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Potential utility of the SAFEHEART risk equation for rationalising the use of PCSK9 monoclonal antibodies in adults with heterozygous familial hypercholesterolemia

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HIGHLIGHTS

- The SAFEHEART risk equation is useful for selecting those patients with FH at the highest risk.
- The SAFEHEART risk equation may also be useful to choose the most suitable patients with FH for treatment with PCSK9 mAbs.
- This study shows how to rationalise the management of FH from a unidimensional lipid-target approach to a patient-centric strategy-based assessment of an individual's absolute risk.

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ABSTRACT

Background and aims: Patients with familial hypercholesterolaemia (FH) may require proprotein convertase subtilisin/kexin-type 9 (PCSK9) mAb as add-on therapy to achieve LDL-cholesterol (LDL-C) goals. However, the current cost of these therapies means that choosing suitable patients is based on consensus or clinical judgement rather than a quantitative risk assessment. We used the SAFEHEART Risk Equation (RE) to estimate the number needed to treat (NNT) at different risk thresholds and baseline LDL-C to identify those FH patients more likely to derive the greatest benefit from PCSK9 mAb.

Methods: Five-year event rates were calculated using the SAFEHEART-RE for every patient, overall and across LDL-C strata. A 60% reduction of LDL-C after theoretical treatment with PCSK9 mAb was assumed. Individual absolute risk simulating the effects of PCSK9 inhibition was calculated using the SAFEHEART-RE and, in a similar way, by using the Cholesterol Treatment Trialists' (CTT) Collaboration criteria. Absolute risk reduction and NNTs were calculated.

Results: Of the total SAFEHEART population, 2,153 were FH cases aged 18 years or older, on maximum tolerated lipid lowering treatment. NNTs were dependent of both baseline predicted risk and baseline LDL-C level ranging from 44 to 17 for those with 5-year risk of ≥1 to ≥5. The smallest NNT (12) was observed among those with 5-year risk of ≥5% and LDL-C ≥160 mg/dl. Using the CTT criteria produced similar results.

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Conclusions: The SAFEHEART-RE may provide a useful quantitative tool for rationalising the selection of FH patients who might derive greater absolute benefits from PCSK9 mAb.

1. Introduction

Familial hypercholesterolemia (FH) is the most frequent monogenic disorder associated with elevated LDL-cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular disease (ASCVD) [1]. Its prevalence may be higher than 0.4% [2] and confers a more than three-fold greater risk of premature ASCVD [3] compared with normolipidemic individuals. Early diagnosis and early initiation of statin therapy significantly reduce ASCVD in these patients [4,5].

Recently, proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAb) have been introduced in the clinical setting in a large number of countries [6]. Although these antibodies reduce LDL-C levels in FH subjects and their clinical benefit has been proven in high risk cardiovascular patients [7,8], their cost-effectiveness remains a topic for intense debate relying upon numerous assumptions that contribute to the models [9]. Consequently, recommendations from different expert bodies [10,11] differ, but all include a subgroup of subjects with FH as a target group for treatment with PCSK9 mAb.

In a recently published review [12] the authors used modelled data to estimate 10-year absolute risk of ASCVD in high-risk populations within trials. Modelling the relative risk reduction from the addition of non-statin therapy and they calculated the number needed to treat (NNT) to prevent one ASCVD event. They concluded that adding ezetimibe or PCSK9 mAb to maximally tolerated statin therapy might be cost-effective in very high-risk and high-risk patients, depending on baseline LDL-C levels. Those data were based on summary events and not individual data. Moreover, this concept has not been applied to FH because patients with FH were not specifically included in randomized trials.

While lifetime risk of ASCVD is significantly increased in FH, risk is variable even after statin therapy [13]. Quantifying precisely the ASCVD risk among individuals with FH would help identify those that are likely to derive the greatest absolute benefit from more intensive LLT [14]. A new equation has been developed to assess cardiovascular risk in FH patients, based on prospective follow-up of individuals enrolled in the Spanish Familial Hypercholesterolemia-registry (SAFEHEART), the so called SAFEHEART Risk Equation (SAFEHEART-RE) [13]. On the other hand, the risk-reduction results of the Cholesterol Treatment Trialists' (CTT) Collaboration were also used [15]. Our aim was to estimate the NNT at different cardiovascular risk thresholds within the SAFEHEART-RE, in order to identify those FH patients more likely to derive the greatest benefit from PCSK9 mAb therapy. NNTs estimated by using the risk-reduction results of the Cholesterol Treatment Trialists' (CTT) Collaboration criteria were also obtained [15].

2. Materials and methods

2.1. Study design and population

SAFEHEART is a real-world clinical practice multicentre, nationwide, long-term prospective cohort study in Spain, which includes molecularly defined heterozygous FH patients treated as per local guidelines with LLT, with or without ASCVD at baseline [16]. Data analysed for this work were obtained between January 2004 and October 2015 and only those ≥18 years old subjects with molecularly determined FH were included. This study was approved by the ethics committees and all subjects gave written informed consent. Based on data from this study, the SAFEHEART-RE can be used to estimate the risk of cardiovascular events at 5 and 10 years using 8 simple variables [13]. The SAFEHEART registry was able to provide information to develop a risk prediction equation, the SAFEHEART-RE that can estimate the risk of incident ASCVD events in FH patients using the following variables: Age, gender, history of atherosclerotic cardiovascular disease, presence of hypertension, body mass index (BMI), smoking, and plasma LDL-C and Lp(a) levels. The main advantages of the SAFEHEART-RE, may be summarized as follows: 1) it provides a global approach to the cardiovascular risk, not based only on LDL-C levels; 2) LDL-C, remains in the equation as an important determinant of the risk; 3) Lp(a) plays an important role in the prediction; 4) this model is highly accurate; 5) SAFEHEART-RE may be widely applicable for use in primary and specialist care settings; 6) it can be used for both primary and secondary prevention.

2.2. Statistical analysis

PCSK9 mAb reduce mean LDL-C levels by approximately 60% in FH patients [17–19]. Since there are no large reliable trials of LDL-C lowering with add on therapy to statins among patients with FH, we estimated the potential absolute benefits of adding in PCSK9 inhibitors in two ways.

Firstly, we used the predicted event rate among patients in SAFEHEART after calculating the on-treatment LDL-C that would be achieved after the addition of a PCSK9 inhibitor. This assumption was used in this study to estimate the "on-treatment" LDL-C level if PCSK9 mAb were to be added in the SAFEHEART-RE and thereby, to estimate patients' cardiovascular risk after simulated add on PCSK9 mAb.

In parallel, the effect of PCSK9 mAb was calculated by applying the CTT estimate of the efficacy whereby there is a 22% reduction in relative risk per 1 mmol/L lowering of LDL-C after calculating the simulated absolute LDL-C reduction with a PCSK9 inhibitor. This relative risk reduction was applied to the baseline risk to calculate the predicted event rate of therapy. In this case, the endpoint was the occurrence of major vascular events, defined as the combined outcome of major coronary event, non-fatal or fatal stroke or coronary revascularisation [15].

Variables were analysed for normality using the Kolmogorov-Smirnov test. Qualitative data were expressed as absolute number (percentage). Quantitative data were expressed as mean and standard deviation (SD) or median and IQR if they were not normally distributed Average absolute risk was estimated using the SAFEHEART-RE in every individual using the on-treatment LDL-C after LLT and after the simulated use of PCSK9 mAb. Absolute risk reduction (ARR) was obtained as the difference between absolute risk before and after the simulated use of PCSK9 mAb. Five-year NNT was obtained as 1/ARR. Statistical analyses were carried out using SPSS version 18.0 (SPSS Inc., Chicago, Illinois).

3. Results

Of the total SAFEHEART population, 3,749 were ≥18 years, of which 2,746 were FH cases. The population analysed in the present study comprised 2,153 individuals on maximally tolerated cholesterol lowering treatment, for whom complete data was available. Supplementary Table A shows the main characteristics of the study population. Supplementary Fig. A shows the baseline 5-year distribution of risk in the study population. The distribution of LDL-C at baseline is shown in Supplementary Fig.B. Fig. 1 shows the event rates across 5-year risk categories stratified by baseline LDL-C. Within each 5-year risk category, the risk increased with baseline LDL-C. Within

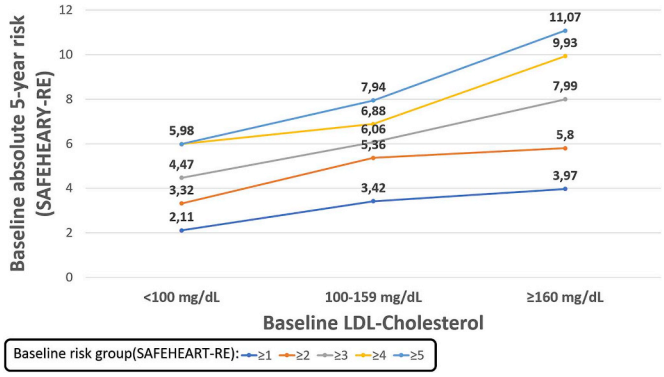

Fig. 1. Real baseline absolute 5-year risk (estimated using the SAFEHEART-RE) according to baseline LDL-cholesterol level and baseline risk category.

each predicted risk category, risk varied by baseline LDL-C. The lowest risk was among those with an overall risk of ≥1% and LDL-C < 100 mg/dl (2.11 (1.78–2.45)) and the highest among those with an LDL > 160 mg/dl and 5-year risk of ≥5% (11.07 (9.65–12.49)).

3.1. Absolute risk reduction according to baseline absolute risk only

Assuming a 60% LDL-C reduction with PCSK9 mAb treatment and estimating the risk by using the SAFEHEART-RE, a mathematical simulation is shown in Table 1. The relationship between the baseline 5-year risk estimated by means of the SAFEHEART-RE and the theoretical ARR and NNT achieved by PCSK9 mAb if a 60% LDL-C reduction was achieved is depicted for different baseline risk cut-off points. A more detailed description based on baseline risk and baseline LDL-C can be found in Table 2.

A cut-off point in the baseline 5-year absolute risk according to SAFEHEART-RE ≥1% would provide an NNT of 44 to prevent one cardiovascular event. If the chosen cut-off point was a 5-year absolute risk according to SAFEHEART-RE ≥5%, NNT = 17 to prevent one cardiovascular event after PCSK9 mAb treatment for 5 years. These NNTs varied according to the baseline LDL-C level, as shown in Table 2, with higher baseline LDL-C associated with greater theoretical benefits at every level of predicted risk.

Tables 3 and 4 show the modelled results of absolute risk reduction and NNTs obtained using the CTT approach after a 60% LDL-C reduction induced by PCSK9 mAb. The absolute risk reduction was slightly lower and, accordingly, NNTs are higher than estimates of benefit applied to the SAFEHEART-RE. Further stratifying results by baseline LDL-C produced directionally concordant results as those observed using the modelling derived solely from the SAFEHEART-RE, with smaller absolute benefits and hence high NNTs. According our data, out of the 2153 subjects included in our cohort, 361 (16.8%) patients would be treated to achieve an NNT of < 30 and 525 (24.4%) to achieve an NNT of < 35 using SAFEHEART-RE.

4. Discussion

This is the first study to demonstrate the application of a quantitative risk equation in rationalising the treatment of patients with FH. We demonstrate the potential of the SAFEHEART-RE, a tool to stratify risk in helping guide the use of PCSK9 mAb in such patients after a maximum tolerated lipid lowering treatment (treatment based on high potency statins with or without ezetimibe at the highest dose without adverse events as considered by his/her treating physician). Application of the SAFEHEART-RE may conversely avoid treating FH patients at lower risk of ASCVD, who are likely or derive less benefit from these expensive agents. The use of the SAFEHEART-RE may lead to more rational and cost-effective care of patients with FH, as cost-effectiveness of PCSK9 mAb for FH has not been evaluated extensively [20].

While the perceived risk among FH patients lifelong is high, the present data among FH patients treated with LLT suggest that the proportion of patients with a 5-year risk ≥5% is low (7.5%). Furthermore, the proportion of people with LDL > 160 mg/dl is also modest (23.7%). These data suggest that among FH patients, where detection occurs as early as in Spain and statin use is high, much of the untreated CVD risk of FH is mitigated. We have previously shown that residual risk can be estimated reliably using the SAFEHEART-RE as it provides a quantitative assessment of event rate. In the present analysis, we observed that, among FH patients, 5-year risk was related to both LDL-C and other factors, and stratifying patients, not just the overall risk, but baseline LDL-C provided more precise estimations of risk and hence potential benefit of add-on therapy with a PCSK9 mAb. Whilst baseline risks is a good starting point for estimating the benefit of additional therapies, they are limited as they do not take into account LDL-C levels, which are a significant determinant of the benefits of lipid lowering therapies [21]. For instance, two patients with the same baseline risk may obtain different benefit from the use of PCSK9 mAb, being higher in the one with the highest baseline LDL-C level [22]. Within the present study, a 5-year absolute risk ≥2%, according to the SAFEHEART-RE, predicts an NNT < 30 to prevent one cardiovascular event over 5 years following treatment with a PCSK9 mAb. However, risk varied markedly from no benefit among those with LDL-C < 100 mg/dl to NNT = 23 among those with LDL-C > 160 mg/dl. Among patients with a baseline LDL-C level below 100 mg/dl, ARR is very low and, accordingly, NNTs are very high in contrast to patients with higher baseline LDL-C within each stratum of 5-year risk. According to recently published studies in the general population, this NNT could usefully guide recommendations on the use of PCSK9 mAb in patients with FH [12,23,24]. Whilst the published data use theoretical 10-year constructs to obtain 10-year absolute risk reduction and derived NNTs, our findings could be extended to 10 years by doubling the absolute benefit and halving the NNT values to generate equivalent 10-year comparisons.

When the CTT criteria are used, the results are supportive of our approach of using the SAFEHEART-RE to estimate the benefits of on treatment LDL-C by simulating LDL-C reduction with a PCSK9 inhibitor. ARR were slightly lower and NNTs were higher but these differences

Table 1
Five-year estimated risk, absolute risk reduction and numbers needed to treat (NNT) with PCSK9 mAb according to different baseline risks for patients with familial hypercholesterolaemia using the SAFEHEART-RE approach (a 60% LDL-C reduction is assumed).

Real absolute 5-year risk before PCSK9 mAb (%)	Real absolute 5-year risk before PCSK9 mAb (%) Mean (95% CI)	Estimated 5-year risk after PCSK9 mAb (%) Mean (95% CI)	Absolute 5-year risk reduction (%) Mean (95% CI)	5-year NNT
≥1	3.54 (3.30–3.79)	1.28 (1.19–1.38)	2.30 (2.10–2.44)	44
≥2	5.46 (5.08–5.83)	1.93 (1.77–2.10)	3.53 (3.15–3.81)	28
≥3	6.69 (6.24–7.15)	2.37 (2.17–2.57)	4.32 (3.98–4.67)	23
≥4	7.89 (7.35–8.43)	2.77 (2.52–3.01)	5.12 (4.70–5.55)	20
≥5	9.09 (8.44–9.74)	3.16 (2.89–3.47)	5.93 (5.90–6.46)	17

NNT: number needed to treat.

Table 2
Five-year estimated risk, absolute risk reduction and numbers needed to treat (NNT) with PCSK9 mAb according to different baseline risks and different LDL-cholesterol levels for patients with familial hypercholesterolaemia using the SAFEHEART-RE approach (a 60% LDL-C reduction is assumed).

Real absolute 5-year risk before PCSK9 mAb (%)	Baseline LDL-cholesterol (mg/dl)	Real absolute 5-year risk before PCSK9 mAb (%) Mean (95% CI)	Estimated 5-year risk after PCSK9 mAb (%) Mean (95% CI)	Estimated absolute 5-year risk reduction (%) Mean (95% CI)	5-year NNT
≥1	< 100	2.11 (1.78–2.45)	2.11 (1.78–2.45)	0	–
	100–159	3.42 (3.16–3.69)	1.40 (1.28–1.50)	2.04 (1.88–2.19)	49
	≥160	3.97 (3.46–4.49)	0.98 (0.79–1.18)	2.99 (2.61–3.38)	33
≥2	< 100	3.32 (2.58–4.05)	3.32 (2.58–4.05)	0	–
	100–159	5.36 (5.0–5.72)	2.18 (2.03–2.33)	3.18 (2.97–3.39)	31
	≥160	5.80 (5.03–6.57)	1.45 (1.14–1.76)	4.35 (3.77–4.93)	23
≥3	< 100	4.47 (3.40–5.54)	4.47 (3.40–5.54)	0	–
	100–159	6.06 (5.68–6.43)	2.47 (2.31–2.63)	3.59 (3.37–3.81)	28
	≥160	7.99 (6.92–9.06)	2.04 (1.56–2.52)	5.95 (5.14–6.76)	17
≥4	< 100	5.98	5.98	0	–
	100–159	6.88 (6.47–7.28)	2.81 (2.64–2.98)	4.07 (3.83–4.31)	25
	≥160	9.93 (8.63–11.24)	2.56 (1.91–3.21)	7.38 (6.38–8.37)	14
≥5	< 100	5.98	5.98	0	–
	100–159	7.94 (7.46–8.41)	3.25 (3.05–3.45)	4.69 (4.41–4.96)	21
	≥160	11.07 (9.65–12.49)	2.87 (2.10–3.64)	8.20 (7.10–9.30)	12

NNT: number needed to treat.

might be explained by two facts: first, the endpoint in CTT is a narrower endpoint, with fewer events than in SAFEHEART, which includes peripheral revascularisation cardiovascular death rather than coronary death; second, SAFEHEART RE has not been evaluated against CTT endpoint; third, whilst our baseline risk predicts a wider range of endpoints, the effect of a 1 mmol/L reduction using CTT can only inform on MACE, and the CTT algorithm has not been assessed using the SAFEHEART endpoints.

A further important characteristic of the SAFEHEART-RE is its capability to assess cardiovascular risk in patients with and without previous clinical ASCVD. This concept is helpful because the risk after a clinical event is highly variable from patient to patient and therefore they should not be classified all together under the simple concept of "very high risk" or high risk as it is currently done within the ESC/EAS Lipid and Prevention Guidelines [25]. Cardiovascular imaging techniques may detect subclinical atherosclerosis and assist in risk stratification. In a recent publication, we found that coronary calcium score was independently associated with cardiovascular risk estimated by the SAFEHEART-RE, supporting the former role in risk prediction in FH [26].

In the present study, NNT was related to baseline absolute cardiovascular risk as well as baseline LDL-C level. This concept agrees with previous studies in which baseline LDL-C level is a key determinant of absolute benefit in non-FH and FH populations and survival depends on baseline and on-treatment levels of LDL-C (lifetime cumulative exposure to LDL-C) [27]. Thus, the SAFEHEART-RE approach fits into this paradigm and extends earlier observations to an FH patient population. Our proposed strategy follows the well stablished approach in primary prevention, where global risk is calculated in statin treatment naive subjects to a statin treated population by assessing the potential benefits of add-on therapy to statins. Whereas global approaches do not estimate treatment benefit based on absolute reductions in LDL-C, the latter approach is gaining considerable attention [28]. Moreover, our approach may provide greater precision around risk estimates than simply using global risk to guide therapy.

Current guidelines recommend the use of PCSK9 mAb as add-on therapy based on expert consensus rather than on precise individual estimates of benefit. Thus, they are population-based approach rather than a precision medicine-based approach. This is reflected by the number of candidates receiving treatment with PCSK9 mAb that varies according to different guidelines [10,11]. An accurate predictive tool would provide risk assessment more precisely on a case by case basis for physicians, payers, and patients. In this study, our findings suggest that SAFEHEART-RE could be a useful tool to select those subjects for potential therapy with PCSK9 mAb based on real-life data.

The strengths and limitations of our study merit careful consideration. The SAFEHEART registry is a nationwide, long-term prospective contemporary cohort of a molecularly-defined FH population that allow the development of a robust FH specific risk prediction equation (SAFEHEART-RE). Given that FH patients have a greater cumulative exposure to LDL-C, the beta coefficient for LDL-C would incorporate this and be more reliable than data derived from non-FH populations [3]. Furthermore, we have previously shown that prognostically relevant variables such as Lp (a) further discriminate risk in FH and, as such, these are included in our models. Whilst we have made inferences about likely cost benefits based on NNTs, we did not do a formal health economic evaluation. The optimal cut-off point for absolute benefit should be determined based on clinical and economic considerations, depending on budgets and healthcare system capabilities. For this reason, we propose SAFEHEART-RE as a reference tool. The estimation of individual therapy benefit requires not only assessment of ARR but also effect size of treatment for patients based on trials [25]. A

Table 3
Five-year estimated risk, absolute risk reduction and numbers needed to treat (NNT) with PCSK9 mAb according to different baseline risks for patients with familial hypercholesterolaemia using the CTT approach (a 60% LDL-C reduction is assumed).

Real absolute 5-year risk before PCSK9 mAb (%)	Real absolute 5-year risk before PCSK9 mAb (%) Mean (95% CI)	Estimated 5-year risk after PCSK9 mAb (%) Mean (95% CI)	Absolute 5-year risk reduction (%) Mean (95% CI)	5-year NNT
≥1	3.54 (3.30–3.79)	1.80 (1.68–1.92)	1.73 (1.59–1.86)	58
≥2	5.46 (5.08–5.83)	2.74 (2.56–2.91)	2.69 (2.46–2.91)	37
≥3	6.69 (6.24–7.15)	3.37 (3.17–3.58)	3.27 (2.98–3.55)	31
≥4	7.89 (7.35–8.43)	3.97 (3.74–4.20)	3.85 (3.49–4.20)	26
≥5	9.09 (8.44–9.74)	4.50 (4.23–4.77)	4.50 (4.05–4.95)	22

Table 4
Five-year estimated risk, absolute risk reduction and numbers needed to treat (NNT) with PCSK9 mAb according to different baseline risks and different LDL-cholesterol levels for patients with familial hypercholesterolaemia using the CTT (a 60% LDL-C reduction is assumed).

Real absolute 5-year risk before PCSK9 mAb (%)	Baseline LDL-cholesterol (mg/dl)	Real absolute 5-year risk before PCSK9 mAb (%) Mean (95% CI)	Estimated 5-year risk after PCSK9 mAb (%) Mean (95% CI)	Estimated absolute 5-year risk reduction (%) Mean (95% CI)	5-year NNT
≥1	< 100	2.11 (1.78–2.45)	1.53 (1.29–1.77)	0.59 (0.49–0.69)	169
	100–159	3.42 (3.16–3.69)	2.02 (1.87–2.18)	1.44 (1.32–1.55)	69
	≥160	3.97 (3.46–4.49)	1.52 (1.31–1.71)	2.41 (2.09–2.74)	41
≥2	< 100	3.32 (2.58–4.05)	2.39 (1.88–2.90)	0.93 (0.70–1.16)	108
	100–159	5.36 (5.0–5.72)	3.17 (2.95–3.38)	2.24 (2.08–2.40)	45
	≥160	5.80 (5.03–6.57)	2.20 (1.89–2.50)	3.52 (3.04–4.00)	28
≥3	< 100	4.47 (3.40–5.54)	3.20 (2.49–3.93)	1.26 (0.89–1.64)	79
	100–159	6.06 (5.68–6.43)	3.60 (3.38–3.83)	2.54 (2.37–2.72)	39
	≥160	7.99 (6.92–9.06)	3.02 (2.60–3.44)	4.83 (4.16–5.49)	21
≥4	< 100	5.98	4.22 (3.93–4.52)	1.76 (1.46–2.05)	57
	100–159	6.88 (6.47–7.28)	4.07 (3.83–4.31)	2.89 (2.70–3.08)	35
	≥160	9.93 (8.63–11.24)	3.80 (3.29–4.30)	5.95 (5.11–6.79)	17
≥5	< 100	5.98	4.22 (3.93–4.52)	1.76 (1.46–2.05)	57
	100–159	7.94 (7.46–8.41)	4.69 (4.40–4.97)	3.36 (3.13–3.59)	30
	≥160	11.07 (9.65–12.49)	4.24 (3.69–4.80)	6.62 (5.69 7.55)	15

limitation of the SAFEHEART-RE is the lack of external validation. Unfortunately, at present, there is no patient cohort comparable to SAFEHEART to externally validate our risk equation [13]. Nevertheless, the SAFEHEART-RE is in accordance with the TRIPOD recommendations [29].

4.1. Conclusion

The SAFEHEART-RE may be a useful tool for selecting the most suitable patients with FH for treatment with PCSK9 mAbs. Our results could rationalise the management of FH from a unidimensional lipid-target approach to a more patient-centric strategy-based assessment of an individual absolute cardiovascular risk.

ClinicalTrials.gov number

NCT02693548.
https://clinicaltrials.gov/ct2/show/NCT02693548?term=NCT02693548&rank=1.

Conflicts of interest

Dr. Perez de Isla has received honoraria for consulting, speaker or researcher activities from Merck, Sharp and Dohme, Astra Zeneca, Esteve, Amgen and Sanofi. Prof. Kausik K. Ray has received research grants from Amgen, Regeneron, Sanofi, MSD, and Pfizer, has provided consultancy services to Amgen, Sanofi, Regeneron, BI, AZ, Kowa, Medco, AKCEA/IONIS, Resverlogix, Esperion, Cerenis, Lilly, and Novo Nordisk, and has participated in Speakers Bureau for Amgen, Sanofi, BI, AZ, Novo Nordisk, Kowa, Medco, and Pfizer. Dr. Watts received honoraria for advisory boards and received research grants from Amgen and Sanofi. Dr. Santos has received honoraria for consulting, speaker or researcher activities: Astra Zeneca, Amgen, Akcea, Biolab, Esperion, Kowa, Novo-Nordisk, Pfizer and Sanofi/Regeneron. Dr. Alonso reports personal fees from Amgen, Aegerion and Ionis. Dr. Mata received honoraria for advisory boards and received research grants from Amgen and Sanofi.

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Author contributions

Every author has contributed to the design, analysis, writing and review of the manuscript. Leopoldo Pérez de Isla, Rodrigo Alonso, Ovidio Muñiz-Grijalvo, Jose Luis Diaz-Diaz and Pedro Mata have also contributed to the enrolment and evaluation as well as the follow-up of patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.05.003.

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