of vascular disease. Despite the established benefits of statins, discontinuation of these agents is frequent. Whether statin discontinuation leads to adverse outcomes is still debated and the most convincing evidence is mainly restricted to patients who experienced an acute vascular event. It is important to establish if this phenomenon extends to other populations, like those without vascular disease but with a high calculated risk. Overall, it appears that even a brief discontinuation of statins might be harmful. Therefore, statin treatment should not be interrupted except if there is a very good reason. Moreover, patients should be instructed as to why they must adhere to their medication. Adherence should be monitored regularly.

Statin discontinuation in coronary heart disease (CHD) and other vascular diseases

Statin treatment is an essential component of both primary and secondary prevention of vascular disease[1–3]. Despite the established benefits of statins, discontinuation of these agents is frequent both in patients with and without vascular disease[4–11]. There is growing, but not definitive, evidence that the abrupt stopping of statins might increase the risk of vascular events. In this context, Daskalopoulou *et al.* recently studied 9939 survivors of acute myocardial infarction (MI) and reported that discontinuation of statins post-MI was an independent risk factor for 1-year all-cause mortality[12]. Those who stopped their statin after their acute MI were 88% more likely to die in the next year than patients who had never used statins [Hazard ratio (HR) 1.88, 95% confidence interval (CI) 1.13–3.07][12]. Patients who started a statin after their MI had a 28% reduction (HR 0.72, 95% CI 0.57–0.90) in 1-year all-cause mortality when compared with those who had never used statins[12]. These findings are broadly in agreement with an earlier report in a similar population[4]. Moreover, survivors of MI who receive statins intermittently appear to have higher mortality than those who are more adherent to treatment[13,14]. It was also reported in this population that those who stopped receiving not only statins but also beta-blockers and aspirin had lower 1-year survival than those who continued treatment with at least one of these agents[4]. Moreover, survivors of MI who filled some or all of their discharge prescriptions had lower 1-year mortality

rates than those who did not fill any of them[15]. In this context, it is of interest that in patients with established CHD, treatment with both aspirin and statins appears to yield more benefit than administration of either drug alone[16]. Therefore, it is likely that discontinuing both drugs is more detrimental than stopping either drug.

Other studies showed that withdrawal of statins during the acute phase of vascular events might also be harmful. In patients with acute MI, those whose statin therapy was discontinued during the first 24 h after admission had higher in-hospital mortality risk than those who did not receive statins either before or during hospitalization[17]. In patients suffering acute coronary syndromes (ACS), withdrawal of statins after admission was associated with increased risk of 30-day mortality and non-fatal MI compared with continuation of therapy[5]. However, in a repeated analysis of the same data, this effect of discontinuation of statins was no longer significant[18].

Negative effects of statin withdrawal were also reported in patients with acute events in other vascular beds. In the acute phase of ischemic stroke, discontinuation of chronic statin treatment increased infarct size and the risk of dependency or death compared with continued treatment[19]. Even patients who were not receiving statins either prior or after stroke had a reduced stroke size and less risk of early neurologic deterioration than patients in whom statins were stopped after stroke[19]. Among stroke survivors who were discharged on statins, discontinuation of statins was associated with increased risk of 1-year all-cause mortality[6]. In addition, earlier discontinuation of statins was associated with higher risk of death[6].

The effects of statin withdrawal are less clear in patients with vascular disease outside the acute setting. In the Treating to New Target (TNT) study, statin withdrawal during a 6-week dietary lead-in/drug-washout period did not increase the risk for vascular events in patients with stable CHD[20]. However, in a more recent population-based cohort study in patients with established vascular disease, discontinuation of statins was associated with increased vascular and all-cause mortality[7]. Moreover, those adherent to statin therapy for more than 80% of the follow-up period had lower mortality rates than those less adherent[7].

In patients who had undergone percutaneous coronary intervention (PCI), discontinuation of fluvastatin was associated with increased risk of vascular morbidity and mortality[8]. In patients undergoing coronary artery bypass graft (CABG) surgery, stopping statins in the immediate postoperative period was associated with increased risk of in-hospital cardiac and all-cause mortality[21]. Similar results were reported in patients undergoing aortic or lower extremity revascularization surgery[22]. Current guidelines recommend continuing statins in patients who are already receiving them and are scheduled for non-cardiac surgery and to administer statins to patients undergoing vascular surgery[23]. Statins appear to reduce perioperative morbidity and mortality in patients undergoing both non-vascular and vascular surgery[24,25].

Patients without established vascular disease are also frequently non-adherent to statin treatment[9,10] and appear to be less adherent than those with vascular disease[9,26]. In the primary prevention setting, patients may be less willing to receive statins since they perceive their vascular risk to be low. Overall adherence to statin therapy may be surprisingly low. In one study, the rate of discontinuation of statins was $\approx$30% in the general population (primary and secondary prevention) within the first year of prescription[10]. In another study using administrative data from Ontario, the 2-year adherence rates to statins were only 40.1% for ACS, 36.1% for chronic CHD, and 25.4% for primary prevention[9].

Better adherence to statins is also associated with improved outcomes in primary prevention. In the West of Scotland Prevention Study (WOSCOPS), better adherence to pravastatin resulted in lower vascular morbidity and mortality and all-cause mortality[27]. Similar results were reported more recently in a population-based study[28].

Mechanisms that may be responsible for an adverse outcome after discontinuing statins

Several mechanisms may be implicated in the adverse effects of statin discontinuation. Statins exert anti-inflammatory effects that are evident soon after their administration[29]. These effects are rapidly abrogated after statin withdrawal[30,31]. Endothelial dysfunction precedes the development of atherosclerosis and statins can improve endothelial function[32]. It was reported that discontinuation of statin treatment results in deterioration of endothelial function within 24–36 h[33,34]. Statins exert beneficial effects on haemostasis and blood rheology[35]. They were also shown to enhance fibrinolysis by increasing the levels of tissue plasminogen activator and this was abrogated soon after statin withdrawal[36]. The activation of proinflammatory and prothrombotic cascades plays an important role in the pathogenesis of acute vascular events[37]. Therefore, the antiinflammatory, antithrombotic and vasculoprotective effects of statins might be more important during

these events[38]. In contrast to their 'pleiotropic' actions, the effects of statins on low density lipoprotein cholesterol (LDL-C) levels are still present during the first days after their discontinuation[5,30,31,36].

It was also suggested that a risk-treatment mismatch might explain, at least in part, the observed detrimental effects of statin discontinuation[12]. For example, patients at higher vascular risk are less likely to receive statins than those with lower risk[39]. Thus, statins might be stopped in patients with short survival expectancy or multiple comorbidities[12]. It is also possible that patients who discontinue statins might be less adherent to their other medication or lifestyle measures. A meta-analysis showed that adherence to placebo is associated with reduced all-cause mortality, suggesting that adherence to treatment might be a marker of a healthier lifestyle[40]. Whatever the reason for not prescribing a statin, it is surprising that, despite international guidelines, ≈23% (2261/9939) of high-risk patients were not prescribed these drugs after MI (non-users + stoppers) in the recently published Daskalopoulou *et al.* study[12].

Concluding statements

It is well established that statins reduce vascular risk[41]. This benefit includes evidence for a less severe presentation, fewer in-hospital complications, and lower hospital death rates in patients presenting with ACS who were on statins before the event compared with patients who were not on statins[42]. Whether statin discontinuation leads to adverse outcomes is still under debate, and convincing evidence is mainly restricted to patients who experienced an acute vascular event. It is important to establish if this phenomenon extends to other populations, like those without vascular disease but with a high calculated risk. Providing a definitive evaluation of the effect of cessation of statin treatment in high risk patients will always be limited by obvious ethical considerations.

Overall, it appears that even a brief discontinuation of statins might be harmful. Therefore, statin treatment should not be interrupted except if there is a very good reason. Moreover, patients should be instructed as to why they should adhere to their medication. Adherence must be monitored regularly. Whether intermittent statin discontinuation caused an underestimation of benefit in statin trials, analysed on an intention to treat basis, remains to be established. Another point worth considering is the future use of 'polypills'. Although there are potential advantages associated with such formulations[43] there is a need to consider the consequences of simultaneously discontinuing several drugs (including a statin and possibly aspirin).

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