Imputation of Baseline LDL Cholesterol Concentration in Patients with Familial Hypercholesterolemia on Statins or Ezetimibe

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BACKGROUND: Familial hypercholesterolemia (FH) is the most frequent genetic disorder seen clinically and is characterized by increased LDL cholesterol (LDL-C) (>95th percentile), family history of increased LDL-C, premature atherosclerotic cardiovascular disease (ASCVD) in the patient or in first-degree relatives, presence of tendinous xanthomas or premature corneal arcus, or presence of a pathogenic mutation in the *LDLR*, *PCSK9*, or *APOB* genes. A diagnosis of FH has important clinical implications with respect to lifelong risk of ASCVD and requirement for intensive pharmacological therapy. The concentration of baseline LDL-C (untreated) is essential for the diagnosis of FH but is often not available because the individual is already on statin therapy.

METHODS: To validate a new algorithm to impute baseline LDL-C, we examined 1297 patients. The baseline LDL-C was compared with the imputed baseline obtained within 18 months of the initiation of therapy. We compared the percent reduction in LDL-C on treatment from baseline with the published percent reductions.

RESULTS: After eliminating individuals with missing data, nonstandard doses of statins, or medications other than statins or ezetimibe, we provide data on 951 patients. The mean ± SE baseline LDL-C was 243.0 (2.2) mg/dL [6.28 (0.06) mmol/L], and the mean ± SE imputed baseline LDL-C was 244.2 (2.6) mg/dL [6.31 (0.07) mmol/L] ($P = 0.48$). There was no difference in response according to the patient's sex or in percent reduction between observed and expected for individual doses or types of statin or ezetimibe.

CONCLUSIONS: We provide a validated estimation of baseline LDL-C for patients with FH that may help clinicians in making a diagnosis.

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Familial hypercholesterolemia (FH)[15] is characterized by increased circulating concentrations of LDL cholesterol (LDL-C) and is transmitted in an autosomal codominant fashion. FH is the most frequent monogenic disorder in clinical practice and is caused by mutations at the LDL receptor (*LDLR*)[16], apolipoprotein B (*APOB*), or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes *(1)*. Other genes have also been shown to be associated with the FH phenotype, but these are rare. Some patients with the FH phenotype may have multiple single-nucleotide polymorphisms in genes that have been shown to exert an effect on LDL-C *(2)*.

The prevalence of FH, once considered to be 1 in 500, has been adjusted in light of more precise diagnostic criteria and is now estimated to be 1 in 250 worldwide *(3)*, with a higher prevalence in populations with founder effects, such as that seen in the French-Canadian population.

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[15] Nonstandard abbreviations: FH, familial hypercholesterolemia; LDL-C, LDL cholesterol; ASCVD, atherosclerotic cardiovascular disease.

[16] Human genes: *LDLR*, LDL receptor gene; *APOB*, apolipoprotein B gene; *PCSK9*, proprotein convertase subtilisin/kexin type 9 gene.

There are 2 widely used and internationally accepted definitions for FH, namely, those from the Dutch Lipid Clinics Network and the Simon Broome Registry criteria. Each relies on documenting an increased LDL-C in an adult (usually >200 mg/dL or >5.0 mmol/L), together with a family history of increased LDL-C in first-degree relatives, or premature atherosclerotic cardiovascular disease (ASCVD) in a first-degree relative, plus the presence of xanthomas, xanthelasmas, or premature corneal arcus (4–9). A DNA diagnosis may confirm the diagnosis unambiguously but is not required for a clinical diagnosis. Other definitions include that from the Japanese Atherosclerosis Society, which has adapted the Simon-Broome Registry criteria, and also the MedPed definition, which is used infrequently because it relies on strict LDL-C cutpoints imposed on first-, second-, and third-degree relatives, making it impractical in a clinical setting (10, 11). A new Canadian definition for FH has also adapted the Simon Broome Registry criteria, but it offers these in a simplified version (6).

FH is frequently undiagnosed worldwide, except for in countries such as the Netherlands, Norway, Switzerland, Iceland, and the UK (1), where national registries have been implemented. The experience from the Netherlands has shown that if recognized and treated early, patients with FH can have a similar rate of coronary heart disease as the general population (12). A precise diagnosis of FH is important. Two recent studies have shown that the risk of ASCVD in patients with an LDL-C >200 mg/dL (>5.0 mmol/L) is increased approximately 6-fold compared with an individual with an LDL-C of 130 mg/dL (3.4 mmol/L). However, if a patient has a mutation in the *LDLR*, *APOB*, or *PCSK9* genes known to cause FH, this risk is increased 10- to 22-fold (13, 14). Once a subject is diagnosed with FH, cascade screening, consisting of screening all first-degree relatives, proves to be a cost-efficient way to identify additional affected individuals (15–19). Many international groups have made awareness, screening, and treatment of FH a priority (7, 8, 20–22).

Often, the baseline pretreatment LDL-C is not available because the patient has initiated and continues to receive lipid-lowering therapy, especially statins. Further, the original baseline LDL-C may predate the current assessment by many years and cannot be easily retrieved. Most guidelines consider that a definite diagnosis of FH mandates lipid-lowering therapy and family screening (1, 6, 21, 23, 24). Access to inhibitors of PCSK9 and more costly medications, such as mipomersen or lomitapide, may depend on a diagnosis of FH in some countries (25–28).

We have provided an application for computers and smartphones to make the diagnosis of FH based on the Simon Broome Registry criteria, the Dutch Lipid Clinics Network criteria, and the new Canadian FH definition

(6) that uses an imputed baseline LDL-C if the patient is on lipid-lowering therapy with either statins and/or ezetimibe. This application can be accessed online (http://www.circl.ubc.ca/english/web_fh.html) (29). We used a metaanalysis that provides the average LDL-C reduction for each statin at indicated prescribed doses. We used the same data for the fixed 10-mg/day dose of ezetimibe as monotherapy or in combination with statins (30). In the present analysis, we present the validation of the imputation of a baseline LDL-C based on the observed impact of current lipid-lowering therapies with statins and/or ezetimibe in FH patients. Access to this algorithm is also available through the website of FH Canada (www.FHCanada.net) (31).

Materials and Methods

We performed a retrospective analysis on data from 1297 patients with FH from 6 clinics across Canada (Co-author involved: RAH; LB; JB, PC; RD, AB, JG, IR; DG, DB) in whom a baseline LDL-C was available before the initiation of statins or ezetimibe and in whom an LDL-C was available within 18 months after the initiation of therapy [mean 7.2 (3.8) months]. We selected the 18-month time point to ensure the patients were on a stable dose of medication. We eliminated patients with missing data or noncompliance to treatment (n = 45), patients with an on-treatment LDL-C determined >18 months after initiation of therapy (n = 120), patients on lipid-lowering drugs other than statins or ezetimibe (n = 128), and patients on nonstandard dose of medication (e.g., rosuvastatin, 5 mg 3 times/week; simvastatin, 30 mg/day) (n = 53) (Fig. 1). All data were deidentified. The protocol for the Canadian FH registry was reviewed and accepted by the Research Ethics Board of the McGill University Health Center.

We used the metaanalysis of Hou et al. (30) to determine the mean percent change from baseline for lovastatin (10, 20, 40, and 80 mg), pravastatin (10, 20, and 40 mg), simvastatin (5, 10, 20, 40, and 80 mg), atorvastatin (10, 20, 40, and 80 mg), fluvastatin (20 and 40 mg), rosuvastatin (5, 10, 20, and 40 mg), and ezetimibe (10 mg; all daily doses). The selection criteria were a diagnosis of FH based on the Dutch Lipid Clinics Network (definite or probable) or the Simon Broome Registry criteria (definite or probable), a baseline LDL-C calculated by the Friedewald formula in a patient naïve to lipid-lowering therapies and a follow-up evaluation, and on-treatment LDL-C obtained within 18 months. In all cases, secondary causes of severe hypercholesterolemia (e.g., hypothyroidism, liver disease, nephrotic syndrome, or medications) were ruled out. For ezetimibe, most patients were taking an optimal dose of statin, and the follow-up LDL-C was then taken as the new baseline. Some patients were started on statin and ezetimibe simul-

Fig. 1. Study flow chart.
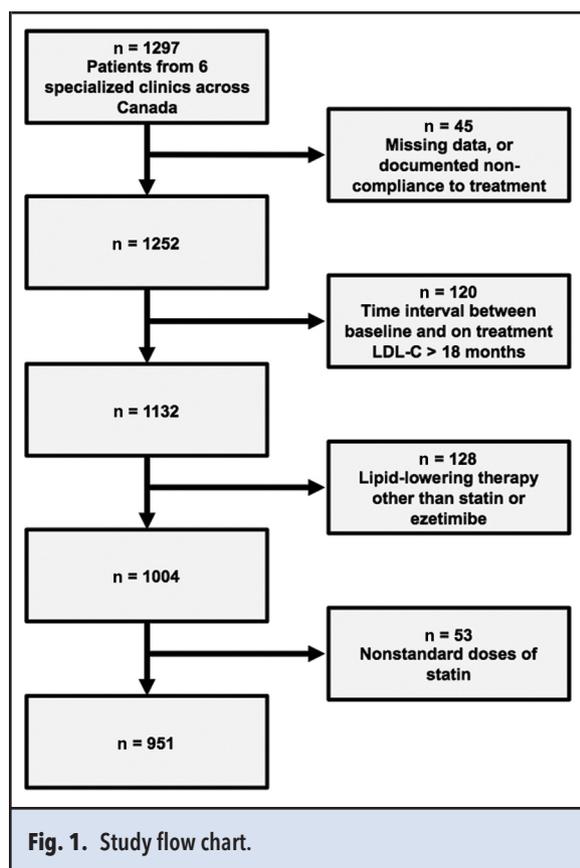
taneously, and the validation of the imputed LDL-C compared with baseline LDL-C was examined separately. We examined the effects of a patient's sex in the comparison of baseline vs imputed baseline LDL-C.

STATISTICAL ANALYSIS

Data are expressed as mean ± SE (see figures) or mean ± SD (see tables). The imputation of the LDL-C was per-

formed by dividing the on-treatment LDL-C by the reciprocal of the expected percent change (Table 1). Patients were then grouped according to the dose and type of statin prescribed. The expected percent change was compared with the observed percent (±SE) change for each dose and type of statin or ezetimibe. Because the expected percent change from baseline is based on a metaanalysis of multiple studies, no SE is provided. Therefore, we used a single-sided t-test to determine statistical significance. For each dose of each medication, the mean baseline LDL-C was compared with the mean of imputed baseline LDL-C by 2-tailed paired t-tests. A Bonferroni adjustment for multiple t-tests was made with the level of significance set at $P < 0.002$ (0.05/23 tests). A correlation between baseline and imputed LDL-C was performed for each dose of each medication by Pearson linear regression, and a correlation coefficient (r) and P value were determined. When available, the association between effect of sex on baseline and imputed LDL-C was determined (n = 788). All statistical analyses were performed using the IBM SPSS Statistics version 22.0.

Results

We obtained data on 1297 patients, and after eliminating those with missing data, nonstandard doses of statins, or medications other than statins or ezetimibe, 951 patients with FH were included in the final analysis (Fig. 1). The mean ± SD age was 43 (14) years (range, 9–80 years; 50% female). The number of patients on each dose of statin is shown in Table 2. The mean baseline LDL-C for all patients receiving a specific dose of a statin, the on-treatment LDL-C, the observed reduction in LDL-C, and the predicted percent reduction [derived from Table 1 of Hou et al. *(30)*] are shown in Table 2. We first compared the predicted percent reduction with the observed reduction: Fig. 2 shows the differences between

Medication	5 mg	10 mg	20 mg	40 mg	80 mg
	Mean reduction by dose: percent change from baseline (divide LDL-C by this factor)				
Rosuvastatin	−40 (0.60)	−46 (0.54)	−52 (0.48)	−55 (0.45)	−
Atorvastatin	−	−37 (0.63)	−43 (0.57)	−48 (0.52)	−51 (0.49)
Simvastatin	−26 (0.74)	−30 (0.70)	−38 (0.62)	−41 (0.59)	−47 (0.53)
Lovastatin	−	−21 (0.79)	−27 (0.73)	−31 (0.69)	−40 (0.60)
Pravastatin	−	−20 (0.80)	−24 (0.76)	−30 (0.70)	−36 (0.64)
Fluvastatin	−	−	−22 (0.78)	−25 (0.75)	−35 (0.65)
Ezetimibe alone	−	−20 (0.80)	−	−	−
Ezetimibe 10 mg added to a statin	−20 (0.80)	−20 (0.80)	−20 (0.80)	−20 (0.80)	−20 (0.80)

Table 1. Expected percent reduction in LDL-C according to dose and statin and ezetimibe.[a]

[a] Data derived from Hou et al. *(30)*.

Table 2. Baseline and imputed baseline LDL-C.[a]

Statin, dose/mg	Number	Baseline LDL-C, mg/dL	On Rx LDL-C, mg/dL	Observed reduction, %	Expected reduction (30), %	Imputed LDL-C, mg/dL	P value[b]	Pearson correlation	
								r value	P value
Lovastatin, 10	9	265.6 ± 89.2	199.8 ± 81.7	24.2 ± 14.6	21	252.9 ± 103.4	0.50	0.85	0.004
Lovastatin, 20	97	255.0 ± 61.4	182.9 ± 48.7	27.6 ± 12.6	27	250.5 ± 66.7	0.32	0.76	<0.001
Lovastatin, 40	63	258.9 ± 60.3	176.0 ± 41.9	30.8 ± 13.8	31	255.1 ± 60.7	0.59	0.58	<0.001
Lovastatin, 80	17	317.1 ± 83.7	218.2 ± 50.3	28.9 ± 17.3	40	363.6 ± 83.8	0.05	0.40	0.107
Pravastatin, 10	18	229.2 ± 52.4	174.5 ± 42.5	22.7 ± 13.4	20	218.1 ± 53.2	0.32	0.62	0.006
Pravastatin, 20	28	258.4 ± 44.8	180.3 ± 37.9	29.4 ± 13.7	24	237.3 ± 49.9	0.03	0.49	0.007
Pravastatin, 40	22	279.1 ± 71.0	183.3 ± 56.9	33.4 ± 16.8	30	261.8 ± 81.3	0.30	0.51	0.015
Simvastatin, 5	7	271.5 ± 101.1	208.8 ± 93.7	24.1 ± 15.5	26	282.2 ± 126.7	0.56	0.94	0.002
Simvastatin, 10	72	246.2 ± 49.1	179.1 ± 44.9	27.3 ± 11.3	30	255.8 ± 64.1	0.04	0.79	<0.001
Simvastatin, 20	97	267.6 ± 53.0	172.3 ± 38.8	34.9 ± 11.8	38	277.9 ± 62.6	0.04	0.66	<0.001
Simvastatin, 40	42	280.1 ± 41.2	185.4 ± 40.6	32.9 ± 15.7	41	314.3 ± 68.8	0.003	0.27	0.09
Simvastatin, 80	6	282.2 ± 49.4	142.6 ± 20.2	48.9 ± 6.9	47	269.1 ± 38.2	0.43	0.67	0.15
Atorvastatin, 10	37	231.4 ± 51.0	154.3 ± 42.5	32.7 ± 14.8	37	244.9 ± 67.5	0.10	0.70	<0.001
Atorvastatin, 20	58	252.6 ± 53.4	146.5 ± 34.0	40.5 ± 12.9	43	257.1 ± 59.7	0.49	0.62	<0.001
Atorvastatin, 40	52	289.9 ± 68.1	157.4 ± 47.0	45.3 ± 12.0	48	302.6 ± 90.4	0.16	0.71	<0.001
Atorvastatin, 80	23	290.8 ± 70.8	131.2 ± 31.9	53.0 ± 13.4	51	267.7 ± 65.1	0.14	0.43	0.04
Fluvastatin, 20	10	226.4 ± 51.0	171.9 ± 39.1	21.8 ± 18.4	22	220.4 ± 50.1	0.76	0.30	0.40
Fluvastatin, 40	7	234.8 ± 35.3	157.4 ± 32.9	32.8 ± 10.5	25	209.9 ± 43.9	0.10	0.66	0.11
Rosuvastatin, 5	34	221.4 ± 47.1	138.8 ± 37.0	37.0 ± 11.6	40	231.4 ± 61.6	0.20	0.70	<0.001
Rosuvastatin, 10	46	236.9 ± 50.3	130.1 ± 41.1	45.4 ± 11.7	46	241.0 ± 76.1	0.58	0.76	<0.001
Rosuvastatin, 20	26	273.6 ± 61.9	139.8 ± 44.8	48.9 ± 10.8	52	291.3 ± 93.3	0.18	0.71	<0.001
Rosuvastatin, 40	6	274.7 ± 57.1	140.9 ± 35.0	45.5 ± 23.1	55	313.1 ± 77.9	0.45	−0.42	0.41
Ezetimibe, 10	172	169.5 ± 43.6	123.5 ± 34.2	26.3 ± 13.7	20	154.3 ± 42.7	<0.001	0.69	<0.001

[a] For each statin (lovastatin, 10, 20, 40, and 80 mg/day), pravastatin (10, 20, and 40 mg/day), simvastatin (5, 10, 20, 40, and 80 mg/day), atorvastatin (10, 20, 40, and 80 mg/day), fluvastatin (20 and 40 mg/day), rosuvastatin (5, 10, 20, and 40 mg/day), and ezetimibe (10 mg/day), the number of subjects, baseline and on-treatment, the observed reduction for each dose of statins and ezetimibe, the expected reduction, and the imputed baseline LDL-C are shown.

[b] P value is for paired t-tests between observed baseline LDL-C and imputed baseline LDL-C. The nominal level of significance for multiple testing is set at P < 0.002. The Pearson linear correlation coefficient (r) and P value for baseline LDL-C and imputed baseline LDL-C are also shown. Results are expressed in mean ± SD. For SI units, please see Table 1 in the online Data Supplement.

Fig. 2. Histogram of observed percent reduction (± SE) vs expected percent reduction from Hou et al. *(30)* for all statins and all doses.
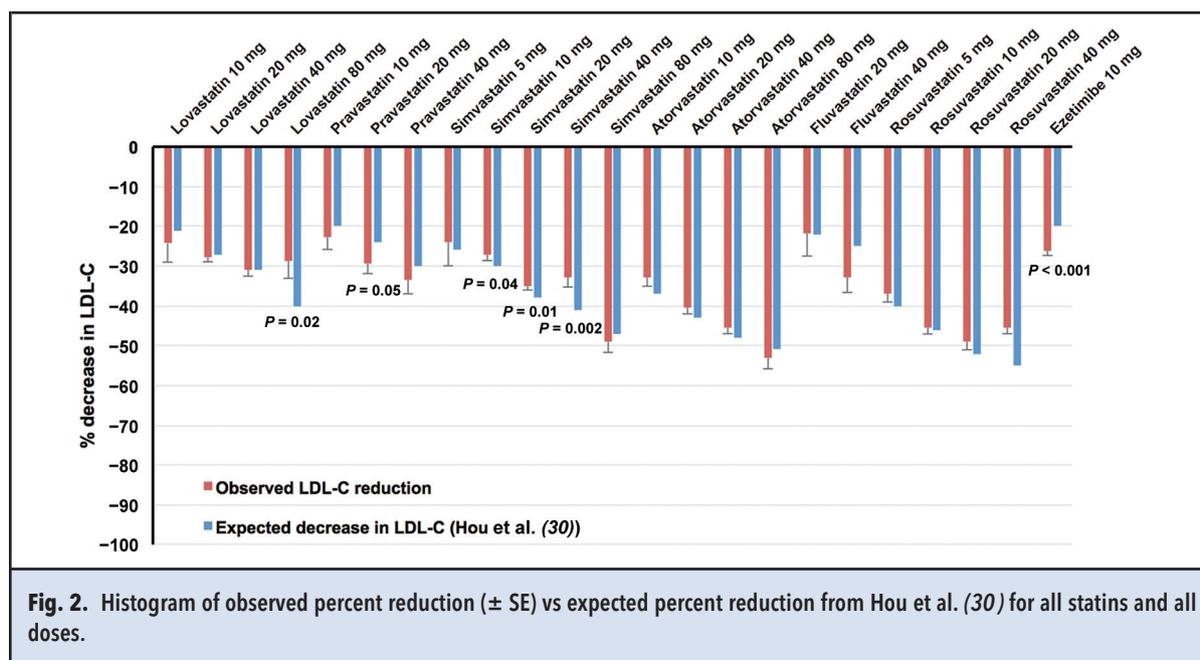
the observed vs expected percent LDL-C reduction for each dose of individual statins. There was a statistically significant difference ($P < 0.002$) between observed and expected percent LDL-C reduction for ezetimibe only.

The imputed baseline LDL-C was compared with the actual baseline LDL-C by paired 2-tailed *t*-test (Fig. 3). There were no statistically significant differences ($P > 0.002$) observed except for ezetimibe ($P < 0.001$). For lovastatin 80 mg, pravastatin 20 mg, and simvastatin 10, 20, and 40 mg, we observed marginal statistical significance. In the overall group, the mean ± SE baseline LDL-C was 243.0 (2.2) mg/dL [6.28 (0.06) mmol/L] and the mean ± SE imputed baseline LDL-C was 244.2 (2.6) mg/dL [6.31 (0.07) mmol/L] ($P = 0.48$) (Fig. 3, inset). There was no difference in response according to the patient's sex (see Figure 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol64/issue2). A DNA mutation in the *LDLR*, *APOB*, or *PCSK9* genes was identified in 429 of 951 (45%) individuals. Results were similar to those of the whole cohort.

The Pearson correlation coefficient for baseline observed and imputed baseline LDL-C was $r = 0.76$ ($P < 0.001$; Fig. 4). Histograms showing the comparison between observed vs expected percent LDL-C reduction (left panels), between baseline vs imputed LDL-C concentrations (middle panel), and the correlations between each dose of statins and ezetimibe (right panels) are shown Figs. 2–8 of the online Data Supplement. The data are presented for individual doses of each statin (lovastatin, 10, 20, 40, and 80 mg; pravastatin, 10, 20, and 40 mg; simvastatin, 5, 10, 20, 40, and 80 mg;

atorvastatin, 10, 20, 40, and 80 mg; fluvastatin, 20 and 40 mg; rosuvastatin, 5, 10, 20, and 40 mg; and ezetimibe, 10 mg).

Discussion

The diagnosis of FH relies on various criteria, each of which includes the concentration of LDL-C before the initiation of lipid-lowering therapy. Clinicians are frequently faced with a patient on lipid-lowering therapy with an on-treatment LDL-C concentration without knowledge of the baseline LDL-C. The reasons for this vary considerably, but inaccessibility of past medical records, changes in care providers, and patients' lack of recall can make the determination of the baseline LDL-C difficult, if not impossible. Current guidelines for the management of increased cholesterol support the use of high-intensity statins (atorvastatin 40–80 mg or rosuvastatin 20–40 mg/day) in high-risk individuals, targeting either a 50% reduction from baseline LDL-C or <70 mg/dL (1.8 mmol/L) *(21, 23, 24)*. In some cases, the LDL-C remains increased despite treatment. This can be because of lack of patient adherence to treatment, a decreased response to the prescribed dose, or an increased baseline LDL-C. Many patients who are compliant to prescribed high-dose statin and who have an on-treatment LDL-C that remains increased may, in fact, have FH.

Here, we provide validation for the calculation of an imputed baseline LDL-C that will help clinicians and raise awareness of the possibility that the patient may have FH, leading to more appropriate and intensive treat-

Fig. 3. Histogram of baseline vs imputed baseline LDL-C (± SE) for all doses of statins and ezetimibe.
Inset: overall comparison of observed baseline vs imputed baseline LDL-C.

Fig. 4. Scatterplot of all data (n = 951 patients), including ezetimibe, of observed baseline vs imputed baseline LDL-C.
The dotted lines indicate the 95% CIs for the regression line.
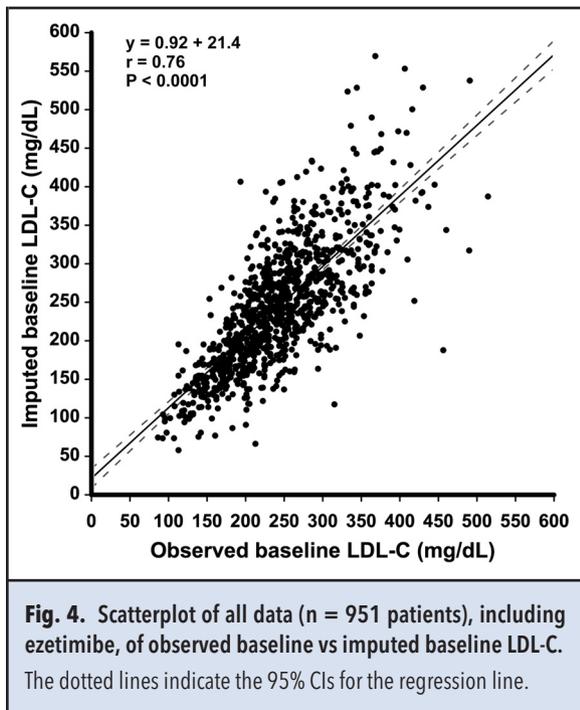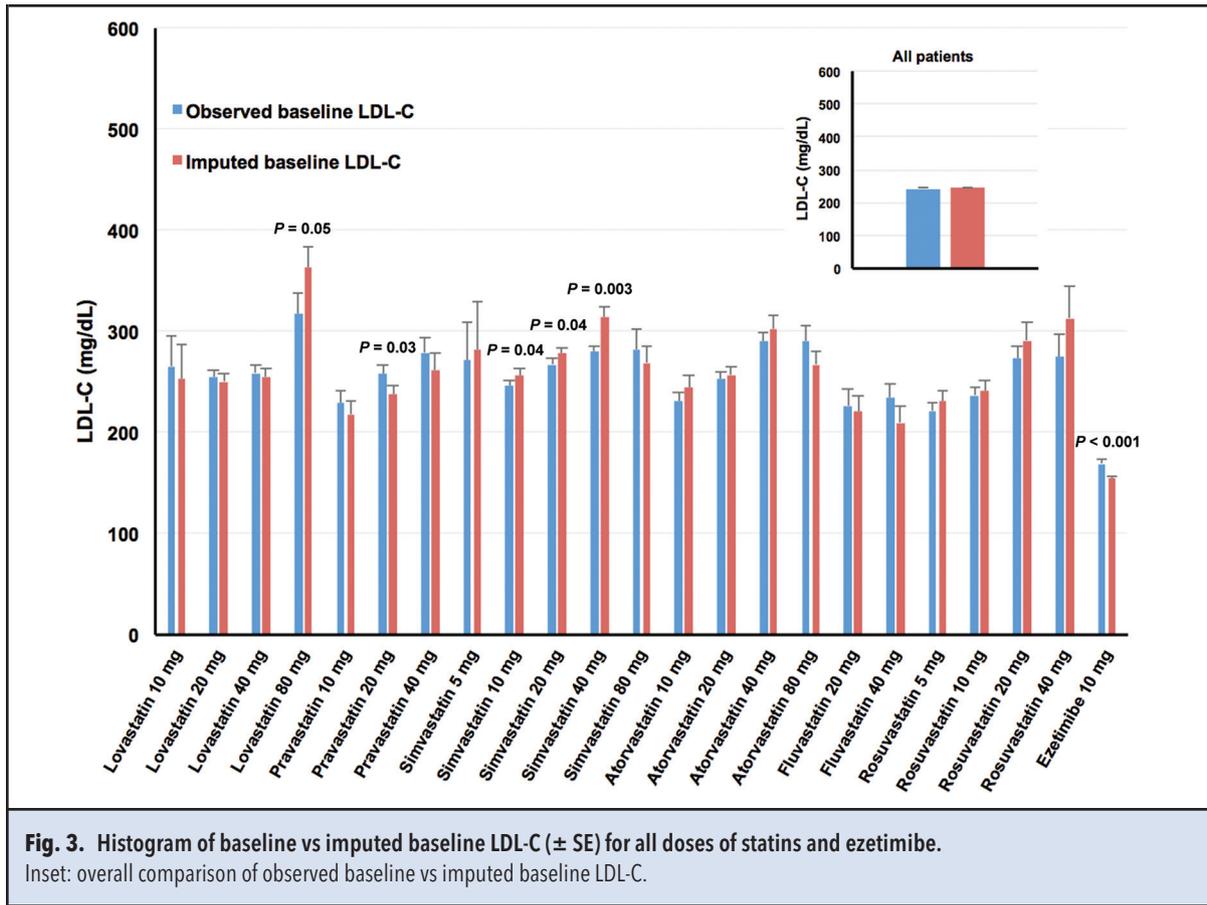
ment. Importantly, an increased LDL-C should spur cascade screening in the family for the detection of affected individuals. To facilitate both the calculation of the imputed baseline LDL-C and the diagnosis of FH, we provide a web-based and smartphone application, the FH Calculator, part of the updated CardioRisk Calculator available online through either the FH Canada website (http://www.fhcanada.net) (31) or http://www.circl.ubc. ca/english/web_fh.html (29). The "app" is also downloadable from the web free of charge.

National guidelines for the identification and treatment of patients with FH strongly recommend the use of statin therapy and/or ezetimibe to lower LDL-C. This is especially important for patients bearing a mutation in *LDLR*, *PCSK9*, or *APOB* genes, in whom the risk of ASCVD is 10- to 20-fold that of a normolipidemic individual (13, 14).

LIMITATIONS

The data are largely derived from retrospective analyses performed in 6 large specialized lipid clinics across Canada. We used the average response to specific doses of medications, but there is considerable interindividual

variability *(32)*. The correlation between baseline and imputed LDL-C ($r = 0.76$) (Fig. 4) shows that our imputed LDL-C can be overestimated (or, in some cases, underestimated); this can be because of patient adherence to treatment, variability in response, and type of mutations in genes causing FH. These results reflect current clinical practice in specialized clinics. Thus, in our large cohort of well-characterized FH patients, each with directly reported untreated LDL-C concentrations, our algorithm provides an excellent estimate of baseline untreated LDL-C concentrations using current treated concentrations together with information on the type of treatment. In FH in particular, baseline LDL-C concentrations are important for diagnosis and monitoring of adequate patient response to treatment, especially in primary prevention.

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Imputation of Baseline LDL-C Concentration in Patients with Familial Hypercholesterolemia on Statins or Ezetimibe

Running head: Imputation of baseline LDL-C in FH

<u>Supplemental Material</u>

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Key words: Familial Hypercholesterolemia, Diagnosis, Baseline LDL-cholesterol levels, Lipid-lowering therapy

Abbreviations: Familial Hypercholesterolemia: FH; atherosclerotic cardiovascular disease: ASCVD; low density lipoprotein cholesterol: LDL-C; standard error of the mean: SEM; standard deviation: SD.

Human genes: LDL receptor gene: *LDLR*; apolipoprotein B gene: *APOB*; proprotein convertase subtilisin/kexin type 9 gene: *PCSK9*.

Supplemental material:

Supplemental Table 1. Baseline and imputed baseline LDL-C (SI units)[&].

Statin, dose	Number	Baseline LDL-C (mmol/L)	On Rx LDL-C (mmol/L)	Observed reduction (%)	Expected reduction (30) (%)	Imputed LDL-C (mmol/L)	p value*	Pearson's correlation	
								r value	p value
Lovastatin 10	9	6.9 ± 2.3	5.2 ± 2.1	24.2 ± 14.6	21	6.5 ± 2.7	0.50	0.85	0.004
Lovastatin 20	97	6.6 ± 1.6	4.7 ± 1.3	27.6 ± 12.6	27	6.5 ± 1.7	0.32	0.76	<0.001
Lovastatin 40	63	6.7 ± 1.6	4.6 ± 1.1	30.8 ± 13.8	31	6.6 ± 1.6	0.59	0.58	<0.001
Lovastatin 80	17	8.2 ± 2.2	5.6 ± 1.3	28.9 ± 17.3	40	9.4 ± 2.2	0.05	0.40	0.107
Pravastatin 10	18	5.9 ± 1.4	4.5 ± 1.1	22.7 ± 13.4	20	5.6 ± 1.4	0.32	0.62	0.006
Pravastatin 20	28	6.7 ± 1.2	4.7 ± 1.0	29.4 ± 13.7	24	6.1 ± 1.3	0.03	0.49	0.007
Pravastatin 40	22	7.2 ± 1.8	4.7 ± 1.5	33.4 ± 16.8	30	6.8 ± 2.1	0.30	0.51	0.015
Simvastatin 5	7	7.0 ± 2.6	5.4 ± 2.4	24.1 ± 15.5	26	7.3 ± 3.3	0.56	0.94	0.002
Simvastatin 10	72	6.4 ± 1.3	4.6 ± 1.2	27.3 ± 11.3	30	6.6 ± 1.7	0.04	0.79	< 0.001
Simvastatin 20	97	6.9 ± 1.4	4.5 ± 1.0	34.9 ± 11.8	38	7.2 ± 1.6	0.04	0.66	< 0.001
Simvastatin 40	42	7.2 ± 1.1	4.8 ± 1.0	32.9 ± 15.7	41	8.1 ± 1.8	0.003	0.27	0.09
Simvastatin 80	6	7.3 ± 1.3	3.7 ± 0.5	48.9 ± 6.9	47	7.0 ± 1.0	0.43	0.67	0.15
Atorvastatin 10	37	6.0 ± 1.3	4.0 ± 1.1	32.7 ± 14.8	37	6.3 ± 1.7	0.10	0.70	< 0.001
Atorvastatin 20	58	6.5 ± 1.4	3.8 ± 0.9	40.5 ± 12.9	43	6.6 ± 1.5	0.49	0.62	< 0.001
Atorvastatin 40	52	7.5 ± 1.8	4.1 ± 1.2	45.3 ± 12.0	48	7.8 ± 2.3	0.16	0.71	< 0.001
Atorvastatin 80	23	7.5 ± 1.8	3.4 ± 0.8	53.0 ± 13.4	51	6.9 ± 1.7	0.14	0.43	0.04
Fluvastatin 20	10	5.9 ± 1.3	4.4 ± 1.0	21.8 ± 18.4	22	5.7 ± 1.3	0.76	0.30	0.40
Fluvastatin 40	7	6.1 ± 0.9	4.1 ± 0.9	32.8 ± 10.5	25	5.4 ± 1.1	0.10	0.66	0.11
Rosuvastatin 5	34	5.7 ± 1.2	3.6 ± 1.0	37.0 ± 11.6	40	6.0 ± 1.6	0.20	0.70	< 0.001
Rosuvastatin 10	46	6.1 ± 1.3	3.4 ± 1.1	45.4 ± 11.7	46	6.2 ± 2.0	0.58	0.76	< 0.001
Rosuvastatin 20	26	7.1 ± 1.6	3.6 ± 1.2	48.9 ± 10.8	52	7.5 ± 2.4	0.18	0.71	< 0.001
Rosuvastatin 40	6	7.1 ± 1.5	3.6 ± 0.9	45.4 ± 23.1	55	8.1 ± 2.0	0.45	-0.42	0.41
Ezetimibe 10	172	4.4 ± 1.1	3.2 ± 0.9	26.3 ± 13.7	20	4.0 ± 1.1	< 0.001	0.69	< 0.001

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Supplemental Figure 1. Baseline and imputed LDL-C in men and women, p=ns (n=788). Conversion to mg/dl: multiply mmol/L by 38.67.

Supplemental Figures 2-8. For each statin (**Suppl. Figure 2**: lovastatin (10, 20, 40 and 80 mg/day); **Suppl. Figure 3**: pravastatin (10, 20, and 40 mg/day); **Suppl. Figure 4**: simvastatin (5, 10, 20, 40 and 80 mg/day); **Suppl. Figure 5**: atorvastatin (10, 20, 40 and 80 mg/day); **Suppl. Figure 6**: fluvastatin (20, and 40 mg/day). **Suppl. Figure 7**: rosuvastatin (10, 20, and 40 mg/day) and **Suppl. Figure 8**: ezetimibe (10 mg/day)), the comparison between expected (according to the data provided in **Table 1**, Hou et al. *(30)*) is shown in the left panels, the middle panel shows the baseline and imputed baseline LDL-C (ns: non-significant by uncorrected t-test) and the right panel shows the Pearson's linear correlation between baseline and imputed baseline LDL-C. Red: observed; Blue: Imputed. Conversion to mg/dl: multiply mmol/L by 38.67.

Suppl. Figure 1
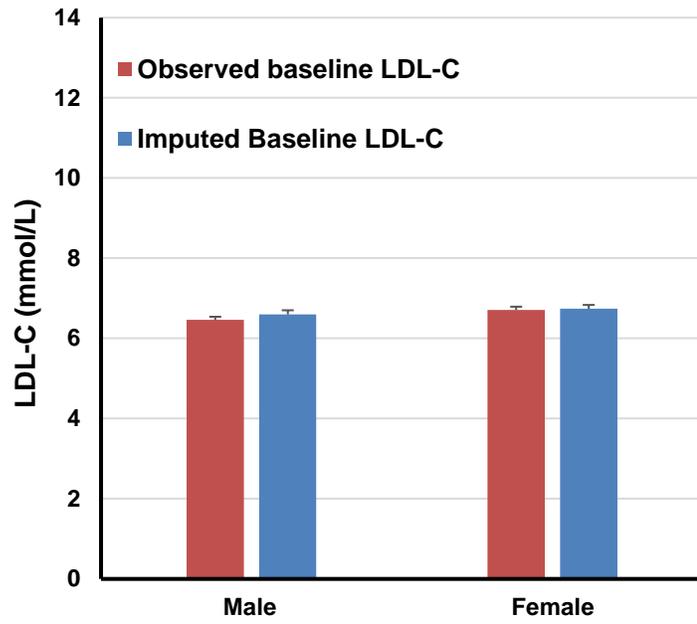
Suppl. Figure 2

Suppl. Figure 3

Pravastatin 10 mg

Pravastatin 10 mg

Pravastatin 10 mg
y = 0.63x + 1.89
r = 0.62
P = 0.006

Pravastatin 20 mg
P = 0.05

Pravastatin 20 mg
P = 0.03

Pravastatin 20 mg
y = 0.55x + 2.46
r = 0.49
P = 0.007

Pravastatin 40mg

Pravastatin 40mg

Pravastatin 40 mg
y = 0.58x + 2.56
r = 0.51
P = 0.015

Suppl. Figure 4

Simvastatin 5 mg

Simvastatin 5 mg

Simvastatin 5 mg

y = 1.18x - 0.98
r = 0.94
P = 0.002

Simvastatin 10 mg

P = 0.04

Simvastatin 10 mg

P = 0.04

Simvastatin 10 mg

y = 1.03x + 0.05
r = 0.79
P < 0.001

Simvastatin 20 mg

P = 0.01

Simvastatin 20 mg

P = 0.04

Simvastatin 20 mg

y = 0.77x + 1.83
r = 0.66
P < 0.001

Simvastatin 40 mg

P = 0.002

Simvastatin 40 mg

P = 0.003

Simvastatin 40 mg

y = 0.44x + 4.91
r = 0.27
P = 0.09

10

Simvastatin 80 mg

% decrease in LDL-C

- Observed LDL-C reduction
- Expected decrease in LDL-C (Hou et al)

Simvastatin 80 mg

LDL-C (mmol/L)

- Observed baseline LDL-C
- Imputed baseline LDL-C

Simvastatin 80 mg

y = 0.52x + 3.20
r = 0.67
P = 0.15

Imputed Baseline LDL-C (mmol/L)

Observed Baseline LDL-C (mmol/L)

Atorvastatin 10 mg (three panels: bar chart of % decrease in LDL-C, bar chart of LDL-C mmol/L, scatter plot with y = 0.92x + 0.80, r = 0.70, P < 0.001)

Atorvastatin 20 mg (three panels; scatter plot with y = 0.69x + 2.12, r = 0.62, P < 0.001)

Atorvastatin 40 mg (three panels; scatter plot with y = 0.94x + 0.76, r = 0.71, P < 0.001)

Atorvastatin 80 mg (three panels; scatter plot with y = 0.40x + 3.93, r = 0.43, P = 0.04)

Suppl. Figure 6

Fluvastatin 20 mg

(Bar chart, % decrease in LDL-C)
Legend: Observed LDL-C reduction; Expected decrease in LDL-C (Hou et al)

Fluvastatin 20 mg

(Bar chart, LDL-C mmol/L)
Legend: Observed baseline LDL-C; Imputed baseline LDL-C

Fluvastatin 20 mg

(Scatter plot, Imputed Baseline LDL-C vs Observed Baseline LDL-C mmol/L)
y = 0.30x + 3.96
r = 0.30
P = 0.40

Fluvastatin 40 mg

(Bar chart, % decrease in LDL-C)
Legend: Observed LDL-C reduction; Expected decrease in LDL-C (Hou et al)

Fluvastatin 40 mg

(Bar chart, LDL-C mmol/L)
Legend: Observed baseline LDL-C; Imputed baseline LDL-C

Fluvastatin 40 mg

(Scatter plot, Imputed Baseline LDL-C vs Observed Baseline LDL-C mmol/L)
y = 0.82x + 0.45
r = 0.66
P = 0.11

Suppl. Figure 7

Rosuvastatin 5 mg

y = 0.91x + 0.76
r = 0.70
P < 0.001

Rosuvastatin 10 mg

y = 1.15x - 0.80
r = 0.76
P < 0.001

Rosuvastatin 20 mg

y = 1.07x - 0.03
r = 0.71
P < 0.001

Rosuvastatin 40 mg

Rosuvastatin 40 mg

Rosuvastatin 40 mg

$y = -0.57x + 12.16$
$r = -0.42$
$P = 0.41$

Suppl. Figure 8