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ORIGINAL RESEARCH

Treatment Inertia in Patients With Familial Hypercholesterolemia

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BACKGROUND: We studied care gap in patients with familial hypercholesterolemia (FH) with respect to lipid-lowering therapy.

METHODS AND RESULTS: We enrolled patients with cardiovascular disease (CVD) or FH and low-density lipoprotein-cholesterol >2.0 mmol/L despite maximally tolerated statin therapy. During follow-up physicians received online reminders of treatment recommendations of 2009 patients (median age, 63 years, 42% women), 52.4% had CVD only, 31.7% FH only, and 15.9% both CVD and FH. Patients with FH were younger and more likely to be women and non-White with significantly higher baseline low-density lipoprotein-cholesterol level (mmol/L) as compared with patients with CVD (FH 3.92±1.48 versus CVD 2.96±0.94, $P<0.0001$). Patients with FH received less statin (70.6% versus 79.2%, $P=0.0001$) at baseline but not ezetimibe (28.1% versus 20.4%, $P=0.0003$). Among patients with FH only, 45.3% were at low-density lipoprotein target (≥ 50% reduction from pretreatment level or low-density lipoprotein <2.5 mmol/L) at baseline and increasing to 65.8% and 73.6% by visit 2 and 3, respectively. Among patients with CVD only, none were at recommended level (≤2.0 mmol/L) at baseline and 44.3% and 53.3% were at recommended level on second and third visit, respectively. When primary end point was analyzed as a difference between baseline and last available follow-up observation, only 22.0% of patients with FH only achieved it as compared with 45.8% with CVD only ($P<0.0001$) and 55.2% with both FH+CVD ($P<0.0001$).

CONCLUSIONS: There is significant treatment inertia in patients with FH including those with CVD. Education focused on patients with FH should continue to be undertaken.

Key Words: familial hypercholesterolemia ■ lipid lowering ■ treatment inertia

Low-density lipoprotein cholesterol (LDL-C) level is a well-established risk factor for cardiovascular disease (CVD) and there is considerable evidence that lowering LDL-C reduces CVD mortality and morbidity[1] including in patients with familial hypercholesterolemia (FH) in whom genetic alterations cause complete or partial absence of LDL receptor expression resulting in elevated LDL-C levels.[2,3]

The Canadian Cardiovascular Society guidelines recommend initiation of LDL-C lowering with high efficacy statin therapy and addition of ezetimibe and / or PCSK9i (proprotein convertase subtilisin/kexin type 9 inhibitor) as needed if LDL-C is not lowered by at least 50% or to the level below 2.0 mmol/L in patients with established CVD. For those with a recent acute coronary syndrome and established coronary disease consideration should be given to more aggressive lowering of LDL-C to below 1.8 mmol/L.[4] The Canadian Cardiovascular Society recommendations for FH indicate the same therapeutic approach with the reduction of LDL-C by at least 50% and an LDL-C level of <2.5 mmol/L as a recommended therapeutic target.[5]

Nonetheless, strategies for lowering LDL-C are often poorly adopted in clinical practice, and many patients fail to reach guideline-recommended levels.[6–10] We have recently reported[11] that physician education based on the reminder system imbedded into clinical practice, improves care significantly as measured by the proportion of patients achieving the recommended LDL-C level in relationship to

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CLINICAL PERSPECTIVE

What is New?

- Physician reminders for specific recommended lipid-lowering therapy for patients with familial hypercholesterolemia resulted in a significant increase in a proportion of patients achieving optimal low-density lipoprotein-cholesterol level.
- The proportion of patients achieving recommended low-density lipoprotein-cholesterol level in response to the educational maneuver was lower among familial hypercholesterolemia as compared with patients with cardiovascular disease.

What are the Clinical Implications?

- There is treatment inertia among patients at higher risk for cardiovascular disease events.
- This maybe overcome to some degree with educational interventions based on reminders for guideline recommendations.

Nonstandard Abbreviations and Acronyms

FH	familial hypercholesterolemia
PCSK9i	proprotein convertase subtilisin/kexin type 9 inhibitor

the greater usage of recommended[12] lipid-lowering therapies.

This analysis explores whether management of patients with FH differed from that of patients with CVD with respect to treatment inertia in lipid-lowering therapy and whether the benefit of therapy optimization resulted in similar benefits in these 2 groups of high-risk patients. We were particularly interested in assessing the care gap in the management of patients with both CVD and FH that would presumably provoke a higher degree of care in lowering their LDL-C.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The (GOAL) Guidelines Oriented Approach to Lipid Lowering Canada [11] was a medical education interventional program supported by Amgen Canada. It was an investigator-initiated study started in 2015 and coordinated by the Canadian Heart Research Centre, an academic research and education physician organization. The intervention studied was physician education based on lipid management reminders applied at the end of each of 3 visits based on data entry in the electronic case report form and the primary end point was proportion of patients achieving recommended LDL-C level of <2 mmol/L in those with CVD and <2.5 mmol/L or ≥50% reduction in those with FH. The study was approved by central and institutional research ethics boards where appropriate, and all enrolled patients provided informed consent.

Invitations to participate were sent to 750 Canadian physicians across Canada from a proprietary (Canada's Anti-Spam legislation Regulation) Canadian Heart Research Centre list of physicians who participated in prior cholesterol-oriented data collection studies[13,14] and 248 agreed to participate. The participating physicians had the primary and exclusive role in the management of their patients and selection of cholesterol lowering therapies as part of their fiduciary responsibility. These physicians were asked to consecutively enroll at least 12 of their patients with either (1) clinical vascular disease such as coronary artery disease, cerebrovascular disease, abdominal aortic aneurysm, peripheral artery disease; or, (2) FH, as defined in Canadian Cardiovascular Society guidelines. In addition, all patients had to have an LDL-C >2.0 mmol/L despite maximally tolerated statin therapy (defined as having tried at least 2 statins, each at least on 2 reduced doses) for at least 3 months before enrollment. Lipid-lowering treatment was assessed on enrollment (visit 1) and twice more during follow-up, each ≈4 to 6 months apart (visits 2 and 3). The medical education intervention consisted of physician reminders to follow Canadian Cardiovascular Society guideline recommendations at each visit; physicians were also asked to provide reason when guidelines were not followed.

Statistical Analysis

Continuous data are shown as means with SD and categorical data as frequencies and percentages. Group comparisons were made using the Chi-squared test or McNemar test and paired *t*-test or Kruskal–Wallis test for discrete and continuous variables, respectively, where appropriate. We used repeated measures analysis of covariance to perform univariate and multivariable regression to determine the outcome across the visits.

A hierarchical multivariable logistic regression model, which used variance components as the working correlation structure, was developed to assess factors independently associated with LDL-C achieving target of ≤2.0 mmol in patients with CVD and ≤2.5 mmol/L in FH. The hierarchical 3-level structure

was used since visits were nested within patients, which were further nested within physicians. The following variables were considered: age, sex, ethnicity, body mass index, baseline LDL-C, smoking, diabetes mellitus, hypertension, chronic kidney disease, premature history of cardiovascular disease, congestive heart failure, use of statin, ezetimibe, and PCSK9i. Adjusted odds ratio (OR) with 95% CI are presented. A value of $P<0.05$ was considered significant for all tests except group comparison in Table 1 where correction for multiple (n=31) comparisons was applied and value of $P\leq0.002$ was considered significant. All statistical analyses were performed in SAS software version 9.4 (SAS Institute, Cary, NC).

Pre-treatment LDL-C was calculated according to imputation formula[15] by the University of British Columbia with assistance of one of the co-authors (G.B.J.M.).

RESULTS

A total of 177 physicians (58% primary care and 42% specialists) enrolled 2009 patients with approximately half of the patients enrolled by each physician group.[16] Among the 2009 enrolled patients, there were 1054 (52.4%) patients with CVD only, 636 (31.7%) with FH only, and 319 (15.9%) with both CVD and FH. Patients with FH as compared with CVD were younger, more likely to be women, and non-White, and had slightly lower systolic and slightly higher diastolic blood pressure and heart rate as well as lower body mass index (Table 1). Patients with CVD as compared with FH, had more cardiovascular risk factors and CVD manifestations (Table 1).

The baseline visit results for cholesterol panel were significantly different between patients with CVD and FH (Table 2); the CVD only group had a slightly higher use of statins compared with the FH only group (79.2% versus 70.6%, $P=0.0001$), whereas ezetimibe use was slightly higher in the FH only group (28.1% versus 20.4%, $P=0.0003$). The use of high-intensity statin was lower in patients with FH only compared with CVD only (46.6% versus 58.1%, $P=0.0001$) or patients with both (67.7%, $P=0.0001$). To gain further insight into lipid-lowering management of patients with FH we calculated presumed pre-treatment LDL-C value using the imputation formula[15] which indicated pre-treatment LDL-C of 5.2±1.9 mmol/L in patients with CVD only, 6.8±3.5 mmol/L in patients with FH only ($P=0.0001$ versus CVD only) and 6.4±2.8 mmol/L in those with FH and CVD ($P=0.0001$ versus CVD alone).

Among patients with FH only, 45.3% were already at LDL target (defined as ≥50% reduction from pre-treatment level or LDL <2.5 mmol/L) at baseline and because of this proportion of patients achieving recommended LDL-C was highest in patients with FH only during the follow-up (Figure 1A). However, when primary end point was analyzed as a difference between baseline and last available follow-up observation, only 22.0% of patients with FH only achieved it as

Table 1. Baseline Clinical Variables

Variables	CVD Only (n=1054) (52.4%)	FH Only (n=636) 31.7%)	Both (n=319) (15.9%)	*P* Value (FH Only vs CVD Only)
Age, y*	66±10	58±12	64±11	<0.0001
Female sex (%)	381 (36.1%)	335 (52.7%)	129 (40.4%)	<0.0001
White (%)	782 (74.2%)	410 (64.5%)	234 (73.4%)	<0.0001
Private insurance	670 (63.6%)	421 (66.2%)	193 (60.5%)	0.27
Systolic BP, mmHg*	130±16	128±16	128±15	0.040
Diastolic BP, mmHg*	76±10	78±10	75.99±9.64	<0.0001
Heart rate, bpm*	71±11	75±11	70±10	<0.0001
BMI, kg/m^2*	29.7±6.2	29.0±6.6	30.1±8.2	0.041
Smoking (current/past)	552 (52.4%)	239 (37.6%)	175 (54.9%)	<0.0001
Diabetes mellitus	406 (38.5%)	198 (31.1%)	104 (32.6%)	0.0022
Hypertension	724 (68.7%)	269 (42.3%)	217 (68.0%)	<0.0001
Chronic kidney disease	107 (10.2%)	30 (4.7%)	26 (8.2%)	0.0001
Atrial fibrillation	85 (8.1%)	35 (5.5%)	21 (6.6%)	0.048
Premature family history of CVD	244 (23.1%)	416 (65.4%)	227 (71.2%)	<0.0001
Cancer	61/1013 (6.0%)	24 of 634 (3.8%)	13 of 318 (4.1%)	0.048
Liver disease	21/1013 (2.1%)	12 of 634 (1.9%)	8 of 318 (2.5%)	0.80
Congestive heart failure	46 (4.4%)	4 (0.6%)	23 (7.2%)	0.0002

BP indicates blood pressure; BMI, body mass index; bpm, beats per minute; CVD, cardiovascular disease; and FH, familial hypercholesterolemia.
*Mean±SD.

Table 2. Baseline (Visit 1) Lipid Profile and Management

Variables	CVD Only (n=1054, 52.4%)	FH Only (n=636, 31.7%)	Both (n=319, 15.9%)	*P* Value (FH Only vs CVD Only)
Total cholesterol	5.02±1.09	6.13±1.49	5.55±1.46	<0.0001
LDL-C, mmol/L	2.96±0.94	3.92±1.48	3.44±1.31	<0.0001
HDL-C, mmol/L	1.3±0.43	1.37±0.43	1.26±0.37	0.0032
Non HDL-C, mmol/L	3.69±1.1	4.78±1.65	4.23±1.44	<0.0001
Triglycerides, mmol/L	1.92±1.34	2.2±2.05	1.97±1.22	0.0004
Statin*	835 (79.2%)	449 (70.6%)	251 (78.7%)	0.0001
Ezetimibe†	215 (20.4%)	179 (28.1%)	117 (36.7%)	0.0003
Bile acid sequestrant	24 (2.3%)	58 (9.1%)	20 (6.3%)	<0.0001
Fibrate	29 (2.8%)	18 (2.8%)	8 (2.5%)	0.92
Niacin	4 (0.4%)	3 (0.5%)	1 (0.3%)	0.78

CVD indicates cardiovascular disease, FH, familial hypercholesterolemia, LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

*Statins used most frequently were rosuvastatin (40%, mean daily dose 22 mg) and atorvastatin (28%, mean daily dose 48 mg).

†Among patients who were not on statin at baseline (n=474), there was no difference in the use of ezetimibe comparing patients with CVD only (27.4%) to those with FH (29.4%) or both (35.3%).

compared with 45.8% with CVD only (*P*<0.0001) and 55.2% with both FH+CVD (*P*<0.0001).

There was significant reduction in the absolute level of LDL-C from baseline to visit 3 in patients with CVD only (–0.83±1.17, *P*<0.0001) and even more so in those with FH alone (–1.40±1.63 mmol/L, *P*=0.0001) or CVD and FH (–1.39±1.39 mmol/L, *P*=0.0001). The reduction in LDL-C from baseline to visit 3 was higher in those patients with FH who were not yet at target at baseline as compared with those who were (–1.57±1.58 versus –1.21±1.67 mmol/L, *P*=0.02).

This significant increase in the proportion of patients achieving recommended LDL-C occurred in association with an increase in the use of recommended non-statin therapy and most notably PCSK9i (Figure 1B): compared with FH only, patients with CVD only had greater use of ezetimibe but not of PCSK9i. The importance of recommended therapy use was seen in multivariable analysis with the strongest predictors of achieving the recommended LDL-C level being PCSK9i (OR, 11.44; 95% CI, 8.71–15.04; *P*<0.0001), statin (OR, 5.28; 95% CI, 4.15–6.72; *P*<0.0001), and ezetimibe (OR, 1.55; 95% CI, 1.28–1.89; *P*<0.0001) as well as FH only status (OR, 2.65; 95% CI, 2.03–3.45; *P*=0.0001). Female sex (OR, 0.62; 95% CI, 0.51–0.75; *P*<0.0001) and baseline LDL-C (OR, 0.78; 95% CI, 0.72–0.85; *P*=0.0001) were associated with lesser likelihood of achieving the recommended LDL-C level.

Participating physicians were asked to provide a single most important reason for not being able to follow the guidelines; Figure 2 provides the details of the responses with respect to the use of ezetimibe (Figure 2A) and PCSK9i (Figure 2B). In patients with FH only compared with CVD only patient refusal (38.5% versus 27.2%, *P*=0.0008) and comorbidities (27.2% versus 18.2%, *P*=0.003) were more common while decision to not add ezetimibe being appropriate less frequently (17.4% versus 27%, *P*=0.0002) as was agreement that additional treatment should be added (9.5% versus 18.2%, *P*=0.0008). These findings were similar to those for not prescribing PCSK9i except the cost was also different as a reason and was less frequent among patients with FX only (most likely related to the public and private coverage of PCSK9i in Canada for FH ahead of CVD (Figure 2B).

DISCUSSION

Established CVD and FH are both associated with major adverse cardiovascular morbidity and mortality. Despite the use of high intensity statin therapy, many patients do not achieve the recommended LDL-C level. The addition of second and third-line non-statin therapies has been shown to reduce residual cardiovascular risk.[17–19]

This post hoc analysis of GOAL Canada study focused on patients with FH and CVD to study treatment inertia in FH population for whom clear treatment guidelines and therapeutic targets exist.[4,5]

We found that <80% of patients were on statin therapy (<68% on high intensity), and <30% were on ezetimibe despite the high risk of enrolled patients. Moreover, patients with FH were less likely to be on statin therapy at baseline despite having a significantly higher LDL-C level by almost 1 mmol/L compared with patients with CVD. These findings are consistent with previously documented treatment inertia.[6–10] It is also noteworthy that given the pre-treatment LDL-C of 5.2±1.9 mmol/L in patients with CVD only, some of these patients could, in fact, have had FH as well as CVD, confirming previously documented underdiagnosis of FH.[5,20,21]

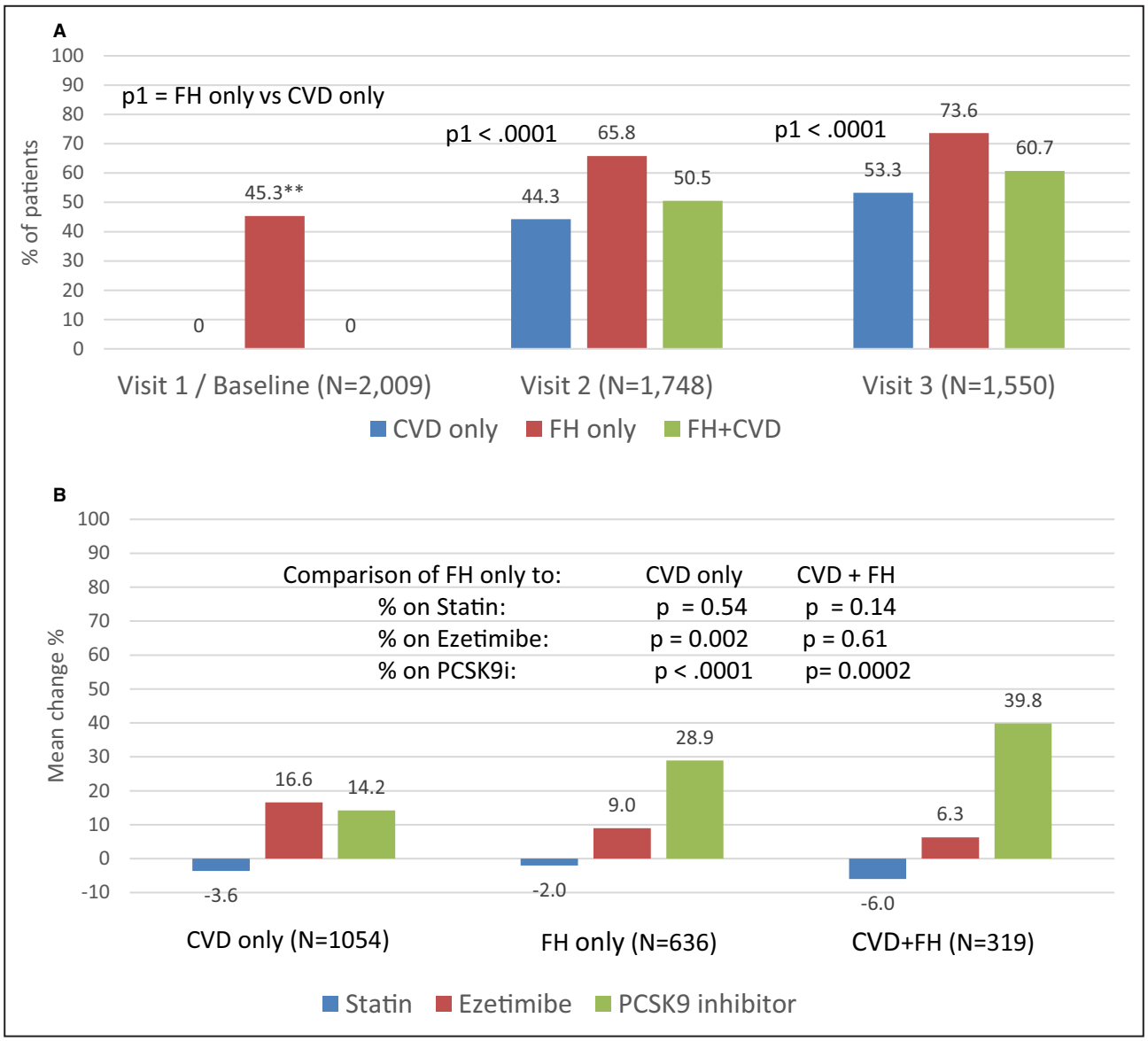

Figure 1. Proportion of patients achieving the recommended low-density lipoprotein cholesterol (LDL-C) level during follow up and change from baseline.

A, Proportion of patients achieving recommended LDL-C level* at each visit. *Recommended LDL-C for cardiovascular disease and cardiovascular disease+familial hypercholesterolemia is <2.0 mmol/L while for familial hypercholesterolemia only <2.5 mmol/L or 50% reduction from pre-treatment level. **Inclusion criteria for all was LDL-C >2 mmol/L. These patients with familial hypercholesterolemia had LDL-C >2 but <2.5 mmol/L. **B**, Change in treatment from baseline to last available observation during follow-up. CVD indicates cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9.

Once enrolled into GOAL Canada, the use of PCSK9i, but not ezetimibe, was readily taken up by physicians in patients with FH and was significantly greater than in patients with CVD only, with the greatest use in patients with both FH and CVD. These findings suggest that once alerted by the educational intervention, physicians recognized the need for additional therapy, particularly in those patients with FH alone or in combination with CVD. Our findings support the feasibility of educational intervention which results in care optimization in patients with either or both FH and CVD. We have previously demonstrated the benefit of educational intervention.[11,22,23] The importance of overcoming treatment inertia was further confirmed by the results of the multivariable analysis with LDL-C lowering therapies being most predictive of achieving the recommended LDL-C level. It is, however, important to note that ≈40% of patients with both CVD and FH were still not achieving the recommended LDL-C level and only additional 16.4% of patients with FH only were achieving primary end point compared with baseline. These findings highlight the continuation

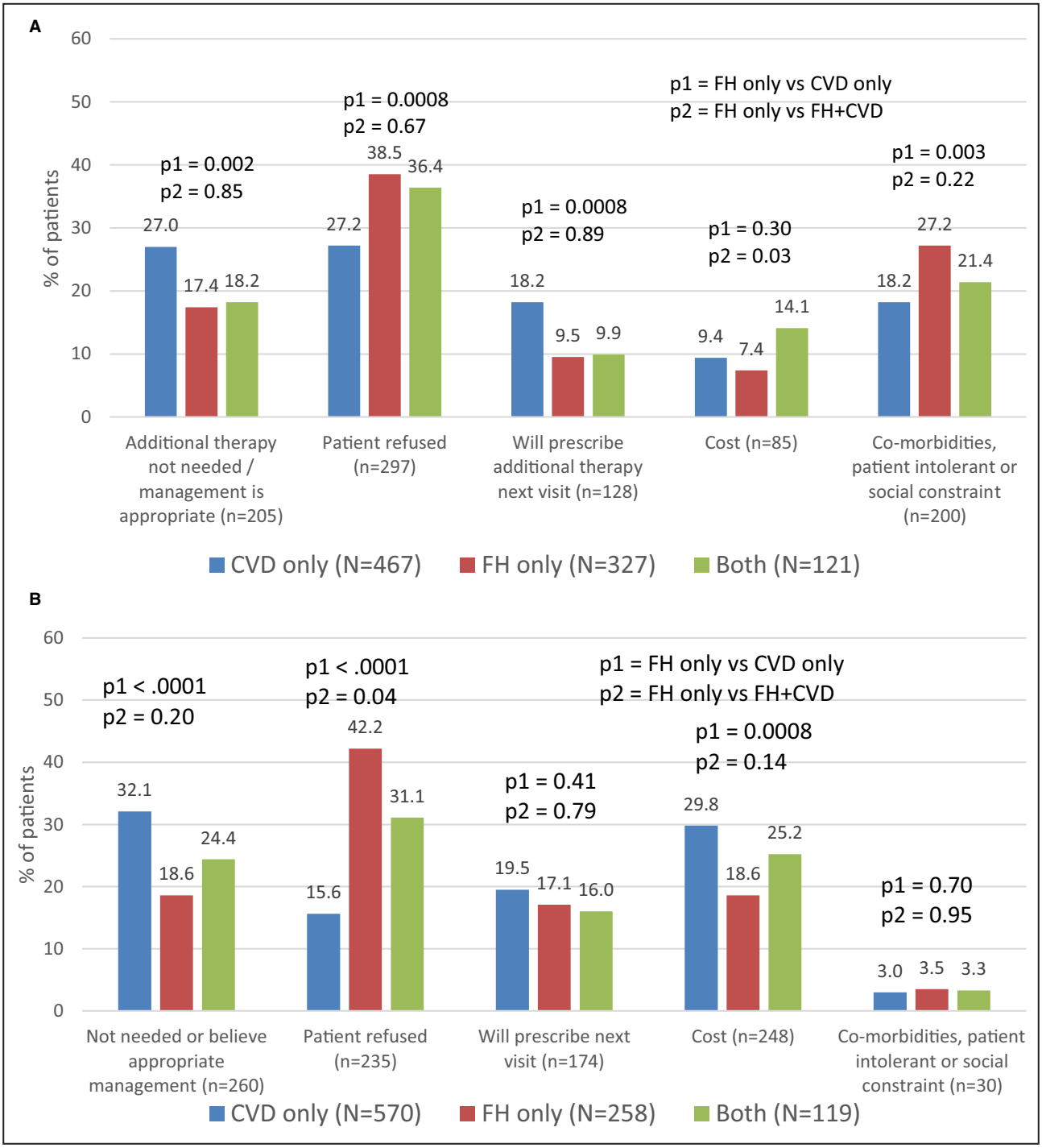

Figure 2. Reasons for not prescribing recommended therapy.
A, Reasons provided by physicians for not following the guidelines with respect to the use of ezetimibe (%) at baseline (visit 1). **B**, Reasons provided by physicians for not following the guidelines with respect to the use of PCSK9 inhibitor (%) at baseline. CVD indicates cardiovascular disease; FH, familial hypercholesterolemia; PCSK9, proprotein convertase subtilisin/kexin type 9.

of the treatment inertia and should serve as a call to action in patients with FH.

It is not clear why the use of ezetimibe was not embraced as much among patients with FH only when compared with CVD only, although the incremental use compared with baseline was low in all groups. Lower use of ezetimibe among CVD + FH group suggests that physicians may have thought that addition of ezetimibe would not be sufficient to significantly lower the LDL-C and therefore opted for a different approach.

The nature and extent of the treatment inertia was studied using physician responses as to why

the guideline recommended treatment was not prescribed. Among patients with FH, patient refusal was almost twice as common as in patients with CVD suggesting a discordance between physicians' estimation of patient cardiovascular risk and use of evidence-based therapy.[24]

The underestimation of patient's risk is further supported by the second most common reason for not following the guidelines among patients with FH being presence of co-morbidities which generally increases the risk and, if anything, should serve as a reason for more intensive treatment. Physician responses detailing challenges in following the guidelines should inform creation of additional educational interventions designed to support physicians and patients in care optimization.

LIMITATIONS

This post hoc analysis is subject to physician and patient selection bias. Physicians invited to participate had prior experience in similar programs and therefore may not be representative of all Canadian healthcare providers. The extent of the care gap detected, and low use of statin and non-statin therapy argues against selection bias of physicians skilled in the LDL-C management.

Almost a thousand patients with FH were enrolled with two thirds being FH alone and this could also be the result of selection bias or even incorrect diagnosis. Since FH is a less well recognized entity in clinical practice, GOAL Canada prompted physicians to seek out these patients using predefined and recommended criteria.[15,20,21] We believe that calculation of the pre-treatment LDL-C which shows significantly higher value for FH as compared with patients with CVD supports correct diagnosis. Moreover, participation of 248 physicians with average expected practice size of 2500 patients would allow for enrollment of patients with FH we saw given the prevalence of FH in 1 of 250 patients. Availability of PCSK9i coverage for patients with FH midway through GOAL Canada enrollment may also have contributed to even more careful search for patients with FH by the participating physicians.

While these selection biases may limit the generalizability of our findings, they in no way diminish the validity of our conclusions about the existence of the treatment inertia and the call to action for greater implementation of evidence-based therapies.

Patient compliance with physician recommendations plays a critical part in achieving optimal management and in this case lipid lowering. We did not measure patient compliance or reasons for non-compliance (for example, fear of needles) and thus have less complete picture of factors contributing to treatment inertia in patients with FH.

CONCLUSIONS

This analysis focused on the management of patients with FH since an overall result was published previously.[11] Despite the pathophysiology of FH and associated cardiovascular morbidity and mortality, there is significant treatment inertia in this group, particularly in those patients with FH who have already developed CVD. Greater physician education and support for implementation of therapeutic recommendations focused on patients with FH should continue to be undertaken.

ARTICLE INFORMATION

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