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RESEARCH ARTICLE

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Treatment and low-density lipoprotein cholesterol levels in patients with hypercholesterolaemia or mixed dyslipidaemia at high or very high cardiovascular risk: a population-based cross-sectional study in the Netherlands

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ABSTRACT

Objective: To describe treatment patterns, low-density lipoprotein cholesterol (LDL-C) levels and healthcare resource utilization (HCRU) in the Netherlands in 2018 of patients with hypercholesterolaemia or mixed dyslipidaemia at high or very high cardiovascular (CV) risk.

Methods: From the PHARMO Database Network adult patients with a diagnosis or receiving lipid lowering therapy (LLT) between 2009 and 2018 were selected. Patients at high or very high CV risk according to 2016 ESC/EAS guidelines with recorded LDL-C levels who were treated with LLT or were characterized as statin intolerant in 2018 were included. LLT treatment patterns, LDL-C levels and HCRU (General Practitioner [GP] consultations and hospitalizations) were assessed.

Results: The study population included 54,346 patients, of which 70% were at very high CV risk and 30% at high CV risk. The majority (93%) received statin monotherapy, mostly of moderate (73%) or high (15%) intensity. Only 3% received a combination of statin and ezetimibe. Statin intolerance, based on a treatment algorithm, was estimated at 3%. Average LDL-C decreased with LLT intensity. Overall, 74% reached LDL-C < 2.5 mmol/l and 34% < 1.8 mmol/l with their current treatment, and 46% reached their LDL-C goal according to 2016 ESC/EAS guidelines. The highest rates of hospitalizations and GP consultations, including home visits, were recorded in patients with peripheral artery disease or polyvascular disease.

Conclusion: The treatment of hypercholesterolaemia and mixed dyslipidaemia in patients at high or very high CV risk in the Netherlands was suboptimal in 2018. To further lower CV risk alternative treatment strategies using add-on therapies are needed.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death in Europe[1,2], with approximately 4.1 million deaths annually and accounting for 47% and 39% of total mortality causes in females and males, respectively, exceeding the number of cancer deaths for both sexes in most countries[3]. Untreated hypercholesterolaemia or mixed dyslipidaemia, characterized by high levels of low-density lipoprotein cholesterol (LDL-C), may lead to LDL-C deposition in the form of plaques in arterial walls, causing atherosclerotic cardiovascular disease (ASCVD)[4–6] including coronary artery disease (CAD), acute coronary syndromes, such as myocardial infarction (MI) or unstable angina, peripheral artery disease (PAD), transient ischaemic attack (TIA), and ischaemic stroke (IS)[7]. ASCVD is not only a leading cause of cardiovascular (CV) death, but also of morbidity[8], which can lead to disability and a reduced quality of life[9,10]. Due to its association with other CV risk factors such as diabetes and hypertension, patients can experience substantial clinical burden[9,11,12].

Dyslipidaemia is associated with increased healthcare resource utilization (HCRU) and costs[13–15]. Hospitalization costs make up the largest component of the total direct medical costs in patients with dyslipidaemia[13,16], while HCRU seems to be higher in patients with suboptimal management of lipid levels[17,18]. The linear and causal relationship between elevated LDL-C and ASCVD has been well documented[5,6,19,20]. Therefore, the European Society of Cardiology/European Atherosclerosis

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Society (ESC/EAS) as well as local Dutch guidelines recommend intensively reducing LDL-C either to defined goals that depend on the patient's assessed CV risk, or by ≥50% relative to the LDL-C level prior to treatment[8,21,22]. For those not achieving their LDL-C goal with statin therapy, the guidelines recommend maximally tolerated statin therapy in combination with other lipid lowering therapies (LLT). Despite oral LLT, up to 80% of patients with hypercholesterolaemia or mixed dyslipidaemia, at high or very high CV risk, have been reported to not meet recommended LDL-C goals[8,23,24]. Many patients thus are left at a high risk of developing ASCVD or recurrent events and might benefit from further intensive reduction of LDL-C[1,25,26].

Objective

The aim of this study was to describe treatment patterns, LDL-C levels and HCRU in the Netherlands in 2018 of patients with hypercholesterolaemia or mixed dyslipidaemia at high or very high CV risk according to the 2016 ESC/EAS guidelines for the management of dyslipidaemias[22].

Methods

Setting

Anonymized and aggregate data for this cross-sectional retrospective observational cohort study were obtained from the PHARMO Database Network, a population-based network that includes linked data from primary and secondary healthcare settings in the Netherlands[27]. Approval for this study was obtained from the PHARMO Compliance Committee, informed consent is not required for the secondary use of anonymized data from electronic health records. For this study the General Practitioner (GP) Database, Outpatient Pharmacy Database and Hospitalization Database were used. Mandatory health insurance and required registration with a GP makes the GP Database representative of the general Dutch population. The Outpatient Pharmacy Database includes dispensed drugs prescribed by GPs as well as specialists and is representative of all patients that are pharmaceutically treated in the Netherlands. The GP and Outpatient Pharmacy Databases have regional coverage representative of the Netherlands. The source population for this study was limited to patients aged ≥18 years in 2018 and who were eligible for registration in all of these databases.

Study population

From the source population, all patients with hypercholesterolaemia or mixed dyslipidaemia in the period 2009–2018 were identified based on diagnoses (International Classification of Primary Care (ICPC) code T93 Lipid disorder or free text information on diagnoses) in the GP Database, or treatment with LLT, i.e. at least one dispensing of any lipid lowering drug (Anatomical Therapeutic Chemical (ATC) code C10) in the Outpatient Pharmacy Database.

The selection was further restricted to patients who were at high or very high CV risk in 2018 using the definitions by the 2016 ESC/EAS guidelines[8] (see Supplementary Figure A.1), based on all available diagnostic history from GP and hospitalization records.

Very high CV risk was based on presence of ASCVD, severe chronic kidney disease (CKD, stage 4 or 5, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) or diabetes mellitus (DM, type 1 or 2) with an additional risk factor (smoking, blood pressure (BP) ≥180/110 mmHg or total cholesterol (TC) >8 mmol/l). ASCVD included CAD (including MI, angina pectoris, coronary sclerosis, coronary artery bypass grafting, percutaneous coronary intervention), cerebrovascular disease (IS, TIA), and PAD. DM with target organ damage could not be determined based on ICPC coding. All DM patients without very high risk classification were classified as high risk patients, as were patients with single elevated risk factors (smoking, elevated BP or elevated TC) and patients with moderate CKD (stage 3, eGFR 30–59 mL/min/1.73 m^2). The SCORE algorithm was not applied as this requires risk factor assessments prior to treatment, which were not available or dated back many years for most patients in the cross-sectional study population in 2018.

The date of last LDL-C measurement in 2018 was defined as index date. Patients without recorded LDL-C measurement in 2018 were excluded, as were patients without LLT in the six months prior to index date (see "Treatment patterns" for determination), unless they met the criteria for statin intolerance (see "Treatment patterns" for definition).

Patient characteristics

The following characteristics were determined at index date: demographics (age, sex), time since first recorded LLT or hypercholesterolaemia diagnosis, history of ASCVD, heart failure, CKD, and DM, and clinical characteristics (smoking status, BP, lipid levels and body mass index (BMI)).

Lipid levels were assessed at the index date. The other clinical characteristics were based on the most recent measurement in the two years prior to the index date.

Treatment patterns

For the determination of treatment patterns, periods of uninterrupted drug use per LLT type were created applying the method of Catalan and Lelorier[28]. Defined drug type categories were low, moderate and high intensity statins[29] (see Supplementary Table A.1), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and other (nicotinic acid, fibrates). Concurrent use was based on overlapping periods of use of different drug types, removing any overlap at the start of a new drug type if the drug type started between the last drug dispensing and the end of the period of use of the prior drug type(s). The resulting periods of (combined) LLT use were categorized into: statin per intensity as monotherapy or combination with ezetimibe, ezetimibe monotherapy, PCSK9 inhibitors combined with any LLT, and other LLT (any LLT not fitting the other categories). The last known LLT use in the six months before the index date was defined as current treatment. Prior treatment was the last known LLT

use before that. If there was no LLT use for at least six months, treatment was recorded as "no LLT." Transitions from prior to current treatment are presented using Sankey plots[30].

Statin intolerance was defined as having been treated with at least two types of statin based on all available dispensing records, of which one at any intensity, followed by at least one low intensity statin, with or without concurrent other LLT (definition based on Banach 2015[31], see Supplementary Table A.1 for statin intensity). The patient should have ceased all statin use before index date, either continuing or ceasing other LLT. Ezetimibe monotherapy, either continued or ceased, was also considered as an indication of statin intolerance, irrespective of prior recorded statin use. However, the definition of statin intolerance applied may have been too strict and may not represent the entirety of clinical practice or patient preferences. For example not all patients may be receptive to trying different types of statin and may therefore not be identified with the aforementioned definition of statin intolerance, or patients may tolerate a low intensity of statins, despite muscle aches, or they may not yet have ceased all statin use at the time of the index date, but cease statin use soon thereafter. We have explored additional analyses with an extended definition of statin intolerance, irrespective of CV risk group:

- patients treated with at least two types of statin based on all available dispensing records, of which one at any intensity, followed by at least one low intensity statin. Both statins may have been used concurrently with ezetimibe or other LLT (not required). The patient should have ceased all statin use before index date, either continuing other LLT, or ceasing all LLT[31].
- patients treated with ezetimibe monotherapy, either continued or ceased, irrespective of prior statin use in the available history of the patient.
- patients treated with low intensity statins, without concurrent ezetimibe use, irrespective of prior statin use or current other LLT use.
- patients treated with low intensity statins, with concurrent ezetimibe use, irrespective of prior statin use.

Healthcare resource utilization

HCRU was determined in the period up to five years prior to the index date and included the rate of GP consultations (all and specifically home visits) and the rate and length of stay in hospital. This analysis was restricted to patients in the study cohort registered in GP practices for which the required contact administration information was available in the database.

Statistical analysis

Descriptive statistics are presented: frequencies and proportions for categorical variables, and mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Where appropriate results were stratified by CV risk. For HCRU, the very high risk group results were further stratified by affected CV bed or polyvascular disease (more than one CV bed affected) to allow interpretation of costs correlated with CV morbidity. HCRU rates (with 95% confidence interval (CI)) were calculated as the summed number of consultations/hospitalizations/hospitalized days during the assessment period divided by the summed person time in the assessment period. The average stay per hospitalization was calculated as the summed number of days in hospital divided by the summed number of hospitalizations, and presented with SD.

Results

The source population consisted of 634,602 adult patients who were registered in the PHARMO GP Database and Outpatient Pharmacy Database and eligible for capturing potential hospital admissions (Table 1). In the source population we identified 173,321 patients (27%) with hypercholesterolaemia or mixed dyslipidaemia, based on a recorded diagnosis (22%) and/or a treatment with LLT in the period 2009–2018 (93%). Of those, 54% were deemed to be at high or very high CV risk. Among those with recorded diagnoses, specification of the diagnosis into subtypes was mostly absent, and differentiation into subtypes such as mixed hyperlipidaemia and familial hyperlipidaemia was not possible. No recorded LDL-C in 2018 led to exclusion of 31% of those, and a further 17% were excluded based on having no LLT at index date, without meeting the criteria for statin intolerance. Of the study population of 54,346 patients, 70% (37,978) were at very high CV risk.

Table 2 describes the characteristics of the study population overall and by CV risk group category. The average age was 71, and 54% were male, with a higher proportion in the very high risk group (58% vs. 46%). Documented ASCVD was present in 66% of the total study population, and 95% of the very high risk group. Coronary disease was the most common type of ASCVD (49%), PAD the least common (5%). Overall, 34% of the study population had diabetes (very high risk 26%, high risk 51%), in 5% DM was combined with another CV risk factor other than ASCVD. Moderate CKD was present in 29% of patients, severe CKD in 2% and for another 2% the stage of CKD was not recorded. Mean BMI was 28 kg/ m^2, mean SBP was 136 mmHg and 15% of the population was recorded as currently smoking.

Statin intolerance based on the defined strict treatment algorithm was estimated at 3% of the high to very high risk population based on our defined criteria (Table 3). However, when applying less strict criteria of statin intolerance to the identified patients with hypercholesterolaemia or mixed dyslipidaemia at low to very high CV risk for which LDL-C measurements were recorded (114,965 (66%) out of 173,321), 7% would be deemed statin intolerant based on the extended definition. The resulting population included 7647 patients, 56% females, with a mean age of 70.7 years (SD 10), a mean LDL-C of 2.8 mmol/l (SD 1.0) of which 81% continued some form of LLT at the index date, and 19% had ceased all LLT

Table 1. Selection of the study population.

Source population All patients aged ≥ 18 years in 2018, and registered in the GP Database and Outpatient Pharmacy Database and eligible for capturing potential admissions in the Hospitalization Database during 2017–2018	***N* = 634,602**
Hypercholesterolaemia and mixed dyslipidaemia (HC/MD) patients identified in the period 2009–2018 Diagnosis of HC/MD only (ICPC code T93 or free text based) OR ever treated with LLT only[a] OR both	***N* = 173,321 (27%)** *N* = 12,558 *N* = 134,789 *N* = 25,974
Exclude *Low or moderate CV risk in 2018*	
High or very high CV risk in 2018 (as per ESC/EAS 2016 guidelines) Very high risk High risk	***N* = 94,224 (54%)** *N* = 68,118 *N* = 26,106
Exclude *No LDL-C available in 2018*	
LDL-C available, last in 2018 = index date	***N* = 65,393 (69%)**
Exclude *No LLT on index date and not statin intolerant*	
Population 2018 using ESC risk categorization (study population) Very high risk High risk	*N* = 54,346 (83%) *N* = 37,978 *N* = 16,368

Abbreviations. GP, General practitioner; CV, Cardiovascular; ESC, European Society of Cardiology; EAS, European Atherosclerosis Society; LDL-C, Low-density lipoprotein cholesterol.
% presented relative to previous step in selection process.
[a]At least one dispensed lipid lowering drug such as statins, ezetimibe.

Table 2. Characteristics of high CV and very high CV risk population cohort.

	Study population	Very high CV risk	High CV risk
	N = 54,346	*N* = 37,978	*N* = 16,368
Age (years), mean ± SD	70.9 ± 10.3	70.7 ± 10.2	71.1 ± 10.6
Sex, male, n (%)	29,535 (54)	22,026 (58)	7509 (46)
Time since first LLT or diagnosis (years), median (IQR)	7.7 (4.3–11.8)	7.5 (4.3–11.7)	8.1 (4.3–12.0)
History of ASCVD, n (%)	35,905 (66)	35,905 (95)	–
Affected vascular bed, n (%)[a]			
Coronary arteries	26,604 (49)	26,604 (70)	–
Cerebrovascular arteries	14,458 (27)	14,458 (38)	–
Peripheral arteries	2847 (5)	2847 (7)	–
Number of affected vascular beds, n (%)			
1	28,285 (52)	28,285 (74)	–
2	7236 (13)	7236 (19)	–
3	384 (1)	384 (1)	–
Heart failure, n (%)	4302 (8)	3729 (10)	573 (4)
CKD, n (%)[b]	18,184 (33)	9937 (26)	8247 (50)
Moderate	15,757 (29)	7785 (20)	7972 (49)
Severe	888 (2)	888 (2)	–
DM type 1, n (%)	205 (<0.5)	128 (<0.5)	77 (<0.5)
DM type 2, n (%)	18,272 (34)	9882 (26)	8390 (51)
DM + risk factor[c], n (%)	2965 (5)	2965 (7)	–
Current smoking, n (%)[d]	5873 (15)	5196 (19)	677 (6)
BMI (kg/m^2), mean ± SD	28 ± 5	28 ± 5	29 ± 5
SBP (mmHg), mean ± SD	136 ± 16	135 ± 16	137 ± 16

Abbreviations. CV, Cardiovascular; IQR, Interquartile range; SD, Standard deviation; LLT, Lipid lowering therapy; CKD, Chronic kidney disease; ASCVD, Atherosclerotic cardiovascular disease; DM, Diabetes mellitus; BMI, Body mass index; SBP, Systolic blood pressure.
[a]ASCVD types are not mutually exclusive.
[b]Includes diagnoses without mentioning CKD stage.
[c]High SBP, high total cholesterol or smoking.
[d]Calculation of percentage based on recorded status, 28% not recorded.

use. In this study sub cohort, 41% (3153) were very high CV risk, 19% (1454) high risk and 40% (3040) moderate/low risk; 39% had history of ASCVD and 10% polyvascular or recurrent CV event.

The majority of patients in the total study population of high and very high risk (*N* = 54,346) were treated with statin monotherapy at index date (93%), 5% with ezetimibe (2% monotherapy and 3% in combination with statin) (Table 3). The majority of patients treated with a statin were on moderate intensity statin monotherapy (73%). High intensity statins were administered to 15%of the patients, and 5% received low intensity statin. Less than 0.5% used PCSK9 inhibitors. Only 1% used other LLT, such as fibrates or nicotinic acid, another 2% did not use any LLT at index date.

Looking at patients with LLT of statin monotherapy at index date, we saw that 35%, 48% and 35% of high (Supplementary Table A.2), moderate and low intensity statin users, respectively, had used the same LLT before. This is an

Table 3. LTT usage at index date.

	Study population $N = 54,346$	Very high CV risk $N = 37,978$	High CV risk $N = 16,368$
LLT at index date	n (%)	n (%)	n (%)
Statins only[a]	50,464 (93)	34,975 (92)	15,489 (95)
Simvastatin	26,547 (49)	17,482 (46)	9065 (55)
Pravastatin	2854 (5)	1941 (5)	913 (6)
Fluvastatin	339 (1)	227 (1)	112 (1)
Atorvastatin	14,331 (26)	10,581 (28)	3750 (23)
Rosuvastatin	6393 (12)	4744 (12)	1649 (10)
High intensity statin	8133 (15)	6542 (17)	1591 (10)
Moderate intensity statin	39,620 (73)	26,673 (70)	12,947 (79)
Low intensity statin	2711 (5)	1760 (5)	951 (6)
Statins and ezetimibe	1566 (3)	1327 (3)	239 (1)
Ezetimibe only	897 (2)	678 (2)	219 (1)
PCSK9 inhibitors ± other LLT	61 (<0.5)	58 (<0.5)	3 (<0.5)
Other LLT	513 (1)	351 (1)	162 (1)
No treatment[b]	845 (2)	589 (2)	256 (2)
Statin intolerance[c]	1799 (3)	1316 (3)	483 (3)

Abbreviations. CV, Cardiovascular; PCSK9, Protein convertase subtilisin/kexin type 9; LLT, lipid lowering therapy; treatment categories (bold headings) are mutually exclusive.
[a]Numbers for statins are mutually exclusive within statin type and within statin intensity categories.
[b]Within the six months prior to index date.
[c]Statin intolerance based on LLT algorithm, see Methods section.

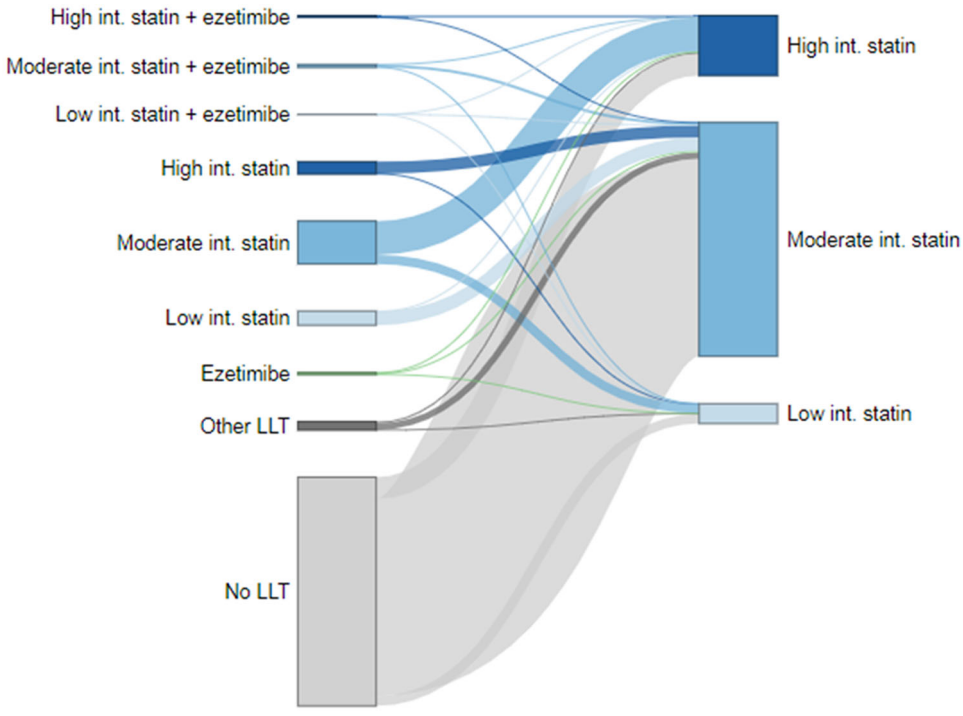

Figure 1. Sankey diagram of treatment patterns in patients receiving statin monotherapy at index date.

indication of non-adherence having a gap between prescriptions which exceeded the allowed grace period of half the prior prescription duration[28], but was shorter than 6 months.

Figure 1 shows the prior treatment (on the left side) for the patients receiving current statin monotherapy at index date (on the right side), i.e. after a switch, an add-on to prior LLT or as (re-)initiation of LLT, as defined in the methods section. No prior LLT was recorded for 24%, 44% and 32% of high, moderate and low intensity statin users (Supplementary Table A.2), respectively, most likely representing the start of LLT. Most patients moved from no LLT to moderate intensity statin monotherapy, the recommended starting therapy in the Dutch guidelines[32] for the treatment of hyperlipidaemia (simvastatin 40 mg). High intensity statin was often started as either initiation of LLT (recommended when patients are at very high risk), or - slightly more often - as treatment intensification (up titration), which is recommended by the Dutch guidelines[32] if patients do not reach the intended treatment goal. Up titration of LLT was observed more often than down titration, e.g. from combinations with ezetimibe to statin monotherapy, or simply from a higher to a lower intensity statin monotherapy.

When examining treatment patterns of patients on combination treatment with ezetimibe at index date (Figure 2) we noted that for the majority of patients ezetimibe was

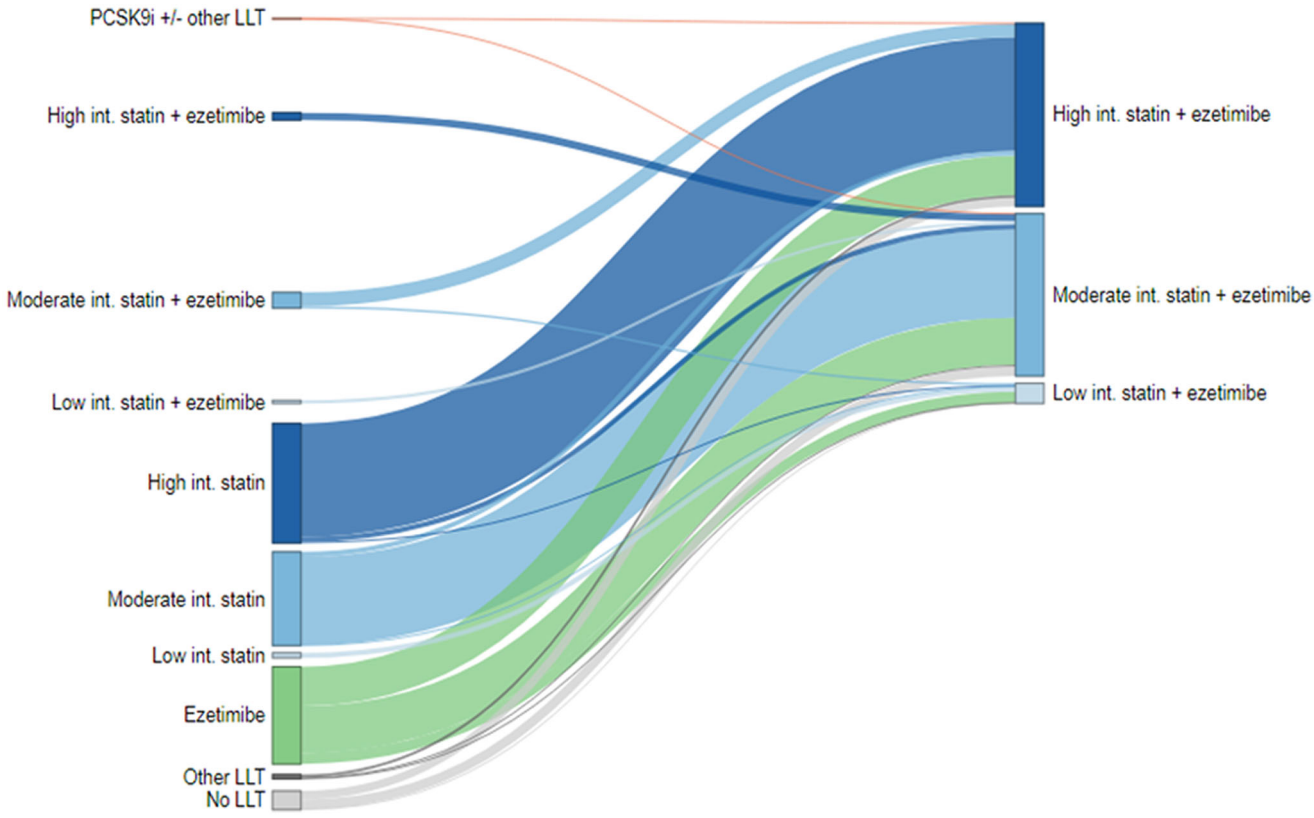

Figure 2. Sankey diagram of treatment patterns in patients receiving statin and ezetimibe combination therapy at index date. Last LLT immediately before LLT at index date is shown on the left, LLT at index date (most recent time point) is shown on the right. Abbreviations. int., Intensity; LLT, Lipid lowering therapy; PCSK9i, Protein convertase subtilisin/kexin type 9 inhibitors.

Table 4. LDL-C distribution at index date.

	Number of patients N	n (%)	Mean LDL-C mmol/l ± SD
Any	54,346		2.2 ± 0.8
<1.4 mmol/l		7237 (13)	
1.4–<1.8 mmol/l		11542 (21)	
1.8–<2.5 mmol/l		21903 (40)	
2.5–<3.4 mmol/l		9623 (18)	
> =3.4 mmol/l		4041 (7)	
By LLT			
None	845		3.7 ± 1.1
Ezetimibe	897		3.0 ± 1.1
Low intensity statin	2711		2.5 ± 0.8
Moderate intensity statin	39,620		2.1 ± 0.7
High intensity statin	8133		2.2 ± 0.8
Statin + ezetimibe	1566		2.0 ± 0.7
PCSK9i ± other LLT	61		1.6 ± 0.8
Other LLT	513		2.4 ± 0.9

Abbreviations. SD, Standard deviation; LDL-C, Low-density lipoprotein cholesterol; PCSK9i, Protein convertase subtilisin/kexin type 9 inhibitors; LLT, Lipid lowering therapy.

added on top of their existing statin treatment, mainly of high or moderate intensity. This is in line with the Dutch treatment guidelines, which suggest intensifying treatment if goals are not met, either by increasing the statin intensity as observed in Figure 1 or by adding on ezetimibe. Escalation from ezetimibe monotherapy to combination therapy with statin and ezetimibe were observed quite frequently (i.e. in 51%, 26% and 20% of patients on low, moderate and high intensity statin combined with ezetimibe, respectively) and may represent patients for whom statin intolerance was assessed by rechallenge with statin treatment after a period of non-use.

Table 4 shows overall LDL-C means and distributions of patients over LDL-C levels, as well as mean LDL-C by received LLT. The overall mean LDL-C was 2.2 (±0.8) mmol/l, with lowest LDL-C levels associated with PCSK-9 inhibitor use and highest levels with no LLT use or ezetimibe monotherapy. Lipid distributions were very similar between high and very high risk groups (data not shown). The LDL-C goal of the 2016 ESC/EAS guidelines of <1.8 mmol/l was reached by 35% of the very high risk group, 74% of those at high risk reached their goal of <2.5 mmol/l (data not shown in Table 4). Combined, these two risk categories resulted in 46% of patients being at goal. The newly defined goal for the very high CV risk group

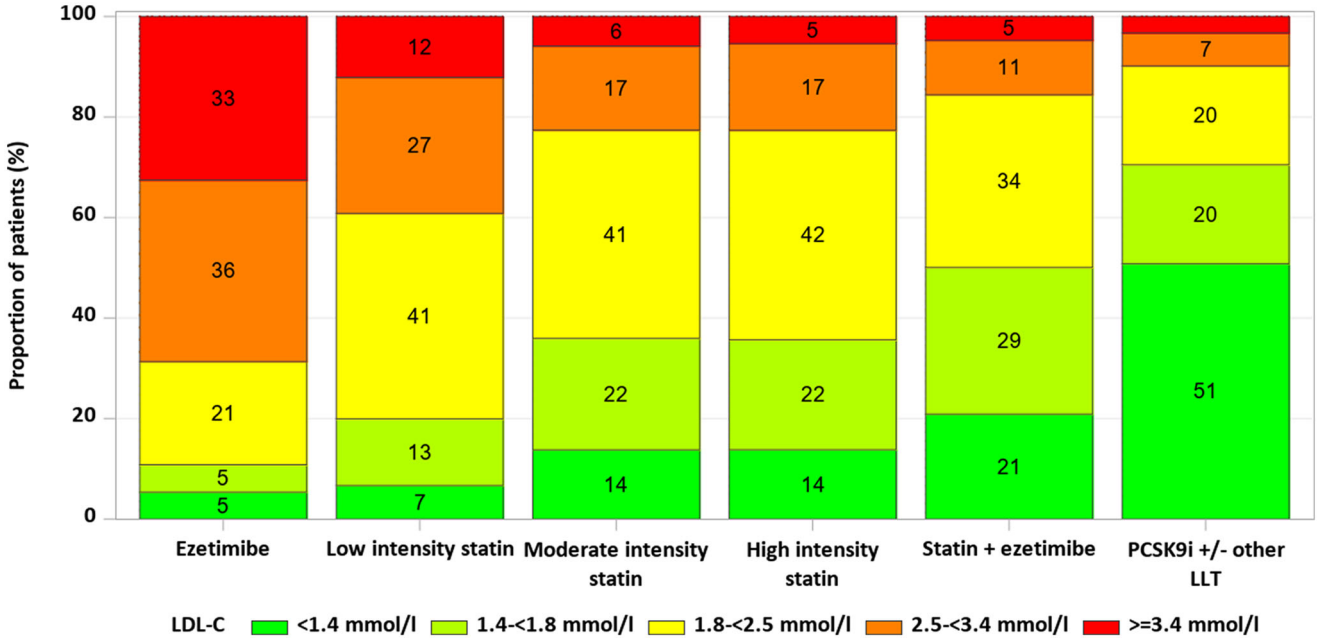

Figure 3. Proportion of patients per LDL-C category by lipid lowering treatment intensity. Abbreviations. LDL-C, low-density lipoprotein cholesterol; PCSK9i, Protein convertase subtilisin/kexin type 9 inhibitors; LLT, Lipid lowering therapy.

of <1.4 mmol/l in the 2019 update of the ESC/EAS guidelines was reached by 13% of patients.

Figure 3 indicates that a higher intensity of LLT (as illustrated by the order of the treatments) is associated with lower LDL-C. Although low intensity statins were associated with higher LDL-C levels than moderate intensity statins, there was no difference between moderate and high intensity statins. Statin and ezetimibe combination therapy was associated with a greater proportion of patients achieving LDL-C < 1.8 mmol/l compared to statin monotherapy (Figure 3), even though the mean LDL-C was very similar for both treatments (Table 4). The greatest proportion reaching LDL-C levels <1.8 mmol/l was observed in patients receiving PSCK9 inhibitors. Of the patients receiving moderate or high intensity statins 36% had LDL-C levels <1.8 mmol/l; this was 50% of patients on statins and ezetimibe and 70% of patients on PCSK9 inhibitors ± other LLT. It should be noted that PCSK9 inhibitor results were based on a small sample size and should be interpreted with caution.

Table 5 shows the HCRU up to five years prior to index date. GP contact administration information was available for 49,293 patients. From secondary care only hospitalizations could be assessed. Patients with ASCVD had higher hospitalization rates than those without ASCVD. Patients with peripheral ASCVD and polyvascular disease had the highest HCRU: high GP (home) consultation rates and hospitalization rates and the longest hospital stays. Overall GP consultation rates were highest in the group with no ASCVD (many with diabetes).

Discussion

Using a contemporary dataset from the Dutch adult population we have characterized patients with hypercholesterolaemia or mixed dyslipidaemia in 2018 treated with LLTs and monitored within a GP database. More than half of those patients with hypercholesterolaemia or mixed dyslipidaemia (54%) were at high or very high CV risk using the definitions of the 2016 EAS/ESC guidelines. As expected, the majority of the patients of interest had documented ASCVD or diabetes at index date.

In our study population the majority of patients (73%) were treated with moderate intensity statin and small proportions were treated with combinations of statin and ezetimibe (3%) or PCSK9 inhibitors (<0.5%); this is consistent with previous studies in similar patient cohorts across Europe that have shown a gap between guidelines and clinical practice with regard to actual lipid management[33,34]. Clinical inertia is common, and clinicians, patients and healthcare system play a key role in avoiding or postponing the use of combination therapy in dyslipidaemia in clinical practice. For the physician time and resource constraints, as well as a wish to avoid side effects, can lead to reactive rather than proactive care. Therapy optimization may take a long time for a patient, particularly if they take multiple medicines because of their comorbid profile. Last but not least, inconsistencies between international guidelines and local reimbursement can create extra complexities and demands for promoting combination therapy, particularly for new and innovative medicines[35]. The LDL-C goals of <2.5 mmol/l) were reached by 74% and <1.8 mmol/l by 34% of the patients with their current treatment. Although less stringent Dutch guidelines were valid at the index date, stating a treatment goal of <2.5 mmol/l LDL-C for patients at high or very high risk[21], physicians were free to apply the ESC/EAS guideline to patients at high risk[36] and specialists were more inclined to do so. The Dutch guidelines were updated in August 2018[37] to match the valid ESC/EAS goals[22]. The less stringent guideline was therefore not expected to have had a large impact on treatment strategies.

Table 5. Healthcare resource utilization.

	High CV risk	Very high CV risk			
	No ASCVD	Coronary ASCVD	Cerebrovascular ASCVD	Peripheral ASCVD	Polyvascular ASCVD
	$N = 14{,}537$	$N = 1824$	$N = 17{,}730$	$N = 6965$	$N = 1058$	$N = 7179$
Person years	70,411	8809	86,241	33,764	5157	34,786
GP consultations						
Patients with any GP consultation (%)	14,498 (>99.5)	1819 (>99.5)	17,679 (>99.5)	6943 (>99.5)	1058 (100)	7161 (>99.5)
Consultations/PY (95% CI)	8.7 (8.7–8.8)	9.6 (9.6–9.7)	8.3 (8.3–8.3)	8.4 (8.4–8.5)	9.1 (9.0–9.2)	9.5 (9.5–9.6)
Patients with home visits (%)	4399 (30)	576 (32)	5560 (31)	2641 (38)	434 (41)	2971 (41)
Home visits/PY (95% CI)	0.3 (0.3–0.4)	0.5 (0.5–0.5)	0.3 (0.3–0.3)	0.5 (0.4–0.5)	0.6 (0.5–0.6)	0.6 (0.6–0.6)
Hospitalizations						
Patients with a hospitalization (%)	6355 (44)	828 (45)	10,438 (59)	4003 (57)	897 (85)	4541 (63)
Hospitalizations / PY (95% CI)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.3 (0.3–0.3)	0.5 (0.5–0.6)	0.4 (0.4–0.4)
Hospitalized days/PY (95% CI)	0.7 (0.7–0.7)	0.9 (0.9–0.9)	1.2 (1.2–1.2)	1.1 (1.1–1.1)	2.2 (2.2–2.3)	1.7 (1.7–1.7)
Length of stay in days per hospitalization, mean ± SD	3.2 ± 4.8	3.7 ± 5.3	3.5 ± 4.8	3.8 ± 5.5	4.1 ± 5.3	4.0 ± 5.6

Notes: Analyses were based on maximally five years prior to the index date, columns contain mutually exclusive groups with available contact administration information. Abbreviations. CV, Cardiovascular; ASCVD, Atherosclerotic cardiovascular disease; PY, Person years; CI, Confidence interval; SD, Standard deviation; GP, General practitioner.

The lack of reaching defined LDL-C goals and the underutilization of combination therapy revealed an unmet need even in a country like the Netherlands, where the standard of care is high. The distribution of LDL-C levels across the various LLT showed that more intense LLT was associated with lower LDL-C and more patients at goal. Although low intensity statins were associated with higher LDL-C levels than moderate intensity statins, there was no difference between moderate and high intensity statins. As a result only the 5% of the population that received low dose statins, might benefit from intensification of statin therapy alone. However, if these patients receive low doses because of statin intolerance, statin intensification may not be an option. Combination therapy could benefit many more patients, as the majority of patients received statin monotherapy. Intensification of therapy was more often observed than de-intensification, but intensification with combination therapy occurred only occasionally.

Due to the low number of patients with recorded diagnostic dyslipidaemia codes (including the subcode for FH) we were not able to determine the LDL-C levels specifically among FH patients in our study. However, in a cross-sectional analysis of a large cohort of genetically identified HeFH patients in the Netherlands[38], patients with coronary heart disease had mean LDL-C level of 7.2 mmol/l while those without had 9 mmol/l. They concluded that based on modelling, less than 10% of HeFH patients with and 50% without CHD would be able to reach treatment targets with maximal dose statin, and add-on therapy could much improve that.

Similar gaps between the guidelines and clinical practice were observed across Europe[33,34]. In a population of patients using LLT, 63% of patients at high CV risk and 39% of patients at very high CV risk reached their recommended LDL-C goals, and ezetimibe and PCSK9 inhibitors in combination with statin were used by 9% and 1%, respectively[33]. In the UK ezetimibe was added to statin treatment in only 1.5% of patients at high or very high risk, and 34–36% of the patients had LDL-C levels <1.8 mmol/l and 72–73% <2.5 mmol/l[34]. A recently released 2019 ESC/EAS guideline[8] sets a new LDL-C goal of <1.4 mmol/l LDL-C for patients at very high risk, which leads the authors of the Da Vinci study to expect even larger gaps between guidelines and clinical practice[33]. In our study only 13% reached the goal of <1.4 mmol/l, confirming the above expectation. A review of lipid management in Europe suggested that that the under-achievement of LDL-C goals was highly prevalent and was broadly similar in national and multinational studies for the high and very high risk secondary prevention subgroups[39]. Greater utilization of combinations of statins with non-statin LLT will be required to reduce those gaps, as our results confirm that combination therapies lower LDL-C more effectively.

Around 3% of the population was deemed statin intolerant. The applied treatment algorithm for statin intolerance was based on criteria (adopted by the ESC/EAS and Dutch physicians) that require re-challenging of patients with lower intensity statins and eventual cessation of all statin therapy if

necessary[31]. This is a conservative estimation, as there are higher estimates of statin intolerance reported (10–15%) using a broader definition[31]. Observations from real world evidence mention that 7–29% of patients complain of statin related muscle symptoms, but also that many patients will tolerate low dose statin therapy for a prolonged period of time[40]. Because re-challenging does not often occur in usual practice, statin intolerance in our population was probably underestimated. In the patient selection process, 17% ($n = 11{,}047$) of patients with available LDL-C levels in 2018 were excluded from the study as not receiving LLT; these could be statin intolerant patients not meeting the strict criteria of our definition. In additional analyses performed to broaden the criteria with an aim to reflect more what may happen in clinical practice (also including patients treated with low intensity statins, with or without concurrent ezetimibe use as described in Methods), we estimated a proportion of 7% patients with hypercholesterolaemia or mixed dyslipidaemia irrespectively of CV risk status that would be deemed statin intolerant. In any case, the statin intolerant segment represents a population of high unmet need. Limited treatment options exist and adding non-statin treatments with a high potency can be a way of getting those patients closer to LDL-C goals.

The current cross-sectional design captures patients at different time points from the start of LLT or first diagnosis of ASCVD till the index day. The differences in HCRU among the various comorbid conditions are likely to be underestimated, and should be interpreted with caution. The results indicate that ASCVD is a driver for HCRU, mainly because of increased hospitalization rates, with PAD and polyvascular ASCVD resulting in the highest rates. Prevention of ASCVD or progression to polyvascular disease are therefore important. Apart from urgent care, GP home visits are indicated for patients with poor mobility, which may explain why the highest rates were observed in patients with PAD, polyvascular and cerebrovascular disease and patients with diabetes. LDL-C levels did not appear to be different across the types of ASCVD. However, the differences in HCRU suggest that in particular patients with PAD and polyvascular disease could benefit from more intensive treatment.

No published Dutch studies on HCRU in a dyslipidaemia population similar to our study population were found to put our findings into context. However, studies from UK showed that hospitalizations generate the largest portion of acute and long-term costs[16], and patients with myocardial infarctions generated most costs, especially within the first year following the event[41]. Using Swedish national registers and electronic medical records, it was shown that the most costs occurred in the first year following the event, with ischaemic stroke accounting for the highest costs[14]. Our study design did not allow analysis of HCRU directly after an event, and did not include actual costs, which may explain the difference between the UK, Sweden and the Netherlands in the type of ASCVD identified as having the highest HCRU. Lowering LDL-C in order to ultimately prevent progression of ASCVD to polyvascular disease or recurrence of cardiovascular events may reduce HCRU and costs.

Strengths and limitations

With the GP as gatekeeper of the Dutch healthcare system, we expect our study to be a good representation of the Dutch dyslipidaemia population at high or very high CV risk who are treated with LLTs. As the scope was to understand contemporary treatment patterns and mean LDL-C in treated patients, we have excluded those lacking LDL-C records in the GP Database. Based on the proportion of patients with prescriptions from secondary care before (16%) and after this exclusion (12%) we estimate to have lost up to a quarter of patients in secondary care due to lacking LDL-C records.

We estimate that around 50% of PCSK9 inhibitors were likely dispensed through specific patient support programs *via* home delivery, and may not be recorded in the Outpatient Pharmacy Database, but since these prescriptions were rare in 2018 this has little impact on the study population. PCSK9 inhibitor use has increased since this study, though.

Although the official definition algorithm of statin intolerance was based on criteria that require re-challenging of patients, thereby underestimating the proportion of statin intolerant patients at 3%, the broadened definition we applied, including low intensity statin therapy as monotherapy or combined with ezetimibe, may overestimate the proportion with true statin intolerance.

The PHARMO Database Network contains data from daily practice, which are primarily recorded for healthcare professionals, not for research. Registration of diagnoses and measurements is not mandatory, and this means diagnoses of hypercholesterolaemia, mixed dyslipidaemia and morbidity used for risk estimation might have been underestimated. Furthermore, we may have missed some high risk patients based on the CV SCORE algorithm[22] because that could not be assessed in this cross-sectional study, where untreated levels of risk factors were often not available. The ICPC coding is not granular enough to allow identification of DM with target organ damage, however, we assumed that all patients with DM would have been allocated to the high risk group based on the SCORE algorithm, if it could be applied.

The complete and accurate recording of risk factors necessary of the calculation of absolute risk is an important component of effective prevention strategies for ASCVD and other chronic diseases. This could be a challenge for GPs. A systematic review reported that GPs may prefer to evaluate the individual risk of their patients through their experience rather than using guidelines which often do not fit their patients' unique circumstances[42]. The lack of differentiating the CV risk of the patients may lead to undertreatment increasing potential the risk particularly for patients with comorbid conditions. Strategies are therefore required to facilitate risk assessment, involving both GPs and specialist in the evaluation and decision making regarding CVD prevention.

Although this study reflects the practice in 2018, and meanwhile new ESC/EAS guidelines were introduced and treatment practices have evolved, the potential for clinical inertia and underestimating CV risk probably still applies.

Although secondary outpatient care was not included in the HCRU analysis, this has limited impact on our conclusions, because other studies have shown that primary care visits and hospitalizations generate the main direct healthcare costs incurred by this population[16].

There is an opportunity for educating patients in terms of disease awareness, risk perception and adherence to LLT, and raising physicians' awareness in terms of improved treatment practices and avoiding clinical inertia. This requires healthcare professional, patient organizations and the scientific medical community to collaborate and cooperate in this healthcare ecosystem.

Conclusion

The treatment of hypercholesterolaemia and mixed dyslipidaemia observed in our study of treated patients at high or very high CV risk in 2018 in the Netherlands was suboptimal. Many patients did not meet the recommended LDL-C goals outlined in the 2016 ESC/EAS guidelines, resulting in high clinical and economic burden. To further lower CV risk and associated burden, add-on therapies should be applied more often in patients at high or very high CV risk. In view of even lower LDL-C goals recommended in the 2019 ESC/EAS guidelines, emerging PCSK9 inhibitors and recently approved bempedoic acid may be considered to further intensify lipid lowering therapies on top of maximum tolerated statins and ezetimibe.

Transparency

Declaration of funding

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Declaration of financial/other relationships

E.M. Heintjes, J.G. Kuiper, F.J.A. Penning-van Beest and R.M.C. Herings are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. A. Anastassopoulou and A. Bilitou are employees of the sponsor company Daiichi Sankyo Europe GmbH. Prof. Postma's contribution to this manuscript was financially supported by Daiichi-Sankyo. Furthermore, Prof Postma reports grants and honoraria from various pharmaceutical companies, all unrelated to this project. Prof. Jukema was speaker (with or without lecture fees) at (continuing medical education accredited) meetings sponsored by, and/or his department has received research grants from among others Amgen, Athera, Astra-Zeneca, Biotronik, Boston Scientific, Dalcor, Daiichi Sankyo, Lilly, Medtronic, Merck-Schering-Plough, Pfizer, Roche, Sanofi Aventis, The Medicine Company, the Netherlands Heart Foundation, CardioVascular Research the Netherlands (CVON), the Netherlands Heart Institute and the European Community Framework KP7 Programme. A peer reviewer on this manuscript has disclosed that they received consultancy fees from Amgen and Novartis. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author contributions

E. Heintjes, J. Kuiper, F. Penning-van Beest, A. Anastassopoulou, and A. Bilitou were involved in the conception and design and analysis and drafting the paper; all authors were involved in interpretation of the data, revising the paper critically for intellectual content and gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, EH, upon reasonable request.

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