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Imputation of untreated LDL-C in treated subjects with homozygous familial hypercholesterolaemia: An international collaboration

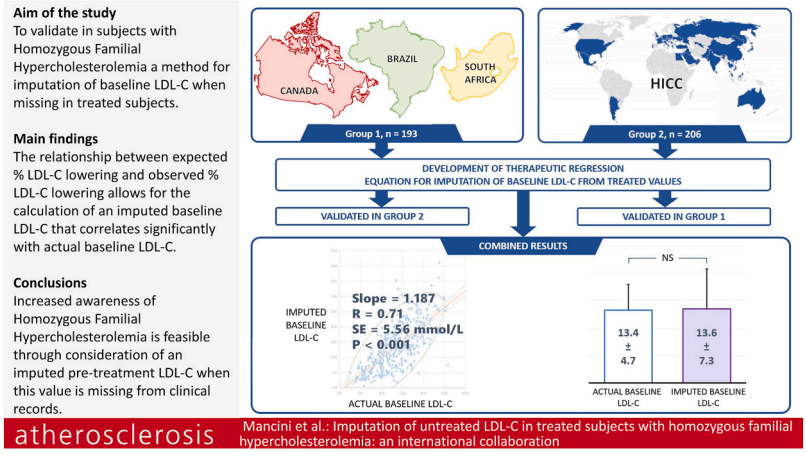
G.B. John Mancini [a,*], Arnold Ryomoto [a], Isabelle Ruel [b], Iulia Iatan [b,c], Frederick J. Raal [d], Raul D. Santos [e,f], Ana Paula Marte [f], Robert A. Hegele [g], Brooke A. Kennedy [g], Liam R. Brunham [c], Daniel Gaudet [h], Miriam Larouche [h], Diane Brisson [h], Willemijn Schonck [i], Laurens F. Reeskamp [i], Jacques Genest [b], on behalf of the Canadian Homozygous Familial Hypercholesterolemia Registry[1], the Homozygous Familial Hypercholesterolemia International Clinical Collaboration[1]

[a] Centre for Cardiovascular Innovation, Dilawri Cardiovascular Institute, Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada
[b] Research Institute of the McGill University Health Center, Department of Medicine, Montreal, Quebec, Canada
[c] Centre for Heart and Lung Innovation, Division of General Internal Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[d] Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[e] Academic Research Organization, Hospital Israelita Albert Einstein, Sao Paulo, Brazil
[f] Lipid Clinic, Heart Institute (InCor) University of Sao Paulo, Medical School Hospital, Sao Paulo, Brazil
[g] Departments of Medicine and Biochemistry, Robarts Research Institute, University of Western Ontario, London, Ontario, Canada
[h] Department of Medicine and ECOGENE-21, University of Montreal, Chicoutimi, Quebec, Canada
[i] Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Amsterdam, the Netherlands

HIGHLIGHTS

- Subjects with Homozygous Familial Hypercholesterolemia have biallelic mutations affecting LDL-C clearance.
- They respond to LDL-C lowering therapy in a variable and diminished fashion compared to other patients.
- Despite this, there is a quantifiable, relationship between intensity of therapy and resulting LDL-C.
- This relationship was validated from international cohorts of patients with Homozygous Familial Hypercholesterolemia.
- If baseline LDL-C is missing, imputed LDL-C can raise the possibility of underlying Homozygous Familial Hypercholesterolemia.

GRAPHICAL ABSTRACT



* Corresponding author. Rm 9111, Diamond Centre 2775 Laurel Street Vancouver, British Columbia, V5Z 1M9, Canada.
E-mail address: mancini@mail.ubc.ca (G.B. John Mancini).
@GBJohnMancini1 (G.B. John Mancini)
[1] Members listed in Supplementary Files.

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ABSTRACT

Background and aims: Diagnosis of Homozygous Familial Hypercholesterolaemia (HoFH) relies on untreated low-density lipoprotein-cholesterol (LDL-C) which is often unknown. We determine whether untreated LDL-C can be imputed from treated LDL-C in HoFH.

Methods: Two groups with HoFH were identified: Group 1 (n = 193) from Canada, Brazil and South Africa; Group 2 (n = 206) from the HoFH International Clinical Collaboration. Pre- and post-treatment LDL-C and lipid lowering therapy (LLT) intensity from Group 1 were used to develop a regression model and applied to treated LDL-C in Group 2 to impute pre-treatment LDL-C. The same process was performed in reverse. A final imputation model was created from combining both groups.

Results: There was a curvilinear relationship between the expected and observed % lowering of LDL-C on LLT ($r = 0.3923$, $p < 0.0001$, Standard Error [SE] = 23 %). Using this relationship, LDL-C was imputed from treated values and showed significant correlation with pre-treatment LDL-C ($r = 0.71$, $p < 0.001$; mean values 13.4 ± 4.7 [Standard Deviation] and 13.6 ± 7.3 mmol/L, respectively, ns). Concordance between actual and imputed values ≥ 10 or <10 mmol/L was 80 %. Whereas 36 % of patients had treated LDL-C ≥ 10 mmol/L, 64 % had treated or imputed pre-treatment LDL-C ≥ 10 mmol/L.

Conclusions: In HoFH, the response to LLT can be quantified and used to impute untreated LDL-C from treated LDL-C. Imputation may augment awareness of possible HoFH in treated subjects lacking records of untreated LDL-C.

1. Introduction

Elevated low density lipoprotein cholesterol (LDL-C) is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) [1]. Cardiovascular risk is greater in patients with mono- or bi-allelic familial hypercholesterolaemia (FH) due to cumulative lifelong exposure to elevated LDL-C compared with patients with non-FH dyslipidaemia [2]. However, because implementation of lipid lowering therapy (LLT) is common and does not require knowledge of underlying genetic determinants of elevated LDL-C, untreated LDL-C levels may not be readily available in clinical records after initiation of treatment in FH. Hence, treated LDL-C may be low enough to prevent suspicion of an underlying genetic dyslipidaemia. This problem prevents recognition and awareness of FH because clinical definitions of FH are dependent upon knowledge of untreated LDL-C levels [3,4]. We have previously explored the imputation of untreated LDL-C to raise awareness of the possibility of underlying mono-allelic, heterozygous FH (HeFH) when untreated LDL-C is unknown [5]. This approach identifies patients that may be at higher risk than otherwise appreciated, and such patients may benefit from genetic testing and cascade screening in their families or may warrant access to restricted medications [6–21].

LDL-C reduction with traditional agents is generally less effective or not effective at all in patients with bi-allelic, homozygous FH (HoFH) compared with other patients due to the marked reduction in residual low-density lipoprotein receptor (LDLR) function [3,6,8,10,12,20]. Therefore, it is unknown whether an LDL-C imputation approach is feasible or practical in treated HoFH subjects. In this study we evaluated responses to LLT in patients with HoFH with the following aims: 1) to establish a model of LDL-C reduction that is specific to HoFH subjects in response to LDLR-mediated lipid lowering by statins, ezetimibe and proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors; 2) to demonstrate the performance of this model for imputing an untreated LDL-C that can be applied in the clinical definition of HoFH; and 3) to demonstrate improved sensitivity for identification of possible cases of HoFH through use of the imputed untreated LDL-C in treated subjects.

2. Methods

2.1. Study population and inclusion criteria

Two independent groups of patients (total n = 399) meeting clinical criteria and enrolled in HoFH programs were identified for this study. The first group was formed through amalgamation of subjects from the Canadian HoFH Registry and from South Africa and Brazil (Group 1; n = 193) [22–29]. The second group was extracted from the Homozygous FH International Clinical Collaboration (HICC) Registry (Group 2; n = 206) [29]. Any duplicate entries in the HICC data set that were already represented in Group 1 were excluded.

Inclusion criteria included subjects in whom clinical criteria for HoFH were met, genetic testing had been performed, pre- and post-treatment LDL-C level was recorded, and pharmacologic LLT drugs and dosage was recorded. Patients on apheresis were included only if their inter-current LDL-C levels were stable, permitting fiducial assessment of additional LDL-C response to pharmacologic LLT. Otherwise, subjects were excluded if receiving the LDLR-independent agents mipomersen, lomitapide and evinacumab.

Subjects provided informed consent for inclusion of their demographic, genetic and treatment data into respective registries at the participating sites. The use of de-identified data for current analyses performed in Vancouver, Canada was approved by the University of British Columbia (H24-03917).

2.2. Therapeutic observations and LDL-C reduction modeling

For Group 1, multiple therapeutic observations were available from some individuals. But to avoid potentially correlated responses to therapy, only the first recorded therapeutic response was used for this analysis. In Group 2, each patient contributed only one observation. Thus, in total, across both groups, there were 399 therapeutic observations. Most observations reflected diverse, multi-intervention therapies and there were too few patients to evaluate responses to specific drugs or dosages individually. Accordingly, we characterized each pharmacologic LLT regimen using the method of Ruel et al. [5] to provide the expected intensity, % LDL-C reduction, of the therapeutic regimen in normal subjects. This expected % LDL-C reduction was compared with the actual % LDL-C reduction on record. When non-standard milligram dosages were identified, we considered the next higher typical dose for calculating the expected % LDL-C lowering (e.g. a patient on rosuvastatin 30 mg was considered to be on 40 mg, a patient on ezetimibe 5 mg was considered to be on 10 mg, etc). Several observations also included use of niacin (6), probucol (4), resins (21), bempedoic acid (1), or inclisiran (1). These observations were not excluded but were assigned appropriate, expected % LDL-C lowering based on published literature [30–34].

2.3. Analytical approach

Analyses were undertaken in 3 steps. In Step A, the Group 1 data set

(n = 193) was used to develop the relationship between expected % LDL-C reduction and actual % LDL-C reduction using linear and polynomial regression analyses. The optimal relationship was applied to the treated LDL-C in Group 2 to "back calculate" or impute a baseline or untreated LDL-C. The imputed LDL-C was compared with the actual pre-treatment LDL-C on the basis of mean values and through linear regression. In Step B, the converse of Step A was studied. Thus, the Group 2 data set (n = 206) was used to develop the optimal relationship between expected % LDL-C reduction and actual % LDL-C reduction. This regression relationship was applied to the treated LDL-C in Group 1 to calculate an imputed, pre-treatment LDL-C. The imputed LDL-C was compared with the actual pre-treatment LDL-C on the basis of mean values and through linear regression. In Step C, Group 1 and Group 2 data sets were amalgamated to develop a final, comprehensive equation derived from the broadest population of subjects. This relationship was applied to the treated LDL-C in the amalgamated data set to calculate an imputed, baseline or pre-treatment LDL-C. The imputed LDL-C was compared with the pre-treatment LDL-C on the basis of mean values and through linear regression.

2.4. Statistics

SAS for Windows 9.4 TS Level 1M8 (Carey, North Carolina) was used for statistical analyses. Calculations of means ± standard deviations were undertaken as appropriate and compared using paired or unpaired t-tests as appropriate when normally distributed; the non-parametric Mann-Whitney/Wilcoxon Ranked Sum test was used for independent samples with non-normal distributions. Distributional, categorical data were analyzed using the Chi-squared test, the Fisher's Exact Test or the Pearson Chi-squared test with a Monte-Carlo Estimate for the Exact Test if cells had expected counts less than 5. Linear and polynomial regression analyses were performed and the best model was determined by the adjusted R-squared selection method as well as visual inspection to ensure smooth curves and to preclude over-fitting. The 95% confidence interval ellipsoid was also plotted as appropriate. Statistical significance was accepted at $p < 0.05$.

3. Results

A summary of patient demographics and treatments is provided in Table 1. Group 2 was of younger age (21.5 ± 18.1 [SD] vs 26.7 ± 15.3 years, p = 0.0001), with more Asian and fewer white subjects (p < 0.001), fewer with prior ASCVD (p < 0.02), and a lower treated LDL-C (7.5 ± 4.6 vs 9.6 ± 4.1 mmol/L, p < 0.0001). There were no differences in sex distribution (55 % female in Group 1 and 53 % in Group 2). Mean pre-treatment LDL-C was the same (13.4 mmol/L) in both groups. There were differences in therapeutic regimens (p < 0.001). There were 48 instances in Group 1 and only 1 in Group 2 reflecting PCSK9 inhibitor monotherapy. In the former, the PCSK9 inhibitor was added to other, stable LLT and the LDL-C values represented only the pre- and post-PCSK9 inhibitor response. In contrast, in Group 2 the single patient was treated solely with PCSK9 inhibitor. There were 53 instances in Group 2 and none in Group 1 reflecting the sum, total change in LDL-C after implementation of triple therapy with statin + ezetimibe + PCSK9 inhibitors. This is because multiple serial responses were recorded in some Group 1 subjects and PCSK9 inhibitor was generally added last. These serial responses were excluded to avoid potentially correlated treatment responses in the individual patients with multiple observations. In Group 2, the baseline and treated LDL-C in response to triple therapy was the only recorded observation in that subject.

Step A: In Group 1 the expected % LDL-C reduction and actual % LDL-C reduction were best correlated with a polynomial regression as shown in Supplemental Fig. 1 (r = 0.204, p = 0.038). Using this relationship, the pre-treatment LDL-C was imputed from the treated LDL-C in Group 2. The mean, imputed LDL-C showed a significant linear correlation with the pre-treatment LDL-C (p < 0.001) with r = 0.716, slope = 1.084 and SE of 4.97 mmol/L (Supplementary Fig. 2A). The mean imputed LDL-C was significantly lower than the measured pre-treatment LDL-C (12.0 ± 7.7 vs 13.4 ± 4.7 mmol/L, respectively, p < 0.001, Supplementary Fig. 2B).

Step B yielded similar results as in Step A but the optimal relationship was linear (r = 0.355, slope = 0.6568, p < 0.0001, Supplementary Fig. 3). In this analysis the imputed LDL-C was significantly higher than the measured pre-treated LDL-C (15.7 ± 6.7 vs 13.4 ± 4.7 mmol/L, respectively, p < 0.001) (Supplementary Fig. 4A and 4B). In Step C, all observations were combined to yield a final regression relationship between intensity of therapy and measured LDL-C. In this step, the optimal relationship was curvilinear (r = 0.3923, p < 0.0001, Fig. 1, and

Table 1
Demographic and treatment information of subjects in Group 1 (n = 193) and Group 2 (n = 206). ASCVD = atherosclerotic cardiovascular disease, LDL-C = low-density lipoprotein cholesterol, mmol/L = millimoles per Litre, ns = not significant, SD = standard deviation.

		Group 1	Group 2	p value
Subjects (n)		193	206	
Male (%)		87 (45 %)	96 (47 %)	ns
Female (%)		106 (55 %)	110 (53 %)	
Age (years)[a] (mean ± SD)		26.7 ± 15.3	21.5 ± 18.1	0.0001
Ethnicity (%)[b]	Asian	15 (8 %)	47 (23 %)	<0.001
	Black	4 (2 %)	5 (2 %)	
	Mixed	9 (5 %)	29 (14 %)	
	White	165 (85 %)	113 (55 %)	
Prior ASCVD (%)[c]	Yes	90 (47 %)	70 (34 %)	<0.02
	No	103 (53 %)	133 (65 %)	
LDL-C, mmol/L (SD)	Baseline	13.4 ± 4.8	13.4 ± 4.7	ns
	Treated	9.6 ± 4.1	7.5 ± 4.6	<0.0001
Treatments	Statin + Ezetimibe	77	78	<0.001
	Statin monotherapy	54	51	
	PCSK9 inhibitor monotherapy	48	1	
	Statin + Ezetimibe + PCSK9 inhibitor	0	53	
	Statin + PCSK9 inhibitor	0	3	
	Statin + Ezetimibe + Inclisiran	0	1	
	Statin + Resin + PCSK9 inhibitor	0	1	
	Statin + Ezetimibe + Resin + PCSK9 inhibitor	0	1	
	Other treatments (listed below)	14	17	
Other treatments	*Statin + Ezetimibe + Resin*	*1*	*6*	–
	Statin + Resin	*3*	*2*	–
	Ezetimibe monotherapy	*0*	*4*	–
	Resin monotherapy	*3*	*1*	–
	Statin + Ezetimibe + Niacin	*4*	*0*	–
	Statin + Ezetimibe + Probucol	*0*	*2*	–
	Statin + Probucol	*1*	*0*	–
	Statin + Ezetimibe + Bempedoic Acid	*0*	*1*	–
	Statin + Resin + Probucol	*0*	*1*	–
	Statin + Ezetimibe + Niacin + Resin	*1*	*0*	–
	Niacin + Resin	*1*	*0*	–

[a] Age at time of entry into the registry or at time of diagnosis or treatment. Age missing for 5 subjects in Group 2.
[b] Ethnicity missing for 12 subjects in Group 2.
[c] Prior ASCVD missing for 3 subjects in Group 2.

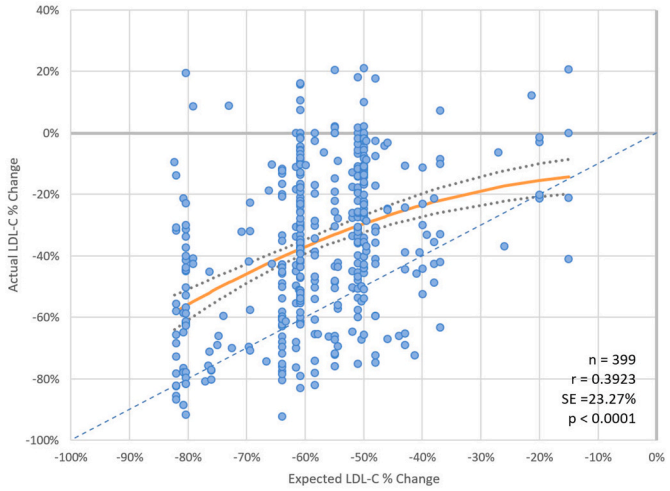

Fig. 1. Relationship between expected percent reduction in LDL-C and actual percent LDL-reduction observed in the combination of Groups 1 and 2. LDL-C = low density lipoprotein cholesterol, n = num of patients, SE = standard error.

Supplementary Fig. 5). The mean, imputed LDL-C showed a significant correlation with pre-treatment LDL-C ($p < 0.001$) with $r = 0.71$, slope = 1.187 and SE of 5.56 mmol/L (Fig. 2A). Based on mean values, Fig. 2B demonstrates that the imputed LDL-C was similar to the actual pre-treatment value (actual = 13.4 ± 4.7 vs imputed 13.6 ± 7.3 mmol/L, p = ns).

Of the 399 observations, there were 297 (74 %) with pre-treatment LDL-C ≥ 10 mmol/L and 64 % (255) with imputed LDL-C ≥10 mmol/L. The overall concordance between pre-treatment LDL-C and imputed LDL-C using a threshold of 10 mmol/L was 80 % with sensitivity of 79 % and specificity of 80 % ($p < 0.001$) (Table 2A). Further application of the regression algorithm for imputation of untreated LDL-C is demonstrated in Table 2B. Based on treated LDL-C, 144 patients (36 %) had values ≥ 10 mmol/L and 255 had values below this. Of the latter, 111 had imputed pre-treatment LDL-C ≥ 10 mmol/L. Thus, sensitivity for identification of subjects known to meet criteria for HoFH before treatment was augmented from 36 % to 64 %, a factor of 1.78 fold, when incorporating the imputation algorithm (Fig. 3).

The algorithm is freely available for use at: https://www.circl.ubc.ca/english/web_fh2025.html. Example vignette 1: A 45 yo male is evaluated who does not know his family history with respect to either

Table 2
Pre-treatment, treated and imputed LDL-C. A) Concordance between pre-treatment LDL-C and imputed pre-treatment LDL-C stratified by LDL-C ≥ or <10 mmol/L. B) Relationship between treated LDL-C and imputed pre-treatment LDL-C.

		Imputed LDL-C		
		≥10 mmol/L	<10 mmol/L	
A) Pre-treatment LDL-C	≥10 mmol/L (n = 297)	235 (59 %)	62 (15 %)	Concordance = 80 % Sensitivity = 79 % Specificity = 80 % p < 0.001
	<10 mmol/L (n = 102)	20 (5 %)	82 (21 %)	

		Imputed LDL-C	
		≥10 mmol/L	<10 mmol/L
B) Treated LDL-C	≥10 mmol/L (n = 144)	144 (36 %)	0 (0 %)
	5 - < 10 mmol/L (n = 145)	110 (27 %)	35 (9 %)
	<5 mmol/L (n = 110)	1 (<1 %)	109 (27 %)
		255 (64 %)	144 (36 %)

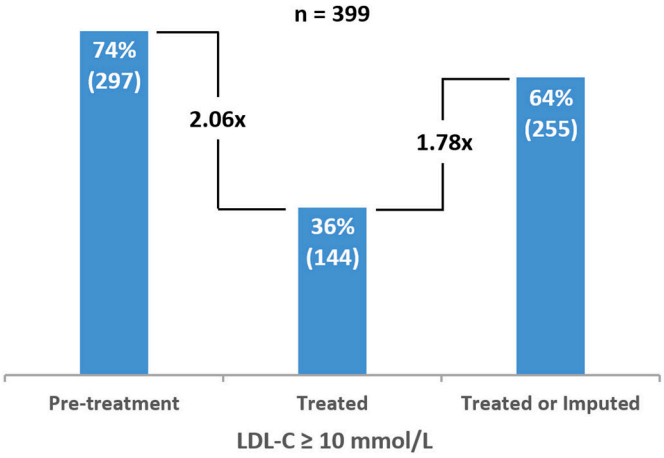

Fig. 3. Percentage of patients with pre-treatment, treated and treated or imputed LDL-C ≥ 10 mmol/L. There were 74 % of patients with LDL-C ≥ 10 mmol/L pre-treatment which fell by 2.08x after treatment to 36 %. Use of imputation, however, increased the proportion by 1.78x to 64 % of subjects meeting at least the lipid criterion for suspecting homozygous familial hypercholesterolemia.

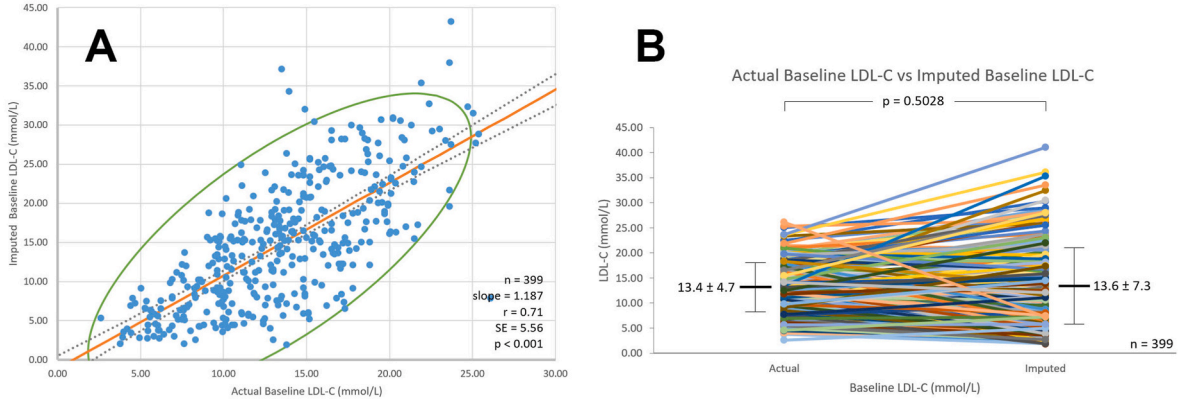

Fig. 2. Imputation of LDL-C from treated LDL-C. Panel A – Linear regression between actual, baseline LDL-C and imputed LDL-C in Groups 1 and 2 using the algorithm developed and shown in Fig. 1. Panel B – Mean values of actual and imputed LDL-C in Groups 1 and 2. Abbreviations as in Fig. 1.

dyslipidemia in the parents or premature cardiovascular disease. He has a xanthoma but does not recall when he first noticed it. He is currently on rosuvastatin 40 mg and ezetimibe 10 mg. The treated LDL-C is 6 mmol/L and no record of pre-treatment LDL-C is available. Although the clinician is confident that the patient has at least HeFH, an imputed LDL-C, assuming absent or dysfunctional LDL receptors is 10.38 suggesting that HoFH should be suspected. Example vignette 2: A 15 yo adopted female is evaluated with no known details of her family history. She is currently taking atorvastatin 10 mg and ezetimibe 10 mg. The treated LDL-C is 7 mmol/L and no record of pre-treatment LDL-C is available. Assuming absent or dysfunctional LDL receptors, the imputed LDL-C is 10.13 raising the suspicion of HoFH.

4. Discussion

In a large international cohort comprising 399 individuals with HoFH we report a modest but quantifiable relationship between the normally expected intensity of LDLR-dependent therapies and actual % LDL-C lowering. This unique relationship can be applied to treated LDL-C to calculate an imputed untreated LDL-C when it is unavailable in subjects already on LLT and who are not known to have HoFH. This approach can substantially increase awareness of underlying HoFH in hypercholesterolemic patients, especially when genotyping is either not known or not accessible and when pre-treatment LDL-C is not available to the physician.

Our results are concordant with the observations of Tromp et al. showing that treated LDL-C in HoFH is inversely proportional to the number of therapies utilized [10]. Conceptually, we have extended this pivotal observation in a more granular and quantitative fashion by comparing the more typically expected average percentage reductions in LDL-C using LDLR-dependent therapies and the observed percentage reductions specific to a worldwide cohort of subjects with HoFH.

From epidemiological analyses worldwide, there is consensus that HoFH is under-appreciated and underdiagnosed, resulting in late and/or inadequate treatment as well as suboptimal outcomes [3,10–12,22,35,36]. The approach proposed in this study has the potential to improve appreciation for the potential diagnosis of HoFH among subjects without access to genotyping and with unknown pre-treatment LDL-C.

The potential clinical diagnostic implications of this imputation approach are underscored by a detailed interpretation of Table 2. It is unsurprising that subjects with a treated LDL-C $\geq$ 10 mmol/L require no imputation algorithms to raise the suspicion of HoFH. Secondly, in the remaining patients with treated LDL-C $<$ 10 mmol/L and thus in a diagnostic “grey zone”, consideration of HoFH would be augmented from 36 % (those with treated LDL-C $\geq$ 10 mmol/L) to 64 % of cases with either treated or imputed LDL-C above this threshold, an increase of 1.78 fold (Fig. 3). Raising suspicion of an underlying diagnosis of HoFH is particularly valuable in the group with treated LDL-C above 5 mmol/L. In the group with treated LDL-C $<$ 5 mmol/L, we identified only 1 instance of an imputed LDL-C $\geq$ 10 mmol/L and in that instance, the untreated LDL-C was also $\geq$10 mmol/L.

This analysis has important, direct and practical implications. The clinical application of this imputation method when untreated LDL-C is unknown would enhance awareness of HoFH and might justify genetic confirmation and cascade screening of families. When genotyping is either inaccessible or impractical, particularly in lower and middle income countries, remote regions or even countries at war, the imputed untreated LDL-C $\geq$ 10 mmol/L could be used to at least fulfill the lipid criterion for suspected HoFH [37,38]. Furthermore, since an optimal outcome is most closely associated with a sustained, low level of LDL-C, access to restricted medications could be justified on the basis of the imputation of untreated LDL-C in the range compatible with HoFH [8–10,14,20,21,39]. Thus, the results of this analysis are potentially far reaching and impactful for many patients with HoFH. We propose for consideration that the diagnostic criteria of the clinical definition of HoFH be updated to include LDL-C $\geq$ 10 mmol/L that is untreated, treated or imputed. In these circumstances, individuals may warrant access to genetic testing, their families should undergo cascade screening and access to non-LDLR-dependent therapies for optimal management should be considered when standard therapies fail to optimize treatment.

5. Limitations

There are limitations to this analysis. First, the original intent of developing a regression equation for imputation in one population and validating it in a separate, independent population was attenuated somewhat by the demographic, and therapeutic differences between the cohorts. In particular, despite equal pre-treatment LDL-C level, the treated LDL-C level in Group 1 was higher than in Group 2. This is probably the dominant reason for the underestimation of true untreated LDL-C in Step A and the overestimation in Step B. However, we have shown that the resultant linear regression equations developed in Steps A and B for imputing LDL-C were similar, justifying the combined analysis in Step C. This also broadens the applicability of the algorithm worldwide. Secondly, it should be apparent that the imputation regression equation shows wide variation of approximately 20% LDL-C lowering and a $\pm$5 mmol/L error in any imputed LDL-C. This is expected, given known inter-individual variability in LLT response in any subject, not only patients living with HoFH, and our analyses are based solely on average responses. Moreover, we are limited by unmeasured confounders affecting LDL-C response to LLT including adherence, functional genotyping, dietary changes and many others. Thus, the imputed point value can only provide a rough guide as to whether a given patient is responding sub-optimally to LDLR-dependent therapies and whether this may be due to underlying HoFH. We believe, however, that the practical implication with respect to raising awareness and confidence in the diagnosis of HoFH outweighs this limitation. Although the imputation algorithm rarely identifies imputed pre-treatment LDL-C $\geq$ 10 mmol/L when treated LDL-C is $<$ 5 mmol/L, the imputation of a value $\geq$ 5–10 mmol/L would still provide suspicion for underlying genetic dyslipidemia such as HeFH and motivation to pursue further clinical work up and intervention as necessary. Analyses of responses based on functional genotyping were not feasible in this proof-of-concept analysis due to the frequency with which this parameter was either not available or ambiguous. However, as a tool for increasing awareness of the possibility of HoFH when pretreatment LDL-C is not available, the inclusion of subjects with a diverse spectrum of functional genotypes ensures that the imputation results are realistic. Finally, since the initiation and submission of this project, the importance of the concept is underscored by a recent publication from Gu et al. [40] which describes a simulation model to estimate pretreatment LDL-C in people living with HoFH. In contrast, our algorithm is the first to be based upon actual patient observations, not simulations. Both approaches are similarly motivated to facilitate education and awareness about HoFH in an effort to reduce the time to implementation of diagnostic testing and implementation of appropriate treatments which should ultimately improve outcomes.

6. Conclusion

In conclusion, imputation of an untreated, baseline LDL-C can be performed in HoFH. In practice, this approach may be valuable in individuals on treatment without a pre-treatment LDL-C on record and not previously suspected to have HoFH. This would improve awareness of the possibility of underlying HoFH, prompting further diagnostic confirmation, referral to lipid specialists, and/or family cascade-screening, genetic testing, and access to additional lipid lowering therapies, all of which should optimize outcomes. Such implementation would also promote equity and patient-centered management even for those living in emerging economies, remote regions and other disadvantaged areas.

Data availability statement

Upon reasonable request, data is available. Please note that data ownership for the data shared with the registries of patients with HoFH remains the property of the individual contributors. Data will not be shared with third parties without the respective contributors' approval.

CRediT authorship contribution statement

GBJM: Visualization, Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing, Funding acquisition, Project administration, Supervision. AR: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. IR: Investigation, Data curation, Writing – review & editing. II: Investigation, Writing – review & editing. JG: Investigation, Writing – review & editing. FJR: Investigation, Writing – review & editing. RDS: Investigation, Writing – review & editing. APM: Investigation, Writing – review & editing. RAH: Investigation, Writing – review & editing. BAK: Investigation, Data curation, Writing – review & editing. LRB: Investigation, Writing – review & editing. DG: Investigation, Writing – review & editing. ML: Investigation, Data curation, Writing – review & editing. DB: Investigation, Data curation, Writing – review & editing. WS: Investigation, Data curation, Writing – review & editing. LFR: Investigation, Writing – review & editing.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **GBJM**: has received research grants, honoraria, or consulting fees for professional input and/or delivered lectures for Amgen, AstraZeneca, Boehringer-Ingelheim, Esperion, HLS Therapeutics, Lilly, Merck, Novartis, Novo Nordisk, Sanofi, Ultragenyx**AR**: none**IR**: none**II**: has served on advisory boards for Amgen, HLS Therapeutics, Novartis and Ultragenyx, and received honoraria from Amgen, Novartis, Sanofi and Ultragenyx.**FJR**: has received research grants, honoraria, or consulting fees for professional input and/or delivered lectures from Amgen, AstraZeneca, MSD, Novartis, Sanofi, Regeneron, Ultragenyx, Chiesi, Cipla, Silence Therapeutics, Verve Therapeutics and LIB Therapeutics. **RDS**: reports consultancies, talks and research sponsored by Ache, Amgen, Amryt, Daiichi-Sankyo, Eli-Lilly, Esperion, Ionis, Kowa, Libbs, MSD, Novartis, Novo Nordisk, PTC Therapeutics, Torrent, Ultragenyx and Sanofi/Regeneron. RDS also receives a scholarship from Conselho Nacional de Pesquisa e Desenvolviment Tenologico, BRAZIL.**APM**: none**RAH**: has received research grants or contracts from Ionis, Arrowhead, Novartis, Amryt; consulting fees from Arrowhead, Amgen, Acasti Pharma, Aegerion Pharmaceuticals, Akcea Therapeutics/Ionis Pharmaceuticals, HLS Therapeutics, Novartis, Pfizer, Regeneron, Sanofi, and Ultragenyx; honoraria from Amgen, Sanofi, HLS Therapeutics, and Ionis; and participation on steering committees for Novartis and Madrigal.**BK**: none**LRB**: reports serving on Advisory board or receiving honoraria from Amgen, HLS Therapeutics, Novartis and Ultragenyx.**DG** reports research grants or consulting fees from Amgen, Amryt, Arrowhead, CRISPRx, Eli Lilly, Esperion, Merck, New Amsterdam Pharma, Novartis, Regeneron, Ultragenyx, and Verve Therapeutics. Research grant payments are received by ECOGENE-21, an academic non-profit research organization.**ML**: has received a PhD grant from ECOGENE-21 and the Centre intersectoriel en sante durable (CISD), Chicoutimi, Quebec, CANADA.**DB**: none**WAMS**: none**LFR**: reports serving on advisory board of Amgen, receiving speakers fee from Novartis, Daiichi Sankyo, and Ultragenyx, and is co-founder of Lipid Tools B.V.**JG:** none**The declaration of interests of individual collaborators are listed in the Supplementary Files**.

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Appendix A. Supplementary data

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