Impact of LDL formula and apo B quantification on UK PCSK9i and ESC/EAS treatment thresholds in patients being investigated for familial combined hyperlipidaemia

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INTRODUCTION

Accurate quantification, by calculation, of low-density lipoprotein cholesterol (LDL-C) is crucial for primary and secondary prevention of cardiovascular disease (CVD). The Friedewald equation, routinely used in UK clinical practice, has several limitations leading to the underestimation of LDL-C. This could cause, for example, under-treatment of patients who are potentially eligible for PCSK9i therapy. Alternative markers include LDL-C calculation by the Martin equation or direct quantification of apo B. ApoB is particularly recommended, instead of LDL-C, for risk assessment and management of patients with high triglycerides (TG), obesity or metabolic syndrome.[1-4] Calculated LDL-C using Martin's formula and apo B were compared to Friedewald to determine the impact on PCSK9i eligibility and treatment targets.

Methods

Laboratory systems were searched over 14 months for patients with a lipid profile and triglycerides <4.5 mmol/L who were being investigated for familial combined hyperlipidaemia (FCH) with an apoB. LDL-C was calculated using Friedewald (LDL-F) and Martin equations (LDL-M). Values were compared to each other, apo B, treatment and risk thresholds (see Tables 1, 2).

LDL-C >3.5	FH * with previous or recurrent CVD Non-FH or mixed dyslipidaemia with recurrent CVD
LDL-C >4	Non-FH or mixed dyslipidaemia with history of CVD
LDL-C >5	FH without CVD

Table 1: NICE recommendations for PCSK9i eligibility based on LDL-C (mmol/L) [TA393, 394]

*Familial hypercholesterolaemia

	LDL-C	Apo B
Very High Risk	**<1.4**	**< 0.65**
High risk	**<1.8**	**< 0.8**
Moderate Risk	**<2.6**	**< 1.0**

Table 2:EAS Recommendations for treatment targets for LDL-C (mmol/L) and Apo B (g/L)[2]

FINDINGS

Although all patients were eligible the only patients found were adult patients from the lipid clinic, 49 in total. LDL-M correlated well with LDL-F but was consistently higher (mean 0.42 mmol/L). If LDL-M is used instead of LDL-F, 4% of patients would move from having LDL-C <3.5 mmol/L to >3.5, 8% <4 to >4 and 12% <5 to >5. The effect of changing formula was larger at higher LDL-C. (Chart 1) The 2 patients with LDL-C <1.8 mmol/L (both formulae) also had an apo B <0.65 g/L.

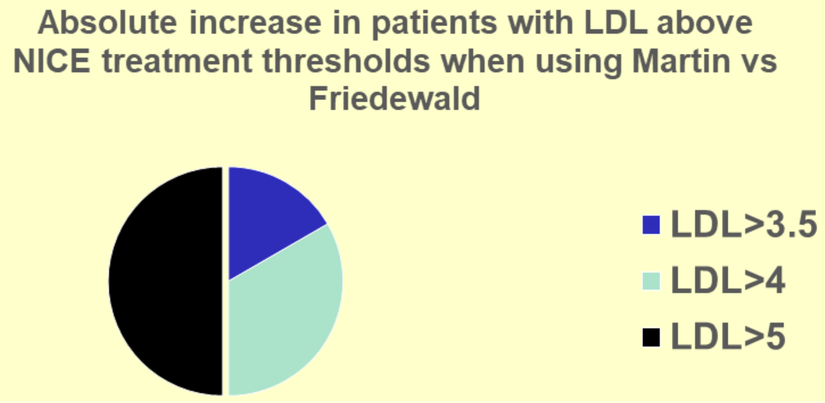

Chart 1: More patients will be eligible for PCSK9i Therapy when using Martin equation

If using EAS risk thresholds for treatment escalation overall more people were treated well according to apo B than LDL (6 <0.8g/L compared to 2 <1.8 mmol/L for high risk category (Chart 2).

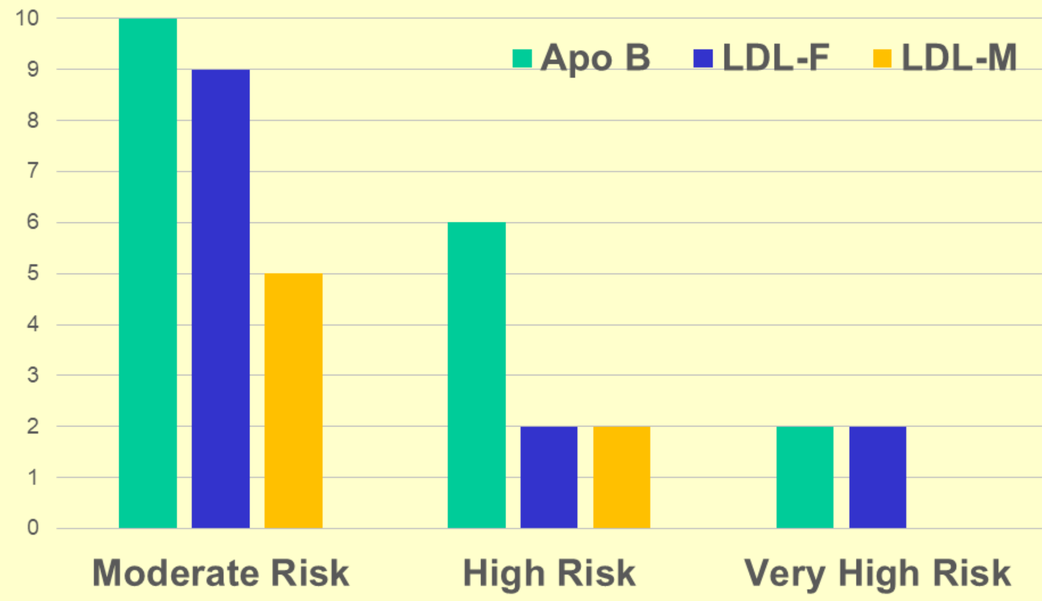

Chart 2: Number of patients reaching EAS treatment targets for moderate, high and very high risk of CVD as defined by LDL-C or Apo B. (see Table 2)

CONCLUSION

The Martin equation provides a greater estimation of LDL-C. Using LDL-M could result in increasing the number of patients eligible for PCSK9i therapy at most by 12% according to UK thresholds. Apo B demonstrated the converse, i.e. better apo B reduction than LDL-F suggested, however this may reflect the population (suspected FCH, defined by mild hypertriglyceridaemia). The cost therefore of an additional test (compared with a calculated value) may more appropriately guide treatment escalation and prevent spend in patients with a mixed dyslipidaemia in whom further apo B-rich particle reduction is not required.

References:
1. Chung S. Update on Low density lipoprotein cholesterol quantification. Curr Opin Lipidol, 2019; 30(4):1.
2. Mach F, et al. 2019 ESC/EAS Guidelines for the management of Dyslipidaemias. Eur Heart J 2019.
3. Metha R,et al. Performance of LDL-C calculated with Martin's formula compared to the Friedewald equation in familial combined hyperlipidaemia. Atherosclerosis, 2018; 277: 204-210
4. Palmer MK, et al. Comparing a novel equation for calculating low-density lipoprotein cholesterol with the Friedewald equation: A VOYAGER analysis. Clin Biochem, 2019; 64: 24-29
5. Langlois MR, et al. Quantifying atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol. Clin Chem 2018; 64(7):1006-1033