Review Article

Therapeutic Approach with PCSK9 Inhibitors for Effective Cardiovascular Risk Reduction in Diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) is a recognised risk factor for cardiovascular disease, being the main cause of death in this specific population. As the direct and indirect healthcare burden attributable to T2DM is notably increasing, patients with diabetes will represent a growing percentage of the population with established cardiovascular disease. Hypercholesterolaemia is a causal factor for the development and progression of atherosclerotic vascular injury [1, 2]; consequently, the awareness of lipid profile is crucial in subjects with diabetes, especially T2DM, both at the time of diagnosis and in the clinical follow-up, in order to achieve therapeutic goals with greater precision [1, 3]. Furthermore, delay in the management of hypercholesterolaemia is associated with a rise in vascular risk and a high

recurrence of cardiovascular events, a fact that undoubtedly entails unacceptable health and social costs [1, 4]. Therefore, it is paramount to optimise the use of pharmacological therapies with proven efficacy in reducing cardiovascular risk in patients with diabetes.

Currently-available lipid-lowering drugs such as statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors enable us *a priori* to achieve strict therapeutic objectives regarding low-density lipoprotein cholesterol (LDL-C) [5]. Different studies and meta-analyses have shown the beneficial effects of an additional reduction in LDL-C levels when statins are combined with ezetimibe or PCSK9 inhibitors, thus confirming the greater reduction in LDL-C concentration and the greater efficacy in cardiovascular prevention [6, 7].

The recommendations of the Cardiovascular Risk Group of the Spanish Diabetes Society (SED) 2018 [8], the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) 2019 [9], the American College of Cardiology (ACC)/American Heart Association (AHA) in primary prevention of cardiovascular disease 2019 [10] and the most recent from the American Diabetes Association (ADA, 2020) [11] and the Endocrine Society 2020 [12] highlight the need to reduce cardiovascular risk in T2DM with proper use of the available therapeutic strategies. The therapeutic goals for the diabetic population according to risk category, time since diagnosis and type of diabetes are shown in Table 1 [9]. Very recently, in the DA VINCI study [13], an 18-European country, cross-sectional, observational study among patients receiving lipid-lowering therapies, fewer than half of high/very high-risk primary and secondary prevention patients achieved 2016 ESC/EAS LDL-C goals, with approximately one-fifth achieving the lower 2019 ESC/EAS goals. Therefore, in the real world, a huge gap exists between the achieved and recommended LDL-C goals by the guidelines for patients at the highest risk.

Since 2015, with the approval of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the pharmacological armamentarium for the treatment of dyslipidaemia has been expanded with two monoclonal antibodies against PCSK9. These new lipid-lowering agents, with considerable clinical evidence of their cardiovascular benefits, provide significant reductions in LDL-C, specifically in patients with high vascular risk who do not achieve the recommended goals despite modifications in lifestyle and statin treatment in monotherapy at the maximum tolerated dose or in combination with ezetimibe, as well as in those with intolerance or contraindication for the use of statins but who have a high risk of cardiovascular events [14-19].

The present report emitted by the Cardiovascular Risk Group of the Spanish Diabetes Society (SED) and the Familial Hypercholesterolemia Foundation (FHF), aimed to facilitate the achievement of therapeutic objectives in LDL-C in the T2DM population through the rational use of lipid-lowering drugs, including PCSK9 inhibitors, evolocumab and alirocumab (Figure 1).

Cardiovascular risk categories	Clinical features			LDL-C goal		Non HDL-C goal	Apo B goal
	TOD[a]	CVRF	Time since DM diagnosis	% reduction	Level (mg/dL)	Level (mg/dL)	Level (mg/dL)
Very high	Yes	≥ 3	Individualise T1DM T2DM > 20 years	> 50	< 55	< 85	< 65
High	No	1-2	Individualise T1DM T2DM 10-20 years	> 50	< 70	< 100	< 80
Moderate	No	0	T1DM < 35 years old T2DM < 40 years old and/or duration < 10 years	30-50	< 100	< 130	< 100

Apo, apolipoprotein; CVRF cardiovascular risk factors; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TOD, target organ damage; CVRF: age, sex, family history, hypertension, smoking, hypercholesterolaemia, overweight/obesity (particularly abdominal obesity) and sedentary lifestyle; *Adapted from the ESC/EAS 2019 guideline [9]. No subject with diabetes is at low cardiovascular risk; [a]TOD is defined as microalbuminuria, retinopathy or neuropathy

Table 1: Stratification of cardiovascular risk and therapeutic objectives in the population with diabetes*.

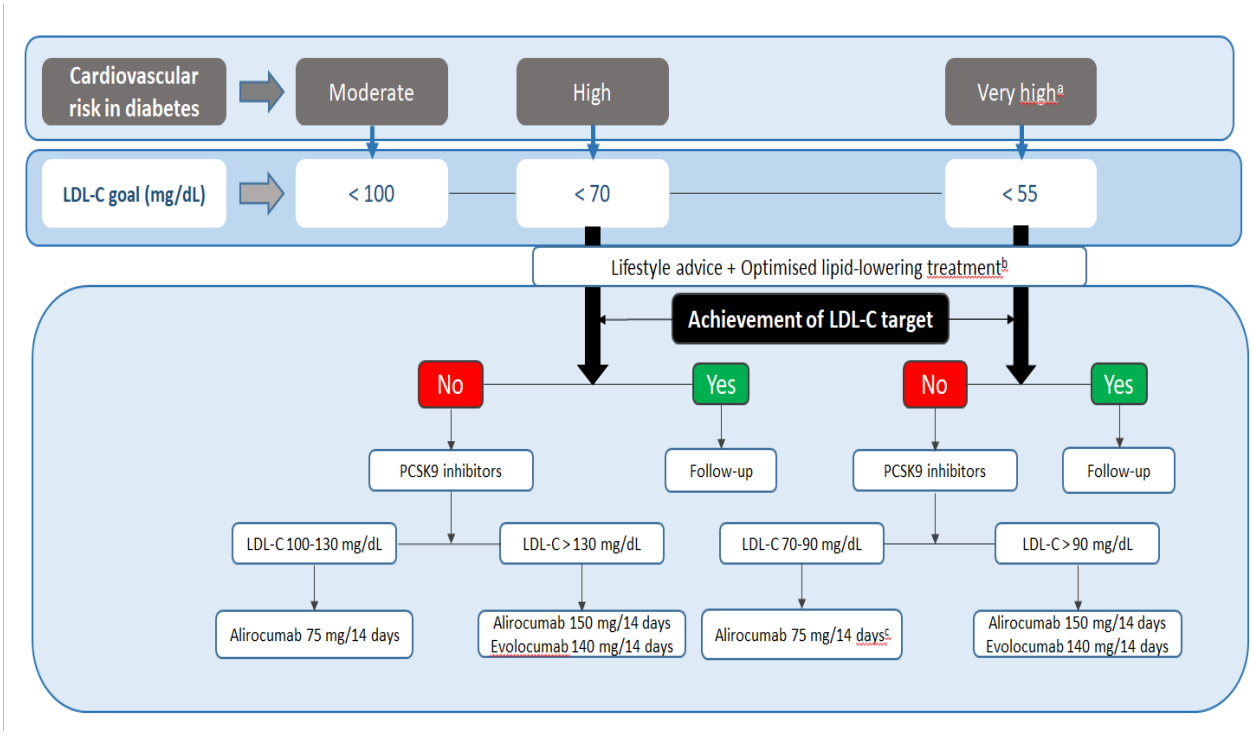

Figure 1: Algorithm of therapeutic approach with PCSK9 inhibitors in diabetic patients for effective cardiovascular risk reduction; [a]Cardiovascular risk category and therapeutic objective not considered in the current therapeutic report of the Spanish Association of Medicines and Health Products; [b]Optimised lipid-lowering treatment leads to a reduction in LDL-C ≥ 50%, either with statin monotherapy or associated with ezetimibe, with adherence of 80%; [c]The option to use full starting doses of either of the two PCSK9 inhibitors may also be valid.

First of all, it should be noted that the attainment of LDL-C targets in patients with diabetes must be individualised, and the proposed therapeutic approach algorithm therefore differs from that of other scientific societies [18]. Second, it is important to take into account that according to recent updated reports on the therapeutic positioning of evolocumab and alirocumab in hypercholesterolaemia of the Spanish Agency for Medicines and Health Products (AEMPS) [20, 21], funding of these drugs is limited to patients with familial hypercholesterolaemia and/or established cardiovascular disease (ischaemic heart disease, ischaemic cerebrovascular disease and peripheral arterial disease) with LDL-C > 100 mg/dL despite the maximum tolerated doses of statins. Thus, to obviate the consequences of adding ezetimibe in patients with diabetes treated with statins for of LDL-C concentrations varying between 100 and 130 mg/dL for those at high/very high risk that would imply the non-indication of PCSK9 inhibitors despite not having achieved the respective therapeutic objectives, we selected the term "optimised lipid-lowering treatment", coined by the Spanish Arteriosclerosis Society (SEA) [22] and defined as one with a relative reduction ≥ 50% in LDL-C with adherence of 80%. In this respect, the difference in the additional reduction in LDL-C compared to baseline with a statin at the maximum tolerated dose or in combination with ezetimibe ranges from 50% to 60%. Therefore, we propose that all high/very high risk patients requiring a > 20% reduction in LDL-C despite receiving the maximum tolerated dose of statin should be additionally treated with a PCSK9 inhibitor. Similarly, since there are two PCSK9 inhibitors with a high LDL-C reduction effect, their choice must also be tailored based on baseline LDL-C and the possibility of dose titration (Figure 1). However, the possibility of using full starting doses with either of the two PCSK9 inhibitors may also be reasonable, particularly in T2DM patients at very high cardiovascular risk.

On the other hand, we must stress two facts: the European guidelines recommend LDL-C < 55 mg/dL with a relative reduction > 50% compared to baseline as a therapeutic goal in patients with very high cardiovascular risk, and very low LDL-C levels can be achieved with the use of PCSK9 inhibitors in combination with statins. Although there does not appear to be a lower limit for plasma LDL-C beyond which no benefits are obtained [23], the lack of long-term safety studies suggests applying appropriate clinical judgement and considering the patient's choice when achieving concentrations of LDL-C < 30 mg/dL [17, 23-26]. Furthermore, in a recent subanalysis of the Odyssey Outcomes trial [27] using a propensity score matching, relative and absolute reductions in major cardiovascular events with alirocumab were similar in patients who achieved LDL-C 25-50 or < 25 mg/dL. These findings do not indicate a clear advantage of targeting LDL-C levels below 25 mg/dL.

In short, it would be desirable to re-review the report by the AEMPS on the therapeutic position of PCSK9 inhibitors and individualise the indications in patients with diabetes at high/very high cardiovascular risk in accordance with the latest clinical practice guidelines. In this respect, the present statement includes, in the therapeutic approach algorithm (Figure 1), a new vascular risk situation not previously contemplated by the AEMPS. The proposed algorithm is simple in design, easy to carry out and eminently practical when the different clinical scenarios of cardiovascular risk in the diabetic population are considered.

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Conflicts of Interest

The authors Arrieta, Iglesias, Aguilar, Mata and Pedro-Botet have no conflict of interest regarding the publication of this article.

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