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INVITED EDITORIAL

‘Keep on keeping on’: persistence with lipid-lowering treatment in familial hypercholesterolaemia

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This editorial refers to ‘Persistence with long-term PCSK9 inhibitors treatment and its effectiveness in familial hypercholesterolemia: data from the SAFEHEART study’ by R. Alonso *et al*. https://doi.org/10.1093/eurjpc/zwac277.

> The only thing I knew how to do was to keep on keeping on like a bird that flew.
>
> Bob Dylan, Tangled up in Blue

Heterozygous familial hypercholesterolaemia (HeFH) has a worldwide prevalence of 1 in 300.[1] Heterozygous familial hypercholesterolaemia patients are at high risk for premature atherosclerotic cardiovascular disease (ASCVD) due to lifelong genetically elevated levels of LDL cholesterol.[1] Current treatment guidelines flag HeFH patients as being at high risk.[2] For instance, European lipid guidelines recommend stringent target levels of LDL cholesterol for HeFH patients with and without established ASCVD, namely 1.4 and 1.8 mmol/L (55 and 70 mg/dL), respectively.[2] Because baseline LDL cholesterol levels are so dramatically elevated in HeFH patients, attaining the recommended levels is challenging and requires focused lifestyle and high intensity pharmacologic intervention.[3] HeFH patients often require combination treatment comprised of a statin plus ezetimibe and/or inhibitors of proprotein convertase subtilisin kexin 9 (PCSK9).[3]

But while combination pharmacologic therapy in clinical trials enables a fairly large proportion of HeFH patients to reach target levels,[4] real-world evidence shows that 30–50% of these patients encounter barriers to optimal LDL cholesterol levels either with statins or adjunctive PCSK9 inhibitor therapy.[5,6] Failure to achieve LDL cholesterol targets in HeFH is due to both physician-level and patient-level factors. Physician-level factors include unfamiliarity with guidelines and inadequate implementation of guideline recommendations.[7] Patient-level factors include compromised access to medication, poor adherence, either from not taking medication consistently—i.e. low compliance—or by outright discontinuation of the medication—i.e. low persistence.[7,8] Observational studies have shown that high adherence with lipid-lowering therapy is associated with improved cardiovascular outcomes.[8] Furthermore, the lowest ASCVD risk was observed among adherent patients receiving high-intensity therapy, while the highest cardiovascular risk was observed among non-adherent patients receiving low-intensity therapy.[9] Thus for HeFH patients, it is imperative to identify treatment regimens that are both maximally efficacious and also ensure high adherence and persistence.

This topic is evaluated in the current issue of the *European Journal of Preventive Cardiology* by Alonso *et al*.[10] The authors report findings from the Spanish Familial Hypercholesterolaemia (SAFEHEART) cohort study. SAFEHEART, a prospective registry comprising >3000 genetically defined patients from Spain, has repeatedly provided practical, real-world information about the trajectory and treatment of HeFH. Here, the authors evaluated 696 HeFH patients aged >18 years, of whom 46% were female. All patients received stable lipid-lowering treatment that included PCSK9 monoclonal antibody inhibitors self-injected subcutaneously bi-weekly: 51% and 49% took evolocumab and alirocumab, respectively. The authors evaluated persistence with treatment, defined as continued use over the study period. Median treated plasma LDL cholesterol before initiating PCSK9 inhibitor therapy was 3.74 mmol/L [interquartile range (IQR) 3.2 to 4.6 mmol/L] or 145 mg/dL (IQR 123–177 mg/dL). After a median follow-up of 3.7 years (IQR 2.3–4.8 years), a total of 27 patients (3.9%) had discontinued PCSK9 inhibitor treatment for at least 60 days. Twenty-two (3.2%) stopped PCSK9 inhibitors permanently for reasons that included physician judgement, adverse events, development of anxiety or depression, and patient request; one discontinuation was related to lack of access. Five patients (0.7%) stopped treatment temporarily, for reasons including COVID-19 precautions, physician judgement, and recovery from a motor vehicle accident; however, all these subjects eventually resumed treatment. Thus, persistence with PCSK9 monoclonal antibodies in their HeFH patients was an impressive 96.1% over almost 4 years.

Unsurprisingly, efficacy of treatment was admirable. For instance, median LDL cholesterol levels achieved after 1 year of treatment and at the last follow-up visit were 1.6 mmol/L (IQR 1.1–2.2 mmol/L) or 63 mg/dL (IQR 43–88 mg/dL) and 1.6 mmol/L (IQR 1.1–2.1 mmol/L) or 61 mg/dL (IQR 44–82 mg/dL), respectively. In tandem, percent reductions of LDL cholesterol after 1 year of treatment and at the last follow-up visit were 58% (IQR 40–69%) and 58% (IQR 44–68%), respectively. European guideline-recommended targets for percent LDL cholesterol reduction and absolute cut points for LDL cholesterol achieved at the last follow-up visit were 77% and 48% of patients, respectively. These are noteworthy metrics of guideline target attainment

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that would have been merely aspirational in the era before PCSK9 inhibitors were introduced.[3] Also, objective measures of quality of life were stable or even slightly improved over the duration of follow-up. The authors concluded that long-term persistence with PCSK9 monoclonal antibody therapy by their HeFH patients was very high, with resulting benefits regarding LDL cholesterol lowering efficacy and improved quality of life.

Persistence reflects the duration over which a patient continues treatment without interruption (i.e. difference between the start and end of the therapy period), in contrast to adherence, which reflects how consistently and regularly the patient takes the medication according to prescription advice (i.e. proportion of days covered). What explains the extraordinarily strong persistence with PCSK9 inhibitor treatment in HeFH patients from the SAFEHEART cohort? For comparison, in the recently reported Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk Open Label Extension (FOURIER-OLE) trial of 6635 patients with established ASCVD treated with evolocumab and followed for up to 8 years, the discontinuation rate of PCSK9 inhibitor therapy was 15%.[11] Why did only 4% of SAFEHEART patients discontinue PCSK9 inhibitor treatment compared to 15% of closely monitored patients in a topflight clinical trial like FOURIER-OLE? The virtually total persistence in SAFEHEART patients is even more remarkable considering that the follow-up period overlapped with the COVID-19 pandemic. Alonso *et al.*[10] suggest that the SAFEHEART registry structure and processes were essential to the high persistence with PCSK9 inhibitor treatment.

The benefits of disease registries in the management of lipid disorders have been recently reviewed.[12] The SAFEHEART registry database has enabled continuous standardized contact with patients and their affected relatives at least annually by health care providers from the co-ordinating centre.[10] Patients enrolled in the SAFEHEART registry almost certainly had superior awareness of HeFH and understood the importance of maintaining consistent, effective lipid-lowering therapy to reduce ASCVD risk. Also, SAFEHEART patients may have been motivated by their personal and family experience with the disease. They may have taken PCSK9 inhibitor therapy more seriously because it is injectable. Notably, access to and cost of treatment did not seem to pose a barrier to persistence. Furthermore, high persistence to PCSK9 treatment may serve as a proxy for global beneficial health behaviours, including better persistence with diet and physical activity.

Although ASCVD outcomes were not evaluated by Alonso *et al.*,[10] there is reason to suspect that the high persistence with PCSK9 inhibitors will yield tangible clinical benefits. For instance, in the FOURIER-OLE with persistence of 85%, major ASCVD outcomes were significantly reduced over a median of 5 years, e.g. 20% lower risk of cardiovascular death, myocardial infarction, or stroke in FOURIER-OLE patients who had been originally randomized to placebo in the parent FOURIER trial.[11] Similar tangible benefits would be expected for the HeFH patients in SAFEHEART. Another important observation from both SAFEHEART and FOURIER-OLE was the remarkably low incidence of adverse events, including no statistical signals for muscle-related events, new-onset diabetes, haemorrhagic stroke, and adverse neurocognitive outcomes. This is reassuring especially considering that these patient groups will require long-term treatment with PCSK9 inhibitors.

A final question is whether the SAFEHEART findings can be extrapolated. In this regard, future studies in other HeFH cohorts would be welcome. In addition, how might longer acting PCSK9 inhibitors, such as semi-annual injections of short interfering RNA drugs, fit into the HeFH treatment paradigm considering that persistence is already >96% with monoclonal antibodies? While answers to these questions are being sought, the findings from Alonso *et al.* provide hope and reassurance for HeFH patients who keep on keeping on with their lipid-lowering therapy.

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Data availability

Data available on request.

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