Application of 2019 ESC lipid guidelines in secondary prevention patients in general practice in Belgium: a morbidity registry-based study

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Masters in Family Medicine

Master's Thesis in General Practice

2025–2026

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Abstract

Background: Cardiovascular diseases remain the leading cause of mortality in Europe. Elevated low-density lipoprotein cholesterol (LDL-C) plays a central causal role in atherosclerotic cardiovascular disease (ASCVD), and the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommend stringent LDL-C targets for secondary prevention: an absolute LDL-C level of < 55 mg/dL combined with a ≥ 50% reduction from baseline. Despite these recommendations, real-world data consistently show that a substantial proportion of high-risk patients fail to achieve guideline-recommended targets.

Aim: To describe the implementation of the 2019 ESC/EAS lipid guidelines in Belgian primary care, to characterise patient profiles associated with target attainment or failure, and to assess the use of lipid-lowering therapies (LLTs).

Design and setting: Retrospective cross-sectional study using data from the Intego-II primary care morbidity registry, comprising routinely collected electronic health record (EHR) data from 135 general practice centres across Flanders in Belgium.

Participants: Patients aged ≥ 40 years with a documented history of ASCVD before 1 January 2024, at least one general practitioner (GP) contact and one lipid-lowering therapy (LLT) prescription in 2024, and at least one LDL-C measurement between 1 July 2023 and 31 December 2024. Patients with familial hypercholesterolaemia were excluded. The final study population comprised 4,626 patients.

Methods: Patients were classified into three non-overlapping subgroups: those achieving the 2019 ESC/EAS target, defined as LDL-C < 55 mg/dL AND ≥ 50% reduction from baseline; those achieving the 2016 ESC/EAS target, defined as 55 mg/dL ≤ LDL-C < 70 mg/dL OR ≥ 50% reduction from baseline if LDL-C ≥ 70 mg/dL; and those not achieving any target, defined as LDL-C ≥ 70 mg/dL AND < 50% reduction from baseline. Socio-demographic variables, clinical parameters, CVD-specific variables, laboratory parameters, comorbidities, comedication, and LLTs were described using descriptive statistics.

Results: A total of 12.6% of patients could be confirmed as fully meeting the 2019 ESC/EAS dual criterion, while 35.6% achieved LDL-C < 55 mg/dL and 26.7% met the 2016 target. A total of 37.8% failed to achieve any guideline-recommended target. Male sex, a history of coronary artery disease, type 2 diabetes mellitus, multimorbidity, polypharmacy, use of high-intensity statins, and statin + ezetimibe combination therapy were more frequently observed in the target-achieving group. In contrast, patients with mental health disorders or long-standing ASCVD were more prevalent in the non-target-achieving group. High-intensity statins were used in 68.5% of patients. A total of 34.1% of

patients used combination therapy, comprising 30.6% on two different LLTs and 3.5% on three different LLTs. 26.9% of patients used statin + ezetimibe combination therapy. Other agents such as PCSK9 inhibitors, inclisiran, anion exchangers, and omega-3 fatty acids were used in fewer than 1% of patients. Bempedoic acid was used in 3.6% of patients across all regimens: as monotherapy or in dual combination with a statin or triple combination with statin and ezetimibe in 2.1%, and in dual combination with ezetimibe in 1.5%. Fibrates were not used in monotherapy but were used in 1% of patients in combination with a statin and ezetimibe.

Conclusion: LDL-C target attainment in Belgian primary care falls short of the 2019 ESC/EAS recommendations, with only 12.6% of secondary prevention patients confirmed to meet the dual criterion. The principal implementation gaps include underutilisation of high-intensity statins, suboptimal statin + ezetimibe combination therapy, and limited uptake of novel agents. Addressing this will require structured ASCVD care pathways tailored to priority subgroups, including women, patients with TIA or PAD, and those with mental health comorbidities.

Introduction

Cardiovascular disease remains the leading cause of mortality in Europe, accounting for approximately 32.7% of all deaths, compared with 22.5% attributed to cancer (1). The principal clinical manifestations of atherosclerotic cardiovascular disease (ASCVD) include coronary artery disease, ischaemic stroke, and peripheral artery disease (PAD) (1). Major modifiable risk factors comprise hypertension, obesity, smoking, diabetes, and dyslipidaemia.

Among these, dyslipidaemia, particularly elevated low-density lipoprotein cholesterol (LDL-C), plays a central causal role in the development of ASCVD and is therefore a primary therapeutic target in cardiovascular prevention (1). Large meta-analyses of randomised controlled trials have demonstrated a log-linear relationship between LDL-C reduction and cardiovascular risk reduction, with an approximate 22% decrease in major cardiovascular events per 1 mmol/L (~40 mg/dL) reduction in LDL-C (2). Statins represent the cornerstone of lipid-lowering therapy (LLT), markedly reducing both LDL-C levels and major vascular events. However, interindividual variability in response, statin intolerance, and suboptimal adherence may limit their effectiveness in routine clinical practice (1).

Additional LDL-C lowering and cardiovascular risk reduction can be achieved through combination therapy with non-statin lipid-lowering therapies (LLTs) such as ezetimibe and PCSK9 inhibitors (3,4). Based on this evidence, the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommend stringent LDL-C targets for secondary prevention: a $\geq$ 50% reduction from baseline and an absolute LDL-C level of < 55 mg/dL for patients with established ASCVD, and < 40 mg/dL for those with recurrent events within two years (1).

Despite these evidence-based recommendations, achieving guideline targets in real-world practice remains challenging. Observational studies consistently show that a substantial proportion of very-high-risk patients fail to meet recommended LDL-C levels, revealing a persistent gap between guideline recommendations and clinical implementation (5). Furthermore, some experts have questioned whether strict numerical LDL-C targets are sufficiently evidence-based, arguing that these targets are largely extrapolated from meta-analyses rather than directly tested in randomised treat-to-target trials. Moreover, practical barriers (including limited access to advanced therapies, high costs, and suboptimal long-term adherence) may limit their applicability in routine clinical practice (6,7). Consequently, a more individualised, risk-based approach to lipid management has been proposed by some authors as an alternative to rigid target-based strategies (6).

European real-world studies further illustrate these challenges. The SANTORINI study specifically assessed attainment of the 2019 ESC/EAS LDL-C targets among high- and very-high-risk patients across primary and secondary care settings in 14 European countries. This study demonstrated that 21.2% of high- and very-high-risk patients achieved the recommended 2019 ESC/EAS LDL-C goals at

baseline, increasing to 33.0% after one-year follow-up, largely due to the increased use of combination LLT (8). Similarly, the EU-wide DA VINCI study showed that approximately 39.0% of very-high-risk patients achieved the previous 2016 ESC/EAS LDL-C target, and 18.0% met the stricter 2019 target (5). This confirms persistent suboptimal implementation of LLTs in routine clinical practice.

However, real-world data on the implementation of the 2019 ESC/EAS lipid guidelines in Belgian primary care remain limited. Most existing European studies pool data from multiple countries and settings, providing limited insight into the specific context in Flemish general practice, which plays an important role in the long-term follow-up and management of patients with established ASCVD. Furthermore, beyond overall target attainment, little is known about which patient profiles are at greatest risk for undertreatment, or about the use of novel LLTs such as bempedoic acid, inclisiran, and PCSK9 inhibitors in routine primary care. Identifying both the implementation gap and the associated patient profiles is essential for prioritising subgroups and supporting targeted improvements in lipid management at the level of general practice.

This study examines how the 2019 ESC/EAS lipid guidelines are applied in Belgian clinical practice. Three objectives were defined: (a) to determine how many secondary prevention patients achieve their LDL-C target; (b) to describe patient characteristics across lipid target groups; and (c) to evaluate the use of LLTs. Together, these objectives aim to provide a clearer picture of LDL-C target attainment and the practical use of current lipid management guidelines in everyday care.

Methods

Study design and population

To collect data from general practices in Belgium, the Intego-II database, managed by the Academic Centre for General Practice at KU Leuven (9), was used. Operating since 1994, the Intego-II network is an operational computerised morbidity registration network, containing coded electronic health record (EHR) data from 135 general practice centres across Flanders, the northern part of Belgium (9). A quality selection procedure minimises recording bias by requiring participating practices to ensure comprehensive diagnostic coding using keywords within the EHR. As of 31 December 2024, the database included records for approximately 512,000 active patients, representing 7.5% of the Flemish population (10). The Intego-II data protocols have been validated by the Belgian Privacy Commission (11,12) and the registry is hosted on the Healthdata platform (12). Intego-II enables GPs to prospectively and automatically collect data during routine clinical practice. Data are recorded using keywords linked to internal codes, which are mapped to the International Classification of Primary Care 2nd edition (ICPC-2), International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10), and Anatomical Therapeutic Chemical (ATC) classifications (9). The resulting dataset

captures a wide range of information, including new diagnoses, prescriptions, laboratory results, and vaccination status. Additionally, biomedical parameters, such as blood pressure, height, and weight, are recorded, along with socio-demographic information, including age and sex (9).

This retrospective cross-sectional study used Intego-II data up to and including 2024. Patients were eligible if they were 40 years or older, had a confirmed ASCVD diagnosis before 1 January 2024, had at least one GP contact in 2024, at least one prescription for LLT in 2024, and at least one LDL-C measurement between 1 July 2023 and 31 December 2024. Patients with familial hypercholesterolaemia (FH) were excluded. ASCVD was defined as any of the following: angina pectoris or unstable angina, myocardial infarction (MI), coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), ischaemic heart disease without angina, history of PAD, transient ischaemic attack (TIA) or stroke, retinal infarction, ischaemic optic neuropathy, or carotid artery surgery. Diagnoses were identified using corresponding ICPC-2 and ICD-10 codes or free-text terms (Appendix 1). Based on these criteria, the final study population comprised 4,626 patients, representing 1% of the total Intego-II database population (Figure 1).

Variables of interest

Three subgroups were defined based on the most recent LDL-C value measured in the 18 months preceding 31 December 2024. The percentage reduction in LDL-C was calculated relative to the most recent pre-treatment LDL-C value recorded before the start date of LLT.

- Group 1: Patients achieving the 2019 ESC lipid target: LDL-C < 55 mg/dL AND a reduction of ≥ 50% from baseline.
- Group 2: Patients achieving the 2016 ESC lipid target: 55 mg/dL ≤ LDL-C < 70 mg/dL OR a reduction of ≥ 50% from baseline if LDL-C ≥ 70 mg/dL.
- Group 3: Patients not achieving any lipid target: LDL-C ≥ 70 mg/dL AND a reduction of < 50% from baseline.

For patients without an available pre-treatment LDL-C value, subgroup assignment was based solely on the attained LDL-C target; the percentage reduction criterion was not applied.

In addition to the variables used for inclusion, a range of socio-demographic, clinical, and laboratory variables were collected. Comorbidities were registered based on ICPC-2 and ICD-10 codes (Appendix 2), and included obesity, chronic kidney disease (CKD), heart failure, atrial fibrillation, hypertension, type 2 diabetes mellitus, musculoskeletal disorders (osteoarthritis, rheumatoid arthritis), and mental health disorders (schizophrenia, anxiety disorder, depressive disorder, personality disorder). A predefined list of 22 chronic conditions was additionally used to quantify multimorbidity across lipid target groups (Appendix 3) (13). Socio-demographic variables included age and sex, whereas clinical parameters comprised smoking status, body mass index (BMI), and systolic and diastolic blood pressure

(SBP and DBP, respectively). Laboratory parameters were retrieved using Medidoc codes and included haemoglobin A1c (HbA1c), baseline LDL-C, and percentage reduction from baseline LDL-C. LLTs were defined based on prescriptions issued at least three months prior to the last LDL-C measurement and were classified according to the WHO ATC classification system (Appendix 4). Comedications included insulin and non-insulin antidiabetic agents, as well as RAAS (renin-angiotensin-aldosterone system) and non-RAAS antihypertensives (Appendix 4).

All analyses were descriptive. Continuous variables are presented as mean and standard deviation (SD), and categorical variables as counts and proportions within each subgroup. Cell counts between one and five were suppressed in accordance with Intego-II privacy requirements. No inferential statistical tests were performed, and no *p*-values were reported; all differences between subgroups are descriptive, and no causal inferences can be drawn.

Results

Lipid target attainment

Of all 4,626 patients, 35.6% (n=1,642) achieved an LDL-C below 55 mg/dL. However, among those patients, 35.6% (n=584) also had a documented ≥ 50% reduction from baseline, corresponding to 12.6% of the total study population. The remaining patients in this group did not have a pre-treatment LDL-C value, precluding calculation of the percentage reduction. These 12.6% fully met the 2019 ESC/EAS dual criterion. A further 26.7% (n=1,235) met the 2016 ESC/EAS target, while 37.8% (n=1,749) failed to achieve any guideline-recommended target (Table 1).

Patient characteristics

Baseline characteristics of the study population are presented in Table 2.

Socio-demographic characteristics

Most patients (78.7%) were aged 65 years or older. The age distribution was similar across the three groups. Of the 4,626 patients, 3,139 (67.9%) were men. A sex difference was observed in target attainment: 24.5% were women in Group 1, 32.5% in Group 2, and 39.1% in Group 3. Conversely, men accounted for 75.5% of Group 1, 67.5% of Group 2, and 60.9% of Group 3.

Clinical parameters

Smoking prevalence (5.4%), BMI (27.8 ± 5.0 kg/m²), SBP (130.6 ± 17.1 mmHg), and DBP (75.6 ± 9.6 mmHg) were comparable across all three groups.

ASCVD history

Differences were observed between the groups in the type of qualifying ASCVD event. Angina pectoris was similar across groups (12.0% in Group 1, 11.3% in Group 2, and 12.8% in Group 3). Unstable angina was slightly more prevalent in Group 1 (5.3%) and Group 2 (6.2%) than in Group 3 (4.5%). Patients in Group 1 had a higher prevalence of prior MI (33.9% in Group 1, 30.8% in Group 2, 25.9% in Group 3), CABG (10.4% in Group 1, 9.1% in Group 2, 7.5% in Group 3), PCI (19.5% in Group 1, 17.2% in Group 2, 15.0% in Group 3), and ischaemic heart disease without angina (39.4% in Group 1, 34.9% in Group 2, 31.7% in Group 3).

Conversely, patients in Group 3 had a higher prevalence of TIA (13.3% in Group 1, 18.6% in Group 2, and 20.1% in Group 3) and PAD (14.3% in Group 1, 15.0% in Group 2, and 17.7% in Group 3). The history of stroke was similar across groups (8.9% in Group 1, 10.0% in Group 2, and 8.6% in Group 3). Retinal infarction (0.5%), carotid artery surgery (0.2%), and ischaemic optic neuropathy (0.1%) each occurred in fewer than 1% of the total population.

Patients in Group 3 had a longer mean time since their first ASCVD diagnosis (3,334 days) compared with those in Group 2 (3,154 days) and Group 1 (2,993 days).

Laboratory parameters

As HbA1c is routinely measured only in patients with diabetes, the results should be interpreted in the context of the type 2 diabetes mellitus prevalence reported below (28.9% overall; 35.2% in Group 1, 27.9% in Group 2, 23.8% in Group 3). Mean HbA1c among patients with available measurement was approximately 6.5 ± 1.0% across all three groups. Patients in Group 3 had a higher mean baseline LDL-C (106.2 mg/dL) compared with Group 2 (103.2 mg/dL) and Group 1 (90.9 mg/dL). The mean percentage reduction in LDL-C was 44.2% in Group 1, 32.2% in Group 2, and 13.2% in Group 3. A ≥ 50% reduction from baseline was documented in 35.6% of Group 1 and 22.7% of Group 2.

Comorbidities

Hypertension was the most prevalent comorbid condition (53.5%) with similar rates across groups. Musculoskeletal disorders were present in 41.8%, predominantly osteoarthritis (40.6%), with similar rates across groups.

Type 2 diabetes mellitus was more prevalent in Group 1 (35.2%) than in Group 2 (27.9%) and in Group 3 (23.8%), with an overall prevalence of 28.9%. CKD (27.0%), atrial fibrillation (18.4%), mental health disorders (17.7%), obesity (16.1%), and heart failure (10.8%) were distributed similarly across groups.

Among mental health disorders, depressive disorder was most common (16.8%), followed by personality disorder (15.2%), anxiety disorder (5.0%), and schizophrenia (0.4%).

Patients with five or more chronic conditions were more frequent in Group 1 (29.4%) compared with Group 2 (28.3%) and Group 3 (26.4%), while those with three or fewer conditions were most common in Group 3 (37.9%).

Concomitant medication

Most patients (74.8%) were prescribed ≥ 5 chronic medications, with a higher rate in Group 1 (80.1%) than in Group 2 (73.4%) and in Group 3 (70.8%). Hypoglycaemic agents were prescribed in 34.1% of the total population and were more frequent in Group 1 (43.2%) than in Group 2 (32.6%) and in Group 3 (26.6%). RAAS-inhibiting antihypertensives were used by 35.1% of patients (38.6% in Group 1, 34.0% in Group 2, 32.8% in Group 3). Non-RAAS antihypertensives were used in 44.8% of patients and were similar across groups (45.2% in Group 1, 44.8% in Group 2, 44.4% in Group 3).

Lipid-lowering therapy

Statin use was high across the entire study population (87.6%), with rates of 87.6% in Group 1, 91.3% in Group 2, and 85.1% in Group 3 (Table 3). High-intensity statins (rosuvastatin or atorvastatin) were used more frequently in Group 2 (73.6%) and Group 1 (73.4%) than in Group 3 (60.3%), while low-intensity statins (simvastatin or pravastatin) were more common in Group 3 (34.3%) than in Group 2 (27.9%) and in Group 1 (24.0%).

Non-statin LLT was used by 13.6% of the total population and was more frequent in Group 1 (15.1%) and in Group 2 (14.0%) than in Group 3 (12.0%). Ezetimibe was used by 11.9% of all patients, with rates of 13.3% in Group 1, 12.1% in Group 2, and 10.4% in Group 3. The use of novel LLTs was limited across the entire study population, regardless of LDL-C target attainment: PCSK9 inhibitors in 0.2% and inclisiran in 0.4% of patients. Bempedoic acid was used by 99 patients (2.1%) and was slightly more frequent in Group 3 (2.6%) than in Group 1 (1.9%) and in Group 2 (1.9%). Anion exchangers were used by 19 patients (0.4%), and omega-3 fatty acids as monotherapy were used in fewer than five patients in total. The use of these agents was similarly low across all three groups.

Combination LLT was used by 34.1% of all patients (47.4% in Group 1, 33.8% in Group 2, and 21.9% in Group 3), comprising double therapy in 30.6% (n=1,414; 43.5% in Group 1, 30.2% in Group 2, and 18.7% in Group 3) and triple therapy in 3.5% (n=164). The most frequently used double combination was statin + ezetimibe, prescribed in 1,245 patients (26.9%) of the total population, and used by 40.3% and 26.6% of patients in Group 1 and Group 2, respectively, compared with 14.6% in Group 3. Rosuvastatin + ezetimibe was the most frequently used combination in Group 1 (27.0%), followed by atorvastatin + ezetimibe (14.1%); both were less common in Group 3 (7.7% and 6.2%, respectively).

Combinations involving simvastatin or pravastatin with ezetimibe were used in similar proportions across groups and were used in 2.5% of patients and fewer than five patients, respectively.

Other double combination therapies were used in smaller proportions of the study population. Statin + fibrate combination was used in 117 patients (2.5%), with a slightly higher rate in Group 1 (3.3%) than in Group 2 (2.4%) and in Group 3 (1.9%); fibrates were not prescribed as monotherapy in this study population. Statin + bempedoic acid was used in 74 patients (1.6%), slightly more frequent in Group 3 (1.8%) than in Group 2 (1.4%) and in Group 1 (1.5%). Ezetimibe + bempedoic acid without a statin was used in 68 patients (1.5%) and was more frequent in Group 3 (1.9%) than in Group 2 (1.5%) and in Group 1 (1.0%). Ezetimibe + fibrate combination was used in 36 patients (0.8%), with a higher rate in Group 1 (1.2%) than in Group 2 (0.5%) and in Group 3 (0.6%). Statin + anion exchangers was used in 16 patients (0.3%), statin + inclisiran in 13 patients (0.3%), and ezetimibe + inclisiran and ezetimibe + PCSK9 inhibitor in eight (0.2%) and six patients (0.1%), respectively. Statin + PCSK9 inhibitor, statin + omega-3 fatty acids, ezetimibe + anion exchangers, and ezetimibe + omega-3 fatty acids were each used in fewer than five patients in total.

Triple combination therapy was used in 3.5% of the total population (n=164), with comparable rates across groups (3.9% in Group 1, 3.6% in Group 2, and 3.2% in Group 3). The most frequently used triple combination was statin + ezetimibe + bempedoic acid, used in 118 patients (2.6%), with similar prevalence across groups (2.4% in Group 1, 2.6% in Group 2, and 2.7% in Group 3). Statin + ezetimibe + fibrates was used in 48 patients (1.0%), with rates of 1.7% in Group 1, 0.9% in Group 2, and 0.5% in Group 3. Of the remaining triple combinations, statin + ezetimibe + inclisiran was used in six patients (0.1%) across the total population. Statin + ezetimibe + PCSK9 inhibitor and statin + ezetimibe + anion exchangers were each used in fewer than five patients per subgroup. Statin + ezetimibe + omega-3 fatty acids was not prescribed in any patient.

Discussion

Main findings

The present study evaluated the real-world implementation of the 2019 ESC/EAS lipid guidelines in patients with established ASCVD treated in Flemish general practice, using data from the Intego-II primary care registry. The central finding is that the majority of secondary prevention patients in Belgian primary care do not achieve the recommended LDL-C target levels. Of all 4,626 patients, 35.6% achieved an LDL-C < 55 mg/dL, but when the complete dual criterion (LDL-C < 55 mg/dL AND a documented reduction of ≥ 50% from baseline) was applied, 12.6% of the total study population could be confirmed as fully meeting this 2019 ESC/EAS target. A further 26.7% met the less stringent 2016 target, while 37.8% did not achieve any of the targets recommended in the guidelines. These findings reveal a gap between guideline recommendations and daily clinical practice in Belgium.

It should be noted that the subgroup comparisons presented use the three predefined groups based on available LDL-C data; Group 1, therefore, includes all 1,642 patients with LDL-C < 55 mg/dL, not just the 584 who met the full dual criterion, as many patients lacked a documented pre-treatment LDL-C value, making it impossible to calculate the percentage reduction.

In the descriptive analysis, male sex, a coronary ASCVD history, type 2 diabetes mellitus, polypharmacy, multimorbidity, use of high-intensity statins, and combination therapy with statin + ezetimibe were observed more frequently in Group 1. Conversely, patients with mental health disorders or long-standing ASCVD were more prevalent in the non-target-achieving group. LLT was dominated by statin therapy, with high-intensity statins and statin + ezetimibe combination therapy used notably more often in patients achieving LDL-C targets. The use of novel agents such as PCSK9 inhibitors and inclisiran remained below 1%, while bempedoic acid was used in 3.6% of patients across all regimens.

Although these descriptive patterns do not allow for causal conclusions, they do point to useful starting points for improving LDL-C management in primary care.

Comparison with European real-world data

The overall pattern of suboptimal target attainment observed in this study is broadly consistent with findings from major European observational studies, confirming that the gap between guideline recommendations and clinical implementation is not unique to Belgium. The DA VINCI study, a cross-sectional observational study conducted across multiple European countries in 2017–2018, reported that approximately 39.0% of very-high-risk patients achieved the 2016 ESC/EAS target of LDL-C < 70 mg/dL (5). The SANTORINI study, which specifically assessed attainment of the 2019 ESC/EAS targets, found that 33% of secondary prevention patients achieved an LDL-C < 55 mg/dL after one-year follow-up, attributing this largely to the underuse of combination LLTs (8).

In our study, 35.6% of patients achieved LDL-C < 55 mg/dL, which is marginally higher than figures reported in SANTORINI. However, once the full dual criterion is applied, the confirmed attainment decreases to 12.6%, as a substantial proportion of patients lacked a documented pre-treatment LDL-C for calculating the percentage reduction. This discrepancy underscores an important point for clinical practice: systematic documentation of a baseline LDL-C value prior to the initiation of LLT is essential for accurately assessing guideline-concordant target attainment and for clinical audit purposes.

Sex differences in LDL-C target attainment

A pronounced sex difference in target attainment was observed. Women were substantially underrepresented in the group achieving the strictest targets (24.5% in Group 1 versus 39.1% in Group 3). While men constituted 67.9% of the total study population, they accounted for 75.5% of Group 1 and 60.9% of Group 3, indicating disproportionately better target attainment among men.

This pattern is consistent with findings from an Intego-based study by Laleman et al., which similarly demonstrated that men used statins more frequently than women in secondary prevention in Flanders (14), and with data from a population-wide cohort study in Scotland by Thalmann et al., which showed that initiation and adherence to statin therapy were lower in women than in men (15). This sex disparity is also reflected in less frequent LDL-C target achievement in women compared with men (16).

Several factors may contribute to this observed disparity. Women have been shown to be more likely to report statin-associated muscle symptoms and to stop or switch their statin therapy because of side effects compared with men (17,18). Furthermore, data suggest that women are more frequently left uninformed by their clinician about their cardiovascular risk compared with men, which may contribute to lower adherence and less intensive LLT management overall (17), although statin therapy has been shown to be similarly effective for the prevention of major vascular events in both sexes (19). In addition, healthcare providers themselves have been shown to underestimate cardiovascular risk in women, which may further contribute to less intensive risk factor management and lower rates of guideline-concordant LLT prescribing in this group (20). These findings highlight the need for dedicated attention to lipid management and patient education in women with established ASCVD in primary care.

Type of index ASCVD event and target attainment

In this descriptive analysis, the type of qualifying ASCVD event showed notable differences in LDL-C target attainment. Patients with a predominantly coronary history, including MI, CABG, PCI, or ischaemic heart disease without angina, were more frequently represented in the target-achieving group, with the most pronounced gradient observed for MI (33.9% in Group 1 versus 25.9% in Group 3). Similar gradients were observed for PCI and CABG. Stable angina was distributed similarly across groups, whereas unstable angina was slightly more prevalent in Group 1 and Group 2 than in Group 3. In contrast, patients with non-coronary vascular disease, particularly those with a history of TIA or PAD, were more frequently found in the group not achieving any target, while stroke was distributed similarly across groups.

These patterns are consistent with previous studies reporting lower statin adherence in cerebral disease (21–23) and peripheral disease (24,25) compared with patients with coronary disease. For example, in the DA VINCI study, high-intensity statins were more often used in patients with a history of coronary disease (51.0%) than in patients with a history of cerebral (40.0%) and PAD (39.0%) (5). The similar distribution of stroke across groups in our study, in contrast to TIA, may be explained by findings from Cummings et al., who reported that patients with TIA are prescribed statins less frequently than patients with stroke (22).

Given that the 2019 ESC/EAS guidelines apply equally to all manifestations of ASCVD, these findings suggest that patients with TIA and PAD constitute a priority subgroup for improved lipid management

in Belgian general practice. This raises the question of how lipid management could be improved in these subgroups with lower target attainment. More intensive lipid-focused follow-up through cardiological outpatient care and cardiac rehabilitation programmes has been shown to improve medication adherence in patients following MI (26). For patients with cerebrovascular disease or PAD, similar structured follow-up could be organised by the neurologist or vascular surgeon, respectively, but also represents an opportunity for primary care. The development of structured ASCVD care pathways in general practice, analogous to existing diabetes care pathways, may help improve outcomes in these patients. Such pathways should integrate not only LDL-C monitoring and intensification triggers, but also blood pressure control, antiplatelet/antithrombotic therapy where indicated, lifestyle counselling, and structured follow-up of comorbidities, rather than focusing on lipids alone.

Clinical inertia and time since diagnosis

Patients who did not achieve any lipid target had a longer mean time since their first ASCVD diagnosis (3,334 days) compared with those in Group 1 (2,993 days). This finding is consistent with the study by Colantonio et al., which reported better adherence to high-intensity statins among patients with a more recent MI (26). One possible explanation is that patients who were diagnosed some time ago have had more opportunity to stop taking statins due to side effects, personal beliefs, or a reduced perception of urgency regarding secondary prevention.

This observation is also consistent with the concept of clinical inertia, defined as the failure to initiate or intensify therapy in a patient not at evidence-based treatment goals (27). In the context of lipid management, clinical inertia has been recognised as a major contributing factor to suboptimal LDL-C control in secondary prevention (6). More recently diagnosed patients may have been initiated on therapy in accordance with the 2019 ESC/EAS guidelines, whereas patients with long-standing ASCVD may have remained on suboptimal regimens established under earlier, less stringent guideline versions. This finding underscores the importance of periodic reassessment of LDL-C treatment goals in all patients with established ASCVD, regardless of how long ago their index event occurred.

The role of type 2 diabetes mellitus, comorbidities, and comedication

A notable finding was the higher prevalence of type 2 diabetes mellitus among patients achieving the 2019 target (35.2% in Group 1 versus 23.8% in Group 3), mirrored by a higher rate of hypoglycaemic medication use (43.2% versus 26.6%). This is consistent with previous studies showing higher rates of statin use in secondary prevention patients with diabetes (14,22). Furthermore, patients with diabetes are more likely to have their lipid levels checked in the year after PCI and to achieve the 2016 ESC LDL-C target (16). While diabetes is itself a cardiovascular risk factor and might be expected to complicate LDL-C management, this result may reflect the influence of structured diabetes care pathways in Belgian general practice. Regular monitoring of HbA1c, more frequent general practitioner (GP) contacts, and involvement of multidisciplinary care teams may create additional opportunities to

assess and optimise the lipid profile. This interpretation is consistent with evidence suggesting that structured disease management programmes are associated with more intensive cardiovascular risk factor control (6).

This pattern of better target attainment was not observed for other chronic conditions. Hypertension and atrial fibrillation were similarly distributed across groups, suggesting that these comorbidities do not differentiate patients in terms of LDL-C target attainment in this population. By contrast, patients with CKD and heart failure were slightly more prevalent in Group 1 than in Group 3, but these differences were small and are not consistent with findings in the literature: Ellins et al. reported that patients with CKD were less likely to have their lipid levels checked after PCI and to achieve the target LDL-C level (16); Setoguchi et al. found lower use of statins after MI in patients with heart failure (28). The absence of a clear favourable association for CKD and heart failure, in contrast to diabetes, may reflect the lack of similarly structured care pathways for these conditions in Belgian general practice.

Polypharmacy (≥ 5 chronic medications) was more prevalent in Group 1 (80.1%) than in Group 3 (70.8%). Similarly, RAAS-inhibiting antihypertensives and hypoglycaemic medication were more frequently used in Group 1. This is consistent with a Japanese cohort study reporting a higher proportion of comedication prescriptions after ischaemic stroke or TIA in patients with good statin adherence (21). However, the literature is not uniform: Colantonio et al. reported lower statin adherence in patients with polypharmacy after hospitalisation for MI (26), and Rosenson et al. found that patients using more than ten different medications had lower initiation of high-intensity statins, although the concurrent use of a beta-blocker or an antiplatelet agent was associated with a higher initiation of high-intensity statin use (29). As seen in other studies, this could imply that patients with good adherence to other medications (e.g. antiplatelet or antihypertensive agents) have an overall better adherence to cardiovascular preventive medication and are therefore more likely to use statins (14,21,30). In contrast, polypharmacy could lead to difficulties in medication prescription because of possible medication interactions and a higher prevalence of adverse effects. These findings may reflect the dual nature of polypharmacy: rather than the number of medications per se, it may be the nature of comedication that reflects overall adherence to cardiovascular preventive therapy, although this interpretation requires confirmation in studies with individual-level adherence data.

Patients with multimorbidity (≥ 5 chronic conditions) were also more frequently represented in Group 1, which contrasts with studies reporting lower statin initiation and higher discontinuation in patients with multiple comorbidities (15,26). These conflicting findings may reflect the heterogeneity of multimorbidity: patients with well-managed chronic conditions may benefit from more frequent healthcare contacts with frequent lipid monitoring and treatment adjustments, whereas those with complex comorbidities may face a higher risk of treatment complications and side effects. Also, patients suffering from poorly controlled comorbidities could have competing clinical priorities that reduce attention to lipid management.

Taken together, these descriptive findings raise the question of whether the introduction of systematic LDL-C monitoring programmes, analogous to the HbA1c monitoring embedded in diabetes care pathways, could help close the implementation gap for all secondary prevention patients, not only those with diabetes. This hypothesis would, however, require prospective evaluation.

Mental health disorders and lipid management

Patients with mental health disorders were slightly more prevalent in Group 3 (18.0%) than in Group 1 (17.2%). Although this difference is small and should be interpreted with caution, it is directionally consistent with a growing body of literature suggesting that mental health disorders are associated with less optimal lipid management. In a national retrospective cohort study in Scotland, patients hospitalised for an ASCVD event with a history of specialist mental healthcare admission had lower odds of statin initiation and a higher hazard of discontinuation compared with patients without such a history (15). Similarly, another retrospective cohort study with data from patients who underwent PCI in Wales showed a lower likelihood of having their lipids monitored and of reaching ESC lipid targets in patients with a history of depression (16). Finally, a large meta-analysis by Mitchell et al. showed a 39.0% lower prescribing rate of statins in patients with severe mental health disorders after pooling 36 analyses (31). Within this category, the difference was most apparent for anxiety disorders (4.3% in Group 1 versus 5.9% in Group 3), whereas depressive and personality disorders were similarly distributed across groups. These findings suggest that patients with mental health disorders may warrant particular attention in the context of cardiovascular secondary prevention in primary care.

Lipid-lowering therapy patterns and the underuse of combination and novel agents

Statin use was high across the study population (87.6%). This rate is in line with European real-world data, where statin-based monotherapy accounted for 94% of all LLT in secondary prevention patients in the DA VINCI study (5). The prescription of high-intensity statins (rosuvastatin or atorvastatin), which reduce LDL-C by approximately 50% (1), was more frequent in Group 1 (73.4%) than in Group 3 (60.3%), while low-intensity statins were more common in non-achieving patients (34.3% versus 24.0%). This pattern is consistent with guideline recommendations that high-intensity statin therapy should be the preferred first-line approach in secondary prevention (1), and with trial evidence demonstrating that more intensive LDL-C lowering is associated with greater cardiovascular risk reduction (2).

The most clinically notable finding in the analysis of LLT use concerns statin + ezetimibe combination therapy, used in 26.9% of the total study population. This combination was used in 40.3% of patients in Group 1, compared with 14.6% in Group 3. Rosuvastatin + ezetimibe was the most frequently used combination in Group 1 (27.0%), followed by atorvastatin + ezetimibe (14.1%), both of which were less common in Group 3 (7.7% and 6.2%, respectively). The benefit of adding ezetimibe to statin therapy was established in the IMPROVE-IT trial, which demonstrated an additional LDL-C reduction

of approximately 23–24% and a significant reduction in cardiovascular events, with a favourable safety profile showing no significant increase in muscle-related toxicity, hepatotoxicity, or cancer compared with statin monotherapy (4). This was also seen in the SANTORINI study, with 29.5% of patients in secondary prevention using a combination of statin and ezetimibe, most represented by combinations with high-intensity statins and ezetimibe (20.5%) (32). As recommended in the 2019 ESC/EAS lipid guidelines, if the treatment goals in secondary prevention patients are not achieved with the maximally tolerated dose of a statin, a combination with ezetimibe is recommended (1). More recent studies suggest moving away from intensive statin treatment and treating patients at very-high or extremely high-risk with combination therapy from the beginning (33–36). Given that almost two-thirds of patients are not reaching the 55 mg/dL lipid target, there is a considerable opportunity for increased usage of this combination therapy. The fact that patients are not reaching their recommended treatment goal, but therapy intensification is lacking, aligns with the broader pattern of therapeutic inertia, defined as the failure of healthcare providers to initiate or intensify therapy when indicated (27).

In our study, the observation that 12.6% of patients achieved the guideline-recommended target based on the dual criteria of reaching an LDL-C of < 55 mg/dL and ≥ 50% reduction in LDL-C further illustrates this disconnect between the recognised treatment gap and actual therapy intensification. This value is substantially lower than the target attainment reported in European-wide studies. The SANTORINI study reported target attainment of 21.2% at baseline, increasing to 33% at one-year follow-up among patients with ASCVD (32). LLT was escalated in 29.3% and unchanged in two-thirds of all patients over one-year follow-up, despite the overall target attainment of 21.2% (high- and very-high-risk patients). Specifically, among patients with ASCVD history, the increase in the use of high-intensity statin monotherapy was 4.7%, and the increase in statin + ezetimibe combination use was 10.8%. Similarly, in the DA VINCI study, 18.0% of very-high-risk patients achieved the 2019 ESC/EAS LDL-C goal, and 39.0% achieved the older 2016 goals (5). The lower achievement of 2019 ESC/EAS LDL-C goals may be explained by the study period (June 2017 to November 2018), which preceded publication of the new lipid targets in 2019.

Although these comparisons suggest that LDL-C goal attainment in Belgian primary care lags behind the broader European average, this was not reflected in the proportion of patients achieving 2019 lipid targets across countries as represented in the SANTORINI study, where Belgium, similar to Austria and Denmark, showed a high proportion of patients achieving lipid targets (32). If the additional criterion of an LDL-C reduction of ≥ 50% from baseline is not applied in our study, the proportion of patients achieving < 55 mg/dL LDL in our study (35.6%) is comparable to the overall percentage of patients who met the target in all countries (33%) and in Belgium (39.3%), as reported in the SANTORINI study (32). Similarly, the proportion of combination therapy used in our study (34.1%) lies close to the number after one-year follow-up of Belgian patients included in the SANTORINI study (38.5%) (32).

The use of novel LLTs was limited across the entire study population, regardless of LDL-C target attainment. PCSK9 inhibitors were rarely used, both as monotherapy (0.2%) and in combination with statins (< 0.01%) or ezetimibe (0.1%). These findings are consistent with European real-world data: in the DA VINCI study, PCSK9 inhibitor use in combination with any other LLT was reported in 1% of secondary prevention patients (5). Similarly, in the SANTORINI study, PCSK9 inhibitor monotherapy was reported in 1.6% of secondary prevention patients at baseline and 2.2% at one-year follow-up, with combined use 4.8% at baseline and 6.7% at one-year follow-up (32). This is in line with the recommendations for pharmacological LDL-C lowering of the ESC 2019 lipid guidelines, advising the use of a combination with a PCSK9 inhibitor if the goal is not achieved with the maximally tolerated dose of statin and ezetimibe, and implies that combination therapy with ezetimibe should be considered first before starting a PCSK9 inhibitor (1). Therefore, the lower prevalence of this medication could be normal, but therapeutic inertia could also be possible when targets are not attained without maximally tolerated use of combination therapy with statin and ezetimibe. Further studies investigating the underuse of PCSK9 inhibitors are therefore needed to investigate this hypothesis.

Inclisiran was prescribed in 17 patients (0.4%) overall, with statin + inclisiran used in 13 patients (0.3%) and ezetimibe + inclisiran in 8 patients (0.2%). Notably, inclisiran was not yet available at the time of the DA VINCI study, precluding any comparison, while in the SANTORINI study, its use was not separately reported, likely reflecting its very recent market introduction during the study period.

PCSK9 inhibitors reduce LDL-C levels by approximately 55–60% and significantly lower the risk of major adverse cardiovascular events by 15%, as demonstrated in the FOURIER and ODYSSEY OUTCOMES trials, respectively (37,38), though no reduction in cardiovascular mortality was demonstrated. Despite this strong evidence, the uptake of PCSK9 inhibitors remains very low. This low use is likely due to several reinforcing barriers. As noted in the SANTORINI study, the limited use of PCSK9 inhibitors across Europe may be attributed to the stepwise approach recommended in the 2019 ESC/EAS guidelines, the relatively higher cost of injectable therapies, and country-specific restrictions in access and reimbursement (32). In Belgium, these barriers are particularly pronounced: reimbursement of PCSK9 inhibitors for secondary prevention is limited to patients with documented ASCVD who maintain an LDL-C level ≥ 100 mg/dL despite at least six weeks of treatment with a maximally tolerated statin dose in combination with ezetimibe (39,40). Furthermore, prescribing is restricted to specialists in cardiology, internal medicine, neurology, or endocrinology-diabetology (39,40). This effectively excludes GPs from initiating these therapies, creating a significant access barrier for patients managed exclusively in primary care who would need referral to a specialist. Without reimbursement, the cost of PCSK9 inhibitors represents a substantial financial barrier for most patients in this setting.

Similar reimbursement conditions apply to inclisiran, a small interfering RNA that inhibits hepatic PCSK9 synthesis and has been available for reimbursement in Belgium since February 2023 (39,40).

Although inclisiran induces substantial LDL-C reductions of approximately 50% (41), unlike PCSK9 inhibitors, its benefit in terms of cardiovascular morbidity and mortality has not yet been established, although dedicated cardiovascular outcome trials are currently ongoing. Combined with its recent market introduction, high cost, and specialist-only prescribing requirements, this further explains its very low uptake. These structural constraints help explain why the use of novel LLTs in Belgian primary care falls even below the already low rates observed across Europe.

Bempedoic acid was used by 3.6% of the total population across all regimens and was slightly more frequent in Group 3 (4.5%) than in Group 1 (2.9%) and in Group 2 (3.4%), suggesting its role as a rescue or add-on therapy in patients with inadequate LDL-C control or statin intolerance (1). Its use in triple combination with statin and ezetimibe, the most frequently observed triple therapy in our study at 2.6%, may reflect stepwise intensification in patients failing dual therapy. This is in line with the SANTORINI study, in which bempedoic acid use remained marginal, reflecting its recent introduction into the European healthcare system from 2020 onwards (32). Notably, unlike PCSK9 inhibitors and inclisiran, bempedoic acid (Nilemdo®) and its fixed-dose combination with ezetimibe (Nustendi®) can be prescribed by any physician in Belgium without restriction to specialist care; these prescribing conditions were already in place during the study period (39,40). Reimbursement requires that patients at high cardiovascular risk maintain an LDL-C ≥ 70 mg/dL, or that patients at very-high-risk maintain an LDL-C ≥ 55 mg/dL, despite treatment with a maximally tolerated statin dose in combination with ezetimibe. Reimbursement is also available for patients with documented statin intolerance or contraindication (39,40). Despite this more accessible prescribing framework, the use of bempedoic acid in our study remained very low at 2.1%, suggesting that barriers beyond prescribing authority, such as recent market availability or uncertainty regarding its cardiovascular benefit, may play a role. In this regard, the CLEAR Outcomes study demonstrated that bempedoic acid reduces LDL-C by approximately 21% and significantly lowers major adverse cardiovascular events in statin-intolerant patients, providing a stronger evidence base for its use in this population (42). Notably, statin + ezetimibe + bempedoic acid was the most frequently observed triple therapy in our study (2.6%), with similar rates across groups, suggesting that this combination is increasingly used as a next step in patients who remain above target on dual therapy with statin and ezetimibe.

Statin + fibrate combination therapy was used in 117 patients (2.5%), with a marginally higher rate in Group 1 (3.3%) than in Group 3 (1.9%). Fibrates were not prescribed as monotherapy in this study population, which is consistent with current guideline recommendations that reserve fibrate use primarily for patients with severe hypertriglyceridaemia rather than for LDL-C lowering in secondary prevention, given the absence of proven benefit on cardiovascular and total mortality (1). Their limited and similar use across groups suggests they play no meaningful role in LDL-C target attainment in this study population. Anion exchangers were used by 19 patients (0.4%), with no apparent difference across groups, consistent with their limited evidence for cardiovascular risk reduction and poor tolerability

profile, as patients in secondary care have more direct access to specialist-initiated treatments and more intensive LLT (1). Omega-3 fatty acids were used in fewer than five patients, exclusively in combination therapy in Group 3. Although high-dose omega-3 fatty acids (> 2 g/day) can reduce triglyceride levels, effects on other lipoproteins are lacking and evidence of overall effect on cardiovascular events and total mortality remains inconclusive (1).

In summary, LLT in this Belgian primary care population is dominated by statin monotherapy, with combination therapy, particularly statin + ezetimibe, used markedly more often in patients achieving LDL-C targets. The use of novel agents such as PCSK9 inhibitors, inclisiran, and bempedoic acid remains marginal, reflecting a combination of restrictive reimbursement conditions, specialist-only prescribing requirements, recent market availability, and therapeutic inertia. These findings highlight that, despite the availability of effective combination therapies, structural and behavioural barriers continue to limit LDL-C target attainment in routine Belgian primary care.

Are stricter LDL-C targets clinically meaningful?

Regardless of whether targets are reached, it is worth reflecting critically on the clinical relevance of the absolute thresholds themselves. The strict 2019 ESC/EAS LDL-C targets have been questioned, as they are largely extrapolated from meta-analyses of LDL-C lowering trials rather than directly tested in randomised treat-to-target studies (6). The LODESTAR trial demonstrated that titrating statin intensity to an LDL-C target of 50–70 mg/dL was non-inferior to fixed high-intensity statin therapy for major cardiovascular events at three years, supporting a tailored approach that accounts for individual variability in drug response and tolerability (7). Although the LODESTAR target is less stringent than the 2019 ESC/EAS threshold of < 55 mg/dL, these findings suggest that individualised target assessment, taking into account drug response, tolerability, and patient preferences, may be more appropriate than rigid adherence to a single threshold value, particularly in the primary care setting.

Practical implications

Three practical implications emerge for Belgian general practice. First, systematic documentation of a pre-treatment LDL-C value should become standard before initiating LLT, both to enable guideline-concordant assessment and to support audit and feedback. Second, combination therapy with statin plus ezetimibe is substantially underused despite being guideline-recommended, widely available, reimbursed, and safe; earlier intensification rather than stepwise escalation may be warranted in very-high-risk patients. Third, structured follow-up pathways analogous to the existing diabetes care trajectory, with predefined LDL-C monitoring intervals and explicit intensification triggers, could specifically target the subgroups identified here as at risk of undertreatment: women, patients with TIA or PAD, patients with mental health comorbidity, and patients with long-standing ASCVD. Prospective interventional studies are needed to confirm whether closing this implementation gap reduces recurrent

cardiovascular events and whether expanding access to novel LLTs in primary care is both cost-effective and feasible within the Belgian healthcare system.

Strengths

This study has several notable strengths. First, it is based on a large, real-world primary care registry (Intego-II) comprising routinely collected EHR data from 135 general practice centres across Flanders, providing an ecologically valid and representative sample of secondary prevention patients managed in Belgian primary care. Second, the use of validated, coded data enables systematic retrieval of diagnoses, prescriptions, laboratory results, and clinical parameters across a large patient population.

Third, the simultaneous application of both the 2019 and 2016 ESC/EAS target definitions allows direct comparison with major European observational studies such as DA VINCI and SANTORINI. Fourth, the comprehensive ascertainment of socio-demographic variables, clinical and laboratory parameters, comorbidities, comedication, and type of LLT allows a descriptive characterisation of patient profiles across lipid target groups that is of direct clinical relevance for general practice.

Fifth, this study extends beyond the commonly reported categories of statins, ezetimibe, and PCSK9 inhibitors by also describing the use of bempedoic acid, inclisiran, fibrates, anion exchangers, and omega-3 fatty acids. Finally, by using data from 2024, this study is more recent than both DA VINCI (2017–2018) and SANTORINI (2020–2022), thereby capturing agents such as inclisiran and bempedoic acid that were not yet available or only recently introduced during those earlier study periods.

Limitations

Several important limitations must be acknowledged. First, the retrospective, cross-sectional observational design precludes causal inference, and all descriptive differences between groups may be subject to confounding by unmeasured factors. No statistical comparisons were performed between groups; all reported differences are descriptive and should be interpreted accordingly.

Second, the absence of a documented pre-treatment LDL-C value in a large proportion of patients precluded calculation of the percentage reduction from baseline, meaning that the confirmed proportion fully meeting the 2019 dual criterion (12.6%) is likely an underestimate, since patients with an LDL-C level < 55 mg/dL but without a documented baseline value may nevertheless have achieved a reduction of ≥ 50%.

Third, and related to this, the descriptive subgroup comparisons presented in this study are based on the three predefined groups using available LDL-C data rather than the strictly confirmed dual-criterion population. Group 1, therefore, includes all 1,642 patients with LDL-C < 55 mg/dL, rather than only the 584 patients who demonstrably met both components of the 2019 target. The 1,058 patients without a documented baseline LDL-C are unlikely to be missing at random. They may, for example, have been diagnosed longer ago, have had their initial lipid profile recorded in another care setting, or have had

earlier laboratory data that predate electronic registration. Observed associations such as the overrepresentation of male sex, coronary ASCVD, type 2 diabetes mellitus, polypharmacy and statin + ezetimibe use in Group 1 should therefore be interpreted with appropriate caution.

Fourth, adherence cannot be assessed from prescription data alone. Patients may have been prescribed LLT without taking it consistently, and dose adjustments over time may not have been fully recorded. Fifth, manual prescriptions and prescriptions issued by specialists were not included, as only patients with an electronic GP prescription of LLT in the preceding year were selected. This may underestimate the true number of secondary prevention patients receiving LLT, and in particular the use of specialist-only agents such as PCSK9 inhibitors and inclisiran. Sixth, a form of selection bias may be present: by including only patients with an active LLT prescription and a recent LDL-C measurement, the study excludes untreated or unmonitored secondary prevention patients, which may overestimate the overall proportion achieving lipid targets.

Seventh, while the Intego-II network is broadly representative of the Flemish population for age and sex, it does not include practices from Wallonia or Brussels, limiting generalisability across Belgium. It may also not fully reflect practices in urban or lower socio-economic environments. Additionally, GPs participating in the Intego-II network may be more guideline-adherent in clinical care than GPs in non-participating practices, potentially overestimating the quality of lipid management in routine Belgian primary care. Furthermore, EHR-based data are prone to coding errors and incomplete recording, although this risk is mitigated by the quality-based selection procedure for participation in Intego-II (9).

Eighth, statin dosage was not included in the analysis, meaning that some patients classified as receiving high-intensity statins may in fact have been on moderate-intensity regimens, potentially overestimating the true rate of high-intensity statin use. Finally, data on the reasons for non-attainment of targets, including clinician and patient preferences, reimbursement restrictions on LLT, risk perceptions, statin intolerance, lifestyle adherence, prior specialist consultations, and socio-economic status, were not available, limiting the ability to fully characterise the mechanisms underlying the observed descriptive patterns.

Conclusion

In this real-world, retrospective cross-sectional study of patients in secondary prevention within Flemish general practice, only a minority achieved the 2019 ESC/EAS LDL-C target: 35.6% reached LDL-C < 55 mg/dL but confirmed attainment of the dual criterion fell to 12.6%, partly owing to frequent absence of documented pre-treatment LDL-C values. A further 26.7% met the less stringent 2016 target, while 37.8% did not meet either. The implementation gap is primarily driven by the underuse of high-intensity statins and statin + ezetimibe combination therapy, as well as the limited uptake of PCSK9 inhibitors, inclisiran, and bempedoic acid. Patients attaining the strictest targets were disproportionately male, had a predominantly coronary ASCVD history, more frequently had type 2 diabetes mellitus, and were more often treated with high-intensity statins and statin + ezetimibe combination therapy. Women, patients with cerebrovascular disease (TIA) or PAD, patients with mental health disorders, and patients with long-standing ASCVD were overrepresented among those not achieving any target. Closing this implementation gap will require structured ASCVD care pathways and earlier intensification of lipid-lowering therapy, tailored to the needs of priority subgroups such as women, patients with cerebrovascular disease or PAD, and those with mental health comorbidities.

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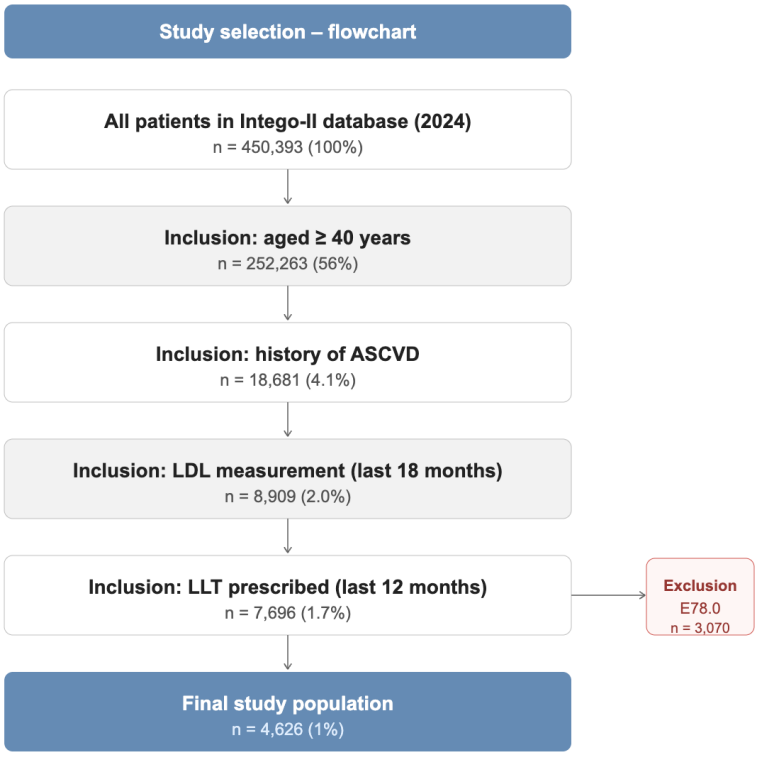
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Tables and Figures

Figure 1. Study population



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; FH, familial hypercholesterolaemia; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision

Table 1. Lipid target attainment

Group	Total	≥ 50% reduction from baseline
Total patients, n (%)	4,626 (100)	864 (18.7)
First lipid target, n (%)	1,642 (35.6)	584 (12.6)
Second lipid target, n (%)	1,235 (26.7)	280 (6.1)
Not reaching lipid target, n (%)	1,749 (37.8)	0 (0.0)

First lipid target: LDL-C < 55 mg/dL AND a reduction of ≥ 50% from baseline (2019 ESC/EAS target). Second lipid target: LDL-C ≥ 55 mg/dL and < 70 mg/dL OR a reduction of ≥ 50% from baseline if LDL-C ≥ 70 mg/dL (2016 ESC/EAS target). Not reaching lipid target: LDL-C ≥ 70 mg/dL AND a reduction of < 50% from baseline. The ≥ 50% reduction column reflects patients with a documented baseline LDL-C value, permitting calculation of percentage reduction; values are expressed as a proportion of the total study population (n=4,626), not of each subgroup.

Table 2. Patient characteristics

Variable	Total (n=4,626)	First lipid target (n=1,642)	Second lipid target (n=1,235)	Not reaching target (n=1,749)
Socio-demographic variables				
Age (years) < 65, n (%)	983 (21.2)	339 (20.6)	247 (20.0)	397 (22.7)
Age (years) 65–74, n (%)	1,439 (31.1)	518 (31.5)	388 (31.4)	533 (30.5)
Age (years) ≥ 75, n (%)	2,204 (47.6)	785 (47.8)	600 (48.6)	819 (46.8)
Women, n (%)	1,487 (32.1)	403 (24.5)	401 (32.5)	683 (39.1)
Men, n (%)	3,139 (67.9)	1,239 (75.5)	834 (67.5)	1,066 (60.9)
Clinical parameters				
Smoker, n (%)	250 (5.4)	91 (5.5)	54 (4.4)	105 (6.0)
BMI (kg/m²), mean (SD)	27.8 (5.0); Range (13.6–48.4); Total 2,387 (51.6)	27.9 (5.0); Range (15.4–47.3); Total 878 (53.5)	27.8 (4.8); Range (15.8–48.4); Total 643 (52.1)	27.7 (5.2); Range (13.6–47.1); Total 866 (49.5)
SBP (mmHg), mean (SD)	130.6 (17.1); Range (65–230); Total 4,144 (89.6)	129.2 (16.3); Range (65–200); Total 1,480 (90.1)	130.9 (17.0); Range (80–188); Total 1,112 (90.0)	131.7 (17.9); Range (80–230); Total 1,552 (88.7)
DBP (mmHg), mean (SD)	75.6 (9.6); Range (40–125); Total 4,139 (89.5)	74.6 (9.2); Range (40–104); Total 1,479 (90.1)	75.8 (9.7); Range (45–110); Total 1,111 (90.0)	76.4 (9.9); Range (40–125); Total 1,549 (88.6)
ASCVD history				
Angina pectoris, n (%)	560 (12.1)	197 (12.0)	140 (11.3)	223 (12.8)
Unstable angina, n (%)	242 (5.2)	87 (5.3)	77 (6.2)	78 (4.5)
MI, n (%)	1,389 (30.0)	556 (33.9)	380 (30.8)	453 (25.9)
CABG, n (%)	415 (9.0)	171 (10.4)	113 (9.1)	131 (7.5)
PCI, n (%)	796 (17.2)	321 (19.5)	212 (17.2)	263 (15.0)
Ischaemic heart disease w/o angina, n (%)	1,633 (35.3)	647 (39.4)	431 (34.9)	555 (31.7)
History of TIA, n (%)	801 (17.3)	219 (13.3)	230 (18.6)	352 (20.1)
History of stroke, n (%)	419 (9.1)	146 (8.9)	123 (10.0)	150 (8.6)
History of PAD or surgery of the leg, n (%)	729 (15.8)	235 (14.3)	185 (15.0)	309 (17.7)
Retinal infarction, n (%)	22 (0.5)	7 (0.4)	1-5	10 (0.6)
History of carotid artery surgery, n (%)	8 (0.2)	1-5	1-5	1-5
Ischaemic optic neuropathy, n (%)	6 (0.1)	1-5	1-5	1-5
Time since first ASCVD diagnosis (days), mean (SD)	3,164.8 (2,969.6); Range (4–34,333)	2,992.7 (2,896.6); Range (4–16,071)	3,153.6 (2,982); Range (9–34,333)	3,334.3 (3,020.3); Range (4–24,137)

Laboratory parameters				
HbA1c (%), mean (SD)	6.5 (1.0); Range (3.9–16.5); Total 2,218 (47.9)	6.6 (1.0); Range (3.9–12.1); Total 919 (56.0)	6.5 (0.9); Range (4.4–11.3); Total 564 (45.7)	6.5 (1.1); Range (4.2–16.5); Total 735 (42.0)
Initial LDL-C (mg/dL), mean (SD)	99.9 (37.7); Range (30–281)	90.9 (36.7); Range (30–281)	103.2 (41.6); Range (33–241)	106.2 (33.8); Range (30–256)
LDL-C reduction from baseline (%), mean (SD)	29.3 (23.9); Range (0–86)	44.2 (22); Range (0–86)	32.2 (21.8); Range (0–71.5)	13.2 (15.6); Range (0–49.7)
≥ 50% LDL-C reduction, n (%)	864 (18.7)	584 (35.6)	280 (22.7)	0 (0.0)
Comorbidities				
Hypertension, n (%)	2,473 (53.5)	875 (53.3)	649 (52.6)	949 (54.3)
Musculoskeletal disorders, n (%)	1,932 (41.8)	686 (41.8)	507 (41.1)	739 (42.3)
Osteoarthritis, n (%)	1,880 (40.6)	668 (40.7)	492 (39.8)	720 (41.2)
Rheumatoid/seropositive arthritis, n (%)	107 (2.3)	37 (2.3)	25 (2.0)	45 (2.6)
Type 2 diabetes mellitus, n (%)	1,338 (28.9)	578 (35.2)	344 (27.9)	416 (23.8)
CKD, n (%)	1,248 (27.0)	466 (28.4)	315 (25.5)	467 (26.7)
Atrial fibrillation, n (%)	853 (18.4)	308 (18.8)	232 (18.8)	313 (17.9)
Mental health disorder, n (%)	817 (17.7)	283 (17.2)	220 (17.8)	314 (18.0)
Depressive disorder, n (%)	778 (16.8)	269 (16.4)	213 (17.2)	296 (16.9)
Personality disorder, n (%)	705 (15.2)	244 (14.9)	187 (15.1)	274 (15.7)
Anxiety disorder, n (%)	232 (5.0)	71 (4.3)	57 (4.6)	104 (5.9)
Schizophrenia, n (%)	19 (0.4)	1-5	6 (0.5)	9 (0.5)
Obesity, n (%)	747 (16.1)	279 (17.0)	203 (16.4)	265 (15.2)
Heart failure, n (%)	501 (10.8)	200 (12.2)	123 (10.0)	178 (10.2)
Number of chronic diseases 0–3 conditions, n (%)	1,677 (36.3)	570 (34.7)	445 (36.0)	662 (37.9)
Number of chronic diseases 4–5 conditions, n (%)	1,656 (35.8)	590 (35.9)	440 (35.6)	626 (35.8)
Number of chronic diseases > 5 conditions, n (%)	1,293 (28.0)	482 (29.4)	350 (28.3)	461 (26.4)
Concomitant medication				
< 5 chronic medications prescribed (last 12 months), n (%)	1,167 (25.2)	327 (19.9)	329 (26.6)	511 (29.2)
≥ 5 chronic medications prescribed (last 12 months), n (%)	3,459 (74.8)	1,315 (80.1)	906 (73.4)	1,238 (70.8)

Hypoglycaemic medication, n (%)	1,579 (34.1)	710 (43.2)	403 (32.6)	466 (26.6)
Antihypertensives RAAS agents (ACE-I or ARB), n (%)	1,626 (35.1)	633 (38.6)	420 (34.0)	573 (32.8)
Antihypertensives non-RAAS agents, n (%)	2,072 (44.8)	743 (45.2)	553 (44.8)	776 (44.4)

First lipid target: LDL-C < 55 mg/dL AND a reduction of ≥ 50% from baseline (2019 ESC/EAS target). Second lipid target: LDL-C ≥ 55 mg/dL and < 70 mg/dL OR a reduction of ≥ 50% from baseline if LDL-C ≥ 70 mg/dL (2016 ESC/EAS target). Not reaching lipid target: LDL-C ≥ 70 mg/dL AND a reduction of < 50% from baseline.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; LDL-C, low-density cholesterol; ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PAD, peripheral arterial disease; TIA, transient ischaemic attack; CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

'1-5' indicates cell suppressed for privacy reasons (n < 5).

Clinical parameter values shown for patients with available data only (not older than 18 months).

HbA1c: Medidoc code 57183; LDL-C: Medidoc code 63026.

Table 3. Lipid-lowering therapies

Variable	Total (n=4,626)	First lipid target (n=1,642)	Second lipid target (n=1,235)	Not reaching target (n=1,749)
Statin therapy				
Statin, n (%)	4,053 (87.6)	1,438 (87.6)	1,127 (91.3)	1,488 (85.1)
High-intensity statin (rosuvastatin or atorvastatin), n (%)	3,169 (68.5)	1,206 (73.4)	909 (73.6)	1,054 (60.3)
Low-intensity statin (simvastatin or pravastatin), n (%)	1,338 (28.9)	394 (24.0)	344 (27.9)	600 (34.3)
Non-statin LLT				
Non-statin LLT, n (%)	631 (13.6)	248 (15.1)	173 (14.0)	210 (12.0)
Ezetimibe, n (%)	551 (11.9)	219 (13.3)	150 (12.1)	182 (10.4)
PCSK9 inhibitor, n (%)	9 (0.2)	1-5	1-5	1-5
Inclisiran, n (%)	17 (0.4)	8 (0.5)	1-5	1-5
Bempedoic acid, n (%)	99 (2.1)	31 (1.9)	23 (1.9)	45 (2.6)
Anion exchangers, n (%)	19 (0.4)	6 (0.4)	8 (0.6)	1-5
Omega-3 fatty acids, n (%)	1-5	0 (0.0)	0 (0.0)	1-5
Fibrates, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Combination LLT				
Combination LLT - double or triple therapy, n (%)	1,578 (34.1)	778 (47.4)	417 (33.8)	383 (21.9)
Combination LLT - double therapy, n (%)	1,414 (30.6)	714 (43.5)	373 (30.2)	327 (18.7)
Statin + ezetimibe, n (%)	1,245 (26.9)	662 (40.3)	328 (26.6)	255 (14.6)
Rosuvastatin + ezetimibe, n (%)	749 (16.2)	443 (27.0)	171 (13.8)	135 (7.7)
Atorvastatin + ezetimibe, n (%)	489 (10.6)	231 (14.1)	149 (12.1)	109 (6.2)
Simvastatin + ezetimibe, n (%)	115 (2.5)	37 (2.3)	40 (3.2)	38 (2.2)
Pravastatin + ezetimibe, n (%)	1-5	1-5	0 (0.0)	1-5
Statin + PCSK9 inhibitor, n (%)	1-5	1-5	1-5	0 (0.0)
Statin + inclisiran, n (%)	13 (0.3)	6 (0.4)	1-5	1-5

Statin + bempedoic acid, n (%)	74 (1.6)	25 (1.5)	17 (1.4)	32 (1.8)
Statin + anion exchangers, n (%)	16 (0.3)	6 (0.4)	6 (0.5)	1-5
Statin + omega-3 fatty acids, n (%)	1-5	0 (0.0)	0 (0.0)	1-5
Statin + fibrates, n (%)	117 (2.5)	54 (3.3)	30 (2.4)	33 (1.9)
Ezetimibe + PCSK9 inhibitor, n (%)	6 (0.1)	1-5	1-5	1-5
Ezetimibe + inclisiran, n (%)	8 (0.2)	1-5	1-5	1-5
Ezetimibe + bempedoic acid, n (%)	68 (1.5)	17 (1.0)	18 (1.5)	33 (1.9)
Ezetimibe + anion exchangers, n (%)	1-5	0 (0.0)	0 (0.0)	1-5
Ezetimibe + omega-3 fatty acids, n (%)	1-5	0 (0.0)	0 (0.0)	1-5
Ezetimibe + fibrates, n (%)	36 (0.8)	20 (1.2)	6 (0.5)	10 (0.6)
Combination LLT - triple therapy, n (%)	164 (3.5)	64 (3.9)	44 (3.6)	56 (3.2)
Statin + ezetimibe + PCSK9 inhibitor, n (%)	1-5	1-5	1-5	0 (0.0)
Statin + ezetimibe + inclisiran, n (%)	6 (0.1)	1-5	1-5	1-5
Statin + ezetimibe + bempedoic acid, n (%)	118 (2.6)	39 (2.4)	32 (2.6)	47 (2.7)
Statin + ezetimibe + anion exchangers, n (%)	1-5	0 (0.0)	1-5	1-5
Statin + ezetimibe + omega-3 fatty acids, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Statin + ezetimibe + fibrates, n (%)	48 (1.0)	28 (1.7)	11 (0.9)	9 (0.5)

First lipid target: LDL-C < 55 mg/dL AND a reduction of ≥ 50% from baseline (2019 ESC/EAS target). Second lipid target: LDL-C ≥ 55 mg/dL and < 70 mg/dL OR a reduction of ≥ 50% from baseline if LDL-C ≥ 70 mg/dL (2016 ESC/EAS target). Not reaching lipid target: LDL-C ≥ 70 mg/dL AND a reduction of < 50% from baseline.

Abbreviations: LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9.

Where a total row is provided, this reflects unique patient counts based on an OR condition; individual subtype rows are not mutually exclusive and do not necessarily sum to the total.

The 'Bempedoic acid' row (n=99, 2.1%) excludes patients receiving bempedoic acid with ezetimibe, who are captured in the 'Ezetimibe + bempedoic acid' row (n=68, 1.5%); together these represent all bempedoic acid users (n=167, 3.6%).

ATC codes are provided in appendices.

'1-5' indicates cell suppressed for privacy reasons.

Appendices

Appendix 1. Selection of study population

Inclusion criteria: history of ASCVD	ICPC-2	ICD-10	Free text terms
Angina pectoris	K74	I20.8	-
Unstable angina	K74	I20.0	-
Myocardial infarction	K75	I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I25.2	-
Coronary artery bypass grafting	A89	Z95.1	Selection of free text terms 'coronary bypass' or 'CABG'
Percutaneous coronary intervention	-	-	Selection of free text term 'stent'
Ischaemic heart disease without angina	K76	I25.0, I25.1, I25.2, I25.5, I25.6	-
Peripheral artery disease	K92	I70.2, I74.4, I73.9, I74.3, R02	-
Surgery of the leg	-	-	Selection of free text terms 'stent' or 'bypass'
Transient ischaemic attack	K89	G45.9	-
Stroke	K90	-	-
Retinal infarction	F99	H34.2	-
Ischaemic optic neuropathy	F99	H47.0	-
Carotid artery surgery	-	-	Selection of free text terms 'carotis endarterectomie' or 'carotisstent'
Exclusion criteria	**ICPC-2**	**ICD-10**	**Free text terms**
Familial hypercholesterolaemia	T93	E78.0	-

Abbreviations: ICPC-2, International Classification of Primary Care, 2nd edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Codes are shown as ICPC-2 and ICD-10 coding. A "-" indicates that no codes of that type were used to define the condition.

Appendix 2. List of comorbidities

List of comorbidities	ICPC-2	ICD-10	Medidoc
Obesity	-	E66.2, E66.8, E66.9	-
Chronic kidney disease	-	-	57710
Heart failure	K77	-	-
Atrial fibrillation	K78	-	-
Hypertension	K86	-	-
Type 2 diabetes mellitus	E11	-	-
Osteoarthritis	-	G55.1, G99.2, M15.0, M15.3, M15.4, M15.9, M16.0, M16.1, M16.2, M16.3, M16.4, M16.5, M16.6, M16.7, M16.9, M17.0, M17.1, M17.2, M17.3, M17.4, M17.5, M17.9, M18.0, M18.1, M18.2, M18.3, M18.4, M18.5, M18.9, M19.0, M19.1, M19.2, M19.9, M43.1, M47.1, M47.2, M47.8, M47.9, M48.0, M50.3, M51.3	-
Rheumatoid arthritis	-	A01.0, A02.2, A03.9, A09, A18.0, A25.1, A39.8, A49.9, A52.1, A54.4, A69.2, A92.1, B06.8, B26.8, B33.1, B34.9, B42.8, B49, B72, B74.9, B83.9, B89, B99, C85.7, C90.0, C95.9, D56.9, D58.2, D66, D69.0, D75.9, D80.1, D86.8, E03.9, E10.6, E11.6, E12.6, E13.6, E14.6, E21.3, E22.0, E34.9, E54, E70.2, E78.8, E83.1, E85.0, E85.4, E88.9, G63.6, G73.7, G95.0, G98, I32.8, I39.8, I41.8, I52.8, J98.9, J99.0, J99.8, K07.6, K63.9, L40.5, L52, M00.0, M00.1, M00.2, M00.8, M00.9, M01.0, M01.1, M01.2, M01.3, M01.4, M01.5, M01.6, M01.8, M02.1, M02.2, M02.3, M03.0, M03.1, M03.2, M03.6, M05.0, M05.1, M05.2, M05.3, M05.9, M06.0, M06.4, M06.8, M06.9, M07.1, M07.3, M07.4, M07.5, M08.0, M08.2, M08.3, M08.4, M08.9, M09.0, M09.1, M09.2, M09.8, M10.0, M11.0, M11.8, M11.9, M12.0, M12.1, M12.2, M12.3,	-

		M12.5, M12.8, M13.0, M13.1, M13.8, M13.9, M14.1, M14.3, M14.4, M14.5, M14.6, M14.8, M15.1, M15.2, M15.9, M19.9, M35.2, M36.1, M36.2, M36.3, M36.4, M45, M46.5, M46.9, M48.3, M49.0, M49.4, M73.8, M75.0, M77.2, M77.9, T70.3, T78.4, Z13.8, Z82.6, Z87.3	
Schizophrenia	P72	-	-
Anxiety disorder	-	F41.0, F41.1	-
Depressive disorder	P76	-	-
Personality disorder	P71, P72, P73, P76, P80	-	-

Abbreviations: ICPC-2, International Classification of Primary Care, 2nd edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision

Codes are shown as ICPC-2 and ICD-10 coding. A "-" indicates that no codes of that type were used to define the condition.

Appendix 3. List of 22 chronic conditions

#	Chronic condition	ICPC-2	ICD-10
1	**Hypertension**	K86	-
2	**Lipid disorders**	T93	E78.5
3	**Angina pectoris / Unstable angina**	K74	I20.0, I20.8
4	**Cardiomyopathy**	K70; K71; K73; K76; K84; K87; T85; T91; T99; A70; A78; B99; W84	K70 + B33.2; I41.2 K71 + I09.0 K73 + I42.4; Q24.8 K76 + I25.1; I25.5 K84 + E05.9; E51.1; E63.9; E85.4; E88.9; I42.0–I42.2; I42.5–I42.9; I43.0; I43.8; O90.3 K87 + I11.9 T85 + I43.8 T91 + I43.2 T99 + I43.1 A70 + A18.8 A78 + B57.0 B99 + D86.8 W84 + O99.4
5	**Myocardial infarction**	K75	I21.0–I21.4; I21.9; I22.0; I22.1; I22.8; I25.2
6	**Transient ischaemic attack**	K89	G45.9
7	**Stroke**	K90	-
8	**Peripheral arterial disease**	K92	I70.2; I73.9; I74.3; I74.4; R02
9	**Episodes of decompensated heart failure**	K84	I51.9
10	**Episodes of atrial fibrillation**	K78	I48
11	**Known valvular disease**	K83	I34.0–I34.2; I34.8; I34.9; I35.0–I35.2; I35.8; I35.9; I36.0–I36.2; I36.8; I36.9; I37.0–I37.2; I37.8; I37.9
12	**Thyroid disease**	T85; T86; T99	-
13	**Respiratory impairment (asthma or COPD)**	R95; R96	R96 + J45.0; J45.1; J45.9; J46 / R95 + J44; J44.0; J44.1; J44.8
14	**Parkinson's disease**	N87	G20
15	**Arthritis**	A23; A70; A74; A77; A78; A88; A92; A98; B72; B73; B74; B78; B83; B99; D70; D71; D73; D82; D94; D96; D99; K70; K84; L70; L83; L84;	A23 + Z82.6; Z87.3 A70 + A18.0 A74 + B06.8 A77 + A92.1; B33.1; B34.9 A78 + A25.1; A39.8; A49.9; A69.2; B42.8; B49; B89; B99; M01.3 A88 + M14.8 A92 + M36.4 A98 + Z13.8 B72 + C85.7 B73 + C95.9 B74 + C90.0 B78 + D56.9; D58.2 B83 + D66; D69.0

		L87; L88; L91; L92; L99; N94; N99; R99; S91; S99; T86; T89; T90; T91; T92; T93; T99; X70; X71	B99 + D75.9; D80.1; D86.8 D70 + A01.0; A02.2; A03.9; M01.3 D71 + B26.8 D73 + A09 D82 + K07.6 D94 + M07.4; M07.5 D96 + B72; B74.9; B83.9 D99 + K63.9 K70 + I32.8; I39.8; I41.8 K84 + I52.8 L70 + A52.1; A54.4; M00.0–M00.2; M00.8; M00.9; M01.0–M01.6; M01.8; M46.5 L83 + M48.3 L84 + M46.9; M48.3 L87 + M12.2; M77.2; M77.9 L88 + G63.6; G73.7; J99.0; J99.8; M05.0; M05.2; M05.3; M05.9; M06.0; M06.4; M06.8; M06.9; M08.0; M08.2–M08.4; M08.9; M45 L91 + M13.0; M13.1; M13.8; M13.9; M15.1; M15.2; M15.9; M19.9 L92 + M19.9; M75.0 L99 + A52.1; A54.4; E03.9; E21.3; E22.0; E34.9; E54; E70.2; E78.8; E83.1; E85.0; E85.4; E88.9; G95.0; G98; J98.9; L40.5; L52; M02.1–M02.3; M03.0–M03.2; M03.6; M09.0–M09.2; M09.8; M12.0; M12.1; M12.3; M12.5; M12.8; M13.0; M14.3; M14.5; M14.6; M14.8; M35.2; M36.1–M36.4; M49.0; T70.3; T78.4 N94 + M05.3 N99 + M05.3; M49.4 R99 + J98.9; M05.1; M14.8; M45 S91 + M07.1; M07.3 S99 + M14.8 T86 + M14.5 T89 + E10.6 T90 + E11.6; E12.6; E13.6; E14.6 T91 + M14.5 T92 + M10.0 T93 + M14.3 T99 + M11.0; M11.8; M11.9; M14.1; M14.4; M14.5 X70 + M01.3; M14.6 X71 + M01.3; M73.8
16	**Osteoarthritis**	L83; L84; L86; L89; L90; L91; L92; N99	L83 + M43.1; M47.2; M47.8; M47.9; M50.3; G55.1; G99.2 L84 + G99.2; M43.1; M47.8; M47.9; M48.0; M51.3 L86 + M47.2; G99.2 L89 + M16.0–M16.7; M16.9 L90 + M17.0–M17.5; M17.9 L91 + M15.0; M15.3; M15.4; M15.9; M18.0–M18.5; M18.9; M19.0–M19.2; M19.9 L92 + M19.0–M19.2; M19.9 N99 + M47.1
17	**Osteoporosis**	-	A52.7; C90.0; E34.9; M80.0–M80.5; M80.8; M80.9; M81.0–M81.6; M81.8; M81.9; M82.0; M82.1; M82.8; M83.8; M90.2
18	**Cancer**	A79; B72–B74; D74–D79; L71; N74; R84; R85; S77; S79; T71; T73; U75; U76; X575; X76–X78; Y77–Y79	-
19	**Depression**	P76	-
20	**Renal insufficiency**	U99	N18.9

21	**Type 1 or 2 diabetes mellitus**	T89; T90	E10 (with T89); E11 (with T90)
22	**Locomotor sequelae of stroke**	N99	G80.2

Abbreviations: ICPC-2, International Classification of Primary Care, 2nd edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; COPD, chronic obstructive pulmonary disease.

Codes are shown as ICPC-2 and ICD-10 coding. For conditions where coding requires combinations of ICPC-2 and ICD-10 (items 4, 11, 13, 15, 16, 21), the ICD-10 column lists the ICD-10 codes that apply for each ICPC-2 code in the form "ICPC-2 + ICD-10". A "-" indicates that no codes of that type were used to define the condition. Code ranges (e.g. M80.0–M80.5) include all integer subcodes within the range.

Appendix 4. Lipid-lowering therapy and comedication

Lipid-lowering therapy

Category	Medication	ATC code
1. Statins		
Statins	Atorvastatin	C10AA05
Statins	Pravastatin	C10AA03
Statins	Rosuvastatin	C10AA07
Statins	Simvastatin	C10AA01
2. Fibrates		
Fibrates	Bezafibrate	C10AB02
Fibrates	Ciprofibrate	C10AB08
Fibrates	Fenofibrate	C10AB05
3. Anion exchangers (bile acid sequestrants)		
Anion exchangers	Colestyramine	C10AC01
4. Ezetimibe		
Ezetimibe	Ezetimibe	C10AX09
5. Omega-3 fatty acids		
Omega-3 fatty acids	Omega-3 fatty acids	C10AX06
6. PCSK9 inhibitors		
PCSK9 inhibitors	Alirocumab	C10AX14
PCSK9 inhibitors	Evolocumab	C10AX13
7. Inclisiran		
Inclisiran	Inclisiran	C10AX16
8. Bempedoic acid		
Bempedoic acid	Bempedoic acid	C10AX15
9. Combination lipid-lowering therapies		
Ezetimibe + statin	Ezetimibe + atorvastatin	C10BA05

Ezetimibe + statin	Ezetimibe + rosuvastatin	C10BA06
Ezetimibe + statin	Ezetimibe + simvastatin	C10BA02
Ezetimibe + statin	Ezetimibe + pravastatin	C10BA03
Bempedoic acid + ezetimibe	Bempedoic acid + ezetimibe	C10BA10
Bempedoic acid + statin	Bempedoic acid + statin	C10AX15 + C10AA07/C10AA05/C10AA01/C10AA03
Bempedoic acid + statin + ezetimibe	Bempedoic acid + statin + ezetimibe	C10BA10 + C10AA07/C10AA05/C10AA01/C10AA03
Anion exchanger + statin	Anion exchanger + statin	C10AC01 + C10AA07/C10AA05/C10AA01/C10AA03
Anion exchanger + ezetimibe	Anion exchanger + ezetimibe	C10AC01 + C10AX09
Anion exchanger + statin + ezetimibe	Anion exchanger + statin + ezetimibe	C10AC01 + C10BA06/C10BA05/C10BA02/C10BA03
Fibrate + statin	Fibrate + statin	C10AB02/C10AB05/C10AB08 + C10AA07/C10AA05/C10AA01/C10AA03
Fibrate + ezetimibe	Fibrate + ezetimibe	C10AB02/C10AB05/C10AB08 + C10AX09
Fibrate + statin + ezetimibe	Fibrate + statin + ezetimibe	C10AB02/C10AB05/C10AB08 + C10BA06/C10BA05/C10BA02/C10BA03
Omega-3 fatty acids + statin	Omega-3 fatty acids + statin	C10AX06 + C10AA07/C10AA05/C10AA01/C10AA03
Omega-3 fatty acids + ezetimibe	Omega-3 fatty acids + ezetimibe	C10AX06 + C10AX09
Omega-3 fatty acids + statin + ezetimibe	Omega-3 fatty acids + statin + ezetimibe	C10AX06 + C10BA06/C10BA05/C10BA02/C10BA03
PCSK9 inhibitor + statin	PCSK9 inhibitor + statin	C10AX13 + C10AA07/C10AA05/C10AA01/C10AA03
PCSK9 inhibitor + ezetimibe	PCSK9 inhibitor + ezetimibe	C10AX13 + C10AX09
PCSK9 inhibitor + statin + ezetimibe	PCSK9 inhibitor + statin + ezetimibe	C10AX13 + C10AA07/C10AA05/C10AA01/C10AA03
Inclisiran + statin	Inclisiran + statin	C10AX16 + C10AA07/C10AA05/C10AA01/C10AA03
Inclisiran + ezetimibe	Inclisiran + ezetimibe	C10AX16 + C10AX09

Inclisiran + statin + ezetimibe	Inclisiran + statin + ezetimibe	C10AX16 + C10BA06/C10BA05/C10BA02/C10BA03

Antihypertensive medications

Category	Medication	ATC Code
1. Thiazides and related agents		
Thiazides and related agents	Chlorthalidone	C03BA04
Thiazides and related agents	Indapamide	C03BA11
2. Loop diuretics		
Loop diuretics	Bumetanide	C03CA02
Loop diuretics	Furosemide	C03CA01
Loop diuretics	Torasemide	C03CA04
3. Beta-blockers		
Beta-blockers	Atenolol	C07AB03
Beta-blockers	Bisoprolol	C07AB07
Beta-blockers	Carvedilol	C07AG02
Beta-blockers	Labetalol	C07AG01
Beta-blockers	Metoprolol	C07AB02
Beta-blockers	Nebivolol	C07AB12
Beta-blockers	Propranolol	C07AA05
4. Calcium channel blockers		
CCB – Dihydropyridines	Amlodipine	C08CA01
CCB – Dihydropyridines	Clevidipine	C08CA16
CCB – Dihydropyridines	Felodipine	C08CA02
CCB – Dihydropyridines	Lercanidipine	C08CA13
CCB – Dihydropyridines	Nicardipine	C08CA04

CCB – Dihydropyridines	Nifedipine	C08CA05
CCB – Dihydropyridines	Nimodipine	C08CA06
CCB – Non-dihydropyridines	Verapamil	C08DA01
CCB – Non-dihydropyridines	Diltiazem	C08DB01
5. RAAS agents		
ACE inhibitors	Captopril	C09AA01
ACE inhibitors	Cilazapril	C09AA08
ACE inhibitors	Enalapril	C09AA02
ACE inhibitors	Fosinopril	C09AA09
ACE inhibitors	Lisinopril	C09AA03
ACE inhibitors	Perindopril	C09AA04
ACE inhibitors	Quinapril	C09AA06
ACE inhibitors	Ramipril	C09AA05
ACE inhibitors	Zofenopril	C09AA15
Angiotensin II receptor antagonists (ARBs)	Candesartan	C09CA06
Angiotensin II receptor antagonists (ARBs)	Eprosartan	C09CA02
Angiotensin II receptor antagonists (ARBs)	Irbesartan	C09CA04
Angiotensin II receptor antagonists (ARBs)	Losartan	C09CA01
Angiotensin II receptor antagonists (ARBs)	Olmesartan	C09CA08
Angiotensin II receptor antagonists (ARBs)	Telmisartan	C09CA07
Angiotensin II receptor antagonists (ARBs)	Valsartan	C09CA03
6. Combination products (antihypertensives)		
Combinations	Beta-blocker + diuretic	C07CB03

Combinations	Beta-blocker + calcium channel blocker	C07FB02
Combinations	Beta-blocker + ACE inhibitor	C09BX02
Combinations	ACE inhibitor + diuretic	C09BA02
Combinations	ACE inhibitor + calcium channel blocker	C09BB04
Combinations	Sartan + diuretic	C09DA06
Combinations	Sartan + calcium channel blocker	C09DB01
Combinations	ACE inhibitor + calcium channel blocker + diuretic	C09BX01
Combinations	Sartan + calcium channel blocker + diuretic	C09DX01
7. Centrally acting antihypertensives		
Centrally acting agents	Clonidine	C02AC01
Centrally acting agents	Methyldopa	C02AB01
Centrally acting agents	Moxonidine	C02AC05
8. Vasodilators		
Vasodilators	Urapidil	C02CA06

Hypoglycaemic medications

Category	**Medication**	**ATC Code**
1. Insulin		
Ultra-rapid acting insulin analogues	Insulin lispro	A10AB04
Ultra-rapid acting insulin analogues	Insulin aspart	A10AB05
Ultra-rapid acting insulin analogues	Insulin glulisine	A10AB06
Rapid-acting insulin	Insulin (regular/soluble)	A10AB01
Intermediate-acting insulin	Insulin (isophane/NPH)	A10AC01
Long-acting insulin analogues	Insulin glargine	A10AE04
Long-acting insulin analogues	Insulin detemir	A10AE05
Long-acting insulin analogues	Insulin degludec	A10AE06

Combination insulins	Combination preparations of human insulins	A10AD01
Combination insulins	Insulin lispro combinations	A10AD04
Combination insulins	Insulin aspart combinations	A10AD05
2. Metformin		
Biguanides	Metformin	A10BA02
3. Hypoglycaemic sulfonylureas		
Sulfonylureas	Gliclazide	A10BB09
Sulfonylureas	Glimepiride	A10BB12
Sulfonylureas	Gliquidone	A10BB08
Sulfonylureas	Glibenclamide	A10BB01
4. Glinides		
Glinides	Repaglinide	A10BX02
5. Glitazones		
Glitazones	Pioglitazone	A10BG03
6. GLP-1 receptor agonists (incretin mimetics)		
GLP-1 receptor agonists	Dulaglutide	A10BJ05
GLP-1 receptor agonists	Exenatide	A10BJ01
GLP-1 receptor agonists	Liraglutide	A10BJ02
GLP-1 receptor agonists	Semaglutide	A10BJ06
7. Gliptins (DPP-4 inhibitors)		
DPP-4 inhibitors	Alogliptin	A10BH04
DPP-4 inhibitors	Linagliptin	A10BH05
DPP-4 inhibitors	Saxagliptin	A10BH03
DPP-4 inhibitors	Sitagliptin	A10BH01
DPP-4 inhibitors	Vildagliptin	A10BH02
8. Gliflozins (SGLT2 inhibitors)		

SGLT2 inhibitors	Canagliflozin	A10BK02
SGLT2 inhibitors	Dapagliflozin	A10BK01
SGLT2 inhibitors	Empagliflozin	A10BK03
9. Dual GIP/GLP-1 receptor agonist		
Dual GIP/GLP-1 receptor agonist	Tirzepatide	A10BJ15
10. Combination products (hypoglycaemic)		
Gliflozin + metformin	Dapagliflozin + metformin	A10BD15
Gliflozin + metformin	Empagliflozin + metformin	A10BD20
Gliptin + metformin	Sitagliptin + metformin	A10BD07
Gliptin + metformin	Vildagliptin + metformin	A10BD08
Gliptin + metformin	Linagliptin + metformin	A10BD11
Gliptin + metformin	Alogliptin + metformin	A10BD13
Insulin + GLP-1 receptor agonist	Insulin degludec + liraglutide	A10AE56