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Prescription patterns of lipid lowering agents among older patients in general practice: an analysis from a national database in the Netherlands

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Abstract

Background:
Dutch cardiovascular risk management guidelines state almost every older adult (≥70 years) is eligible for a lipid lowering drug (LLD). However, life expectancy, frailty or comorbidities may influence this treatment decision.

Objective:
investigate how many older adults, according to age, frailty (Drubbel-frailty index) and comorbidities were prescribed LLDs.

Methods:
data of 244,328 adults ≥70 years from electronic health records of 415 Dutch general practices from 2011–15 were used. Number of LLD prescriptions in patients with (n = 55,309) and without (n = 189,019) cardiovascular disease (CVD) was evaluated according to age, frailty and comorbidities.

Results:
about 69% of adults ≥70 years with CVD and 36% without CVD were prescribed a LLD. LLD prescriptions decreased with age; with CVD: 78% aged 70–74 years and 29% aged ≥90

years were prescribed a LLD, without CVD: 37% aged 70–74 years and 12% aged ≥90 years. In patients with CVD and within each age group, percentage of LLD prescriptions was 20% point(pp) higher in frail compared with non-frail. In patients without CVD, percentage of LLD prescriptions in frail patients was 11pp higher in adults aged 70–74 years and 40pp higher in adults aged ≥90 years compared to non-frail. Similar trends were seen in the analyses with number of comorbidities.

Conclusion:
in an older population, LLD prescriptions decreased with age but—contrary to our expectations—LLD prescriptions increased with higher frailty levels.

Key points

•In a population of adults aged ≥70 years, 69% of adults with cardiovascular diseases (CVD) and 36% without CVD were prescribed a lipid lowering drug (LLD).
•The number of LLD prescriptions decreased with age.
•In contrast to our expectations, the number of LLD prescriptions increased with higher frailty levels.

Introduction

Cardiovascular diseases (CVD) are one of the leading causes of death [1]. Improved therapeutic options have lowered CVD mortality leading to an increasing number of older adults with chronic CVD [2]. Drugs given to prevent new cardiovascular events may negatively influence quality of life due to adverse side effects and drug interactions. According to current Dutch guidelines, patients with a history of CVD are at '(very) high risk' and therefore eligible for a lipid lowering drug (LLD) [3]. For patients without CVD, a risk stratification tool is used to estimate a patient's 10-years risk of a cardiovascular event or death [4]. According to this risk stratification, every male and almost every female ≥70 years of age without CVD has a high (≥20%) 10-years risk of CVD solely based on their age, and is therefore eligible for LLDs to prevent CVD-related morbidity and mortality. Previously reported statin prescription prevalence from 1999 to 2008 showed a lower number of statins prescriptions in older compared with younger patients, with a significant increase in prescriptions over time after introduction of the Dutch cardiovascular risk management (CVRM) guideline in 2006 [5]. Few studies of particular interest have investigated prescription patterns of LLDs in older people, including the oldest old, those with multiple comorbidities and in frail older people. Preventive medication may be prescribed less often, particularly in older and frail adults with a shorter life expectancy as there are less certain benefits and a greater susceptibility to harm [6]. In fact, it has been demonstrated that older patients with and without pre-existing CVD and high levels on a comorbidity-score were less likely to be taking a statin compared with patients with less comorbidities [7]. Also, statins did not reduce risk of institutionalisation and death in frail older men ≥70 years of age [8]. This study set out to assess how many patients aged ≥70 years—with and without existing CVD—were prescribed a LLD according to age, level of frailty and number of comorbidities in a large primary care database in the Netherlands.

Methods

Study design and participants

This study used data from Nivel Primary Care Database (Nivel-PCD). Nivel-PCD collects data from routine electronic health record systems, including consultations, morbidity, prescriptions and diagnostic tests. We used data from a representative sample of 415 general practices in 2011–15,

including 224,328 patients ≥70 years of age [9]. For more information on data collection, see Appendix 1, in the supplementary data, available in Age and Ageing online.

Medication

Prescribed drugs were recorded using the Anatomical Therapeutic Chemical (ATC) classification system [10]. Drugs belonging to the C10 'Lipid modifying agents' section of the ATC classification system, e.g. statins, fibrates, were classified as LLDs. We had access to data on regular and refill prescriptions written by general practitioners. For further details, see Appendix 2, in the supplementary data, available in Age and Ageing online.

Cardiovascular disease, other comorbidities

Vascular and non-vascular comorbidities were recorded using the International Classification of Primary Care-1 (ICPC-1) of the World Health Organization [11]. Comorbidities were categorised using the first three digits of the full ICPC-code. Presence of one or more of the following atherosclerotic related CVDs at baseline was defined as 'having a CVD': angina pectoris, acute myocardial infarction, myocardial infarction >4 weeks ago, transient ischaemic attack (TIA), stroke, and peripheral artery disease. For more information on (risk factors for) CVD, see Appendix 3, in the supplementary data, available in Age and Ageing online. For the assessment of total number of chronic disease at baseline, data on diseases classified as 'chronic' in the Nivel dataset were used.

Frailty

Frailty was assessed using the Drubbel-frailty index (FI), which is designed for use (e.g. research purpose and potential clinical use) in routine healthcare data of general practitioners [12]. The construction of this FI is described in greater detail elsewhere [12]. For the present study, we divided the total FI score into tertiles.
As the original Drubbel-FI contains ICPC-codes describing CVDs which are included in our definition of 'having pre-existing CVD', we performed sensitivity analyses in patients with CVD using modified FIs from which these CVDs were excluded (Appendix 4, in the supplementary data, available in Age and Ageing online).

Statistical analysis

Baseline differences in older adults with and without CVD, not taking and taking a LLD were assessed. Depending on the characteristics and distribution of the variable, we presented the mean, median, and frequencies of the variables.

In older adults with and without CVD, prevalence of LLD use was assessed in the total group of older patients and according to age. For this, we divided the sample into five different age groups (70–74, 75–80, 81–84, 85–90 and ≥91 years of age). In patients with, as well as in patients without CVD at baseline, prevalence of LLD use was determined according to level of frailty. We performed these analyses in each age group separately. Next, we carried out sensitivity analyses in patients with and without CVD using the modified FIs. Additionally, we performed subgroup analyses in extremely fit older adults (FI score below the 10th percentile (p10) versus extremely frail older adults (FI score above the 90th percentile (p90)).

To get a better understanding of the prevalence of LLD use in relatively healthy older adults versus those with many health problems, we analysed LLD use in strata of number of chronic diseases at baseline (0–3, 4–8, ≥9), and number of primary care visits during the first year after baseline (0–3, 4–8, ≥9). Similar to the analyses using the FI, these analyses were performed in patients with, as well as without CVD, and in each age group separately. Lastly, we performed subgroup analyses in patients with a previously experienced acute myocardial infarction or stroke to evaluate potential differences

in prevalence of LLD use compared with older adults with any form of CVD. Identical to the analyses in patients with any form of CVD, we assessed prevalence of LLD use according to age, frailty, number of chronic disease, and primary care visits.

Results

Table 1 presents an overview of the baseline characteristics of the study population. About 68.8% of all patients with CVD (n = 55,309) were prescribed a LLD during or after baseline and 35.7% of all patients without CVD (n = 189,019). In patients with CVD, patients taking LLDs were younger and more often male compared with those not taking a LLD. The same applied to patients without CVD. Older adults taking a LLD had a more unfavourable cardiovascular risk profile, and were prescribed CVRM drugs more often. Patients taking LLDs had lower SBP and DBP lower cholesterol levels and a higher BMI. Especially in patients without CVD, the total number of frailty deficits present, and thus the total score on the FI, was higher in older adults taking a LLD. They also had more chronic diseases, took more drugs, and had more primary care visits during the first year after baseline.

[Table 1]

LLD use according to age

The highest percentage of patients with CVD using a LLD was observed in the youngest age group (70–74 years) in which 77.8% were prescribed a LLD (Figure 1). With increasing age, the prevalence of LLD use declined. In the oldest patients (≥91 years) with CVD, less than a third (28.9%) were prescribed a LLD after baseline. Similar to the trend observed in patients with CVD, the prevalence of LLD use in older patients without CVD decreased with age from 37.4% in those aged 70–74 years to 12.2% in the oldest patients (Figure 1).

[figure 1]

LLD prescriptions according to age and frailty

In patients with pre-existing CVD, in each age group the prevalence of LLD use in the most frail was ~20% points higher compared with the least frail (Figure 2). Thus, in adults aged 70–74 years drug prevalence was 81.5% in those most frail compared with 63.3% in those least frail. In adults aged ≥91 years, the number of older patients taking a LLD was 31.3% in the most frail, and 15.3% in the least frail. The same trends in prevalence of LLD use were seen in the analyses using the modified FI (excluding the CVD ICPC-codes also included in our definition of 'having pre-existing CVD') (Appendix 5, in the supplementary data, available in Age and Ageing online). Also in the analyses with a modified FI in which the 'polypharmacy' deficit was eliminated and in the analyses in the p10 versus the p90 group (results not shown), the most frail patients were prescribed LLDs more often than the least frail.

[figure 2]

In patients without CVD, similar trends in the prevalence of LLD use were observed (Figure 2); drug use declined with age and increased with increasing levels of frailty within each age group.

LLD use, according to age, comorbidities and primary care visits

Patterns in LLD use in patients with chronic diseases (Appendix 6, in the supplementary data, available in Age and Ageing online), and primary care visits (Appendix 7, in the supplementary data, available in Age and Ageing online), were similar to the patterns seen in non-frail, intermediate frail and frail older patients. Within each age group, there was an increasing trend in LLD use with a higher number of chronic diseases, total number of drugs used and primary care visits.

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Secondary analyses in patients with acute myocardial infarction or stroke

Compared with the results of the analyses using the composite CVD score, the overall prevalence of LLD prescriptions was slightly higher in patients who had experienced a myocardial infarction, as well as in patients who had experienced a stroke. Regarding LLD use in different age groups, and according to level of frailty, comorbidities and number of primary care visits, similar trends in LLD use were observed (results not shown).

Discussion

In a primary care cohort of Dutch patients ≥70 years of age, 69% of patients with CVD (n = 55,309) and 36% of patients without CVD (n = 189,019) were prescribed a LLD. As previously reported [7], age was inversely associated with the number of LLD prescriptions. We hypothesised that frail older adults were less likely to be prescribed a LLD due to a lower likelihood of benefits and a greater susceptibility to harms compared with fit older adults. However, in each age group, frail older adults and those with the highest number chronic diseases, were most likely to be prescribed lipid lowering therapy. This holds true for older adults with, as well as for older adults without previously experienced CVD.

Frail older adults are more likely to have a limited life expectancy, and to experience drug–drug interactions and/or unwanted drug side effects [13]. Also, they are more likely to die from non-CVD, i.e. competing risk, which limits the potential beneficial effects of LLDs [6]. However, we observed a contrasting trend illustrating a higher prevalence of LLD use in patients who were most frail in each age group. This may suggest that frail older adults who are less likely to benefit from and more likely to be harmed by lipid lowering therapy are potentially overtreated, while the more fit in whom potential benefit is moerlikely, are undertreated. However, these results may also be inherent to the design of the Drubbel-FI, because the total score on this FI is partially dependent on (risk factors for) CVD and polypharmacy. To eliminate this problem, we performed secondary analyses using modified FIs in which we excluded ICPC-codes describing CVD and polypharmacy. Although the relation between frailty and prevalence of LLDs could partially be explained by CVD and polypharmacy, the prevalence of LLDs was still highest in the frailest older adults. Even extremely frail older adults (FI score >p90) were more likely to be prescribed a LLD compared with the extremely fit older adults (FI score <p10). Another explanation for our finding that frail older adults were more likely to be prescribed a LLD could be the higher number of primary care visits in frail older adults, and thus better monitoring by their general practitioner. After all, the chances of being prescribed a LLD are much higher for patients who regularly visit their general practitioner compared with patients who never visit a physician. This is reflected in our results observing an increase in LLD use prevalence with increasing number of primary care visits (Appendix 7, in the supplementary data, available in Age and Ageing online). Considering the consistency of our results using the modified FIs and the FI with the analyses in strata of comorbidities and primary care visits, it is unlikely that our results are a matter of coincidence. Also, subgroup analyses in patients with a myocardial infarction or stroke showed similar trends.

This study has the strengths of a large representative sample of more than 244,000 older adults with extensive data on medical symptoms, diseases and drug prescriptions. Secondly, as the Drubbel-FI is designed to be used on routine healthcare data, adjusting the framework of this FI was not necessary. However, the results of the analyses using this FI may be somewhat limited by the nature of this FI as the total score of this index is dependent on the degree of ICPC-code registration (e.g. for ‘general deterioration’) by general practitioners. Also, the clinical value of this FI remains challenging, as the total score of the FI does not necessarily portrays a patient’s (physical, cognitive) functional abilities. Further studies should focus on the functional assessment of frailty in relation to LLD use. This is likely to give a better reflection of physicians’ lipid lowering treatment decisions in relation to patients’ actual frailty status. Nonetheless, to get a better understanding of a patient’s overall health status, we

repeated our analyses using number of chronic disease and primary care visits. Results of these analyses were consisted with those using the FI. The number of older adults having pre-existing CVD is likely to underestimate the total number of patients who have ever experienced a cardiovascular event during their lives. This is of importance for an acute myocardial infarction and a TIA, as these are transient cardiovascular events. Consequently, only patients who experienced an acute myocardial infarction or TIA (and no other 'chronic' CVD such as a stroke or myocardial infarction >4 weeks ago) after 2011 were categorised as having a CVD at baseline. This could explain the relatively high number of older patients without CVD taking antiplatelet therapy.

In conclusion, this study indicates that general practitioners are less likely to initiate and/or more likely to discontinue lipid lowering therapy with increasing age in the oldest old. In contrast to our hypothesis, frail older adults seem to be more likely to be prescribed a LLD than non-frail older adults. Frail older adults are less likely to benefit from LLDs and more likely to be harmed. Thus, decision-making on LLDs in older patients calls for a patient-centred approach in which competing risks, time-to-benefit compared with the estimated life expectancy and level of frailty must be taken into account.

Declaration of Conflict of Interest: None.

Declaration of Sources of Funding: None.
Supplementary data

Supplementary Data - docx file

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Figures and Tables

Table 1. Baseline characteristics in older adults with (n = 55,309) and without (n = 189,019) CVD, taking and not taking a lipid lowering drug.

	With CVD		Without CVD	
	Use lipid lowering drug		Use lipid lowering drug	
	Yes (n = 38,049)	No (n = 17,260)	Yes (n = 67,428)	No (n = 121,563)
Demographics				
Age, years (mean, SD)	77.3 (6.0)	81.2 (7.6)	76.0 (5.5)	77.3 (6.9)
Gender (% male)	56.2	42.7	44.9	39.7
CV risk factors[a]				
BMI (mean, SD)	27.8 (4.5)	26.8 (4.6)	28.4 (4.7)	27.3 (4.7)
Current smoker (%)	23.2	17.2	28.2	13.5
Diabetes (%)	33.2	19.5	38.3	10.0
Hypercholesterolaemia (%)	30.7	12.4	33.9	7.2
Hypertension (%)	26.8	22.7	16.6	9.2
SBP (mean, SD)	140 (20)	141 (21)	141 (18.8)	144 (20)
DBP (mean, SD)	76 (10)	76 (11)	78 (10)	79 (10)
Total cholesterol (mean, SD)	4.4 (1.0)	5.3 (1.1)	4.7 (1.2)	5.5 (1.0)
LDL (mean, SD)	2.4 (0.9)	3.2 (0.9)	2.7 (1.0)	3.4 (0.9)
HDL (mean, SD)	1.3 (0.4)	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)
Triglycerides (mean, SD)	1.5 (0.8)	1.5 (0.8)	1.6 (0.8)	1.4 (0.8)
CVRM drugs				
Antihypertensive drugs (%)	77.1	65.8	66.7	37.5
Antidiabetic drugs (%)	25.9	11.3	30.3	7.2
Antiplatelet therapy (%)	73.5	44.3	36.1	12.5
Frailty				
Total number of deficits (median, IQR)	5 (4–7)	5 (3–7)	4 (2–5)	2 (1–4)
Drubbel *et al.* Frailty index (median, IQR)	0.14 (0.11–0.19)	0.14 (0.08–0.19)	0.11 (0.06–0.14)	0.06 (0.03–0.11)
Comorbidities				
Total number of chronic diseases (mean, SD)	11.9 (8.6)	9.3 (6.5)	9.6 (5.5)	8.8 (6.8)
0–1 (%)	2.2	2.8	7.5	24.6
2–3 (%)	9.5	13.6	16.6	22.5
4–6 (%)	21.6	27.9	26.0	24.3
≥7 (%)	66.7	55.7	50.0	28.6
Medication				
Total number of drugs (mean, SD)	11.6 (5.9)	9.9 (7.6)	8.9 (6.8)	9.6 (5.5)
0 drugs (%)	28.5	40.9	28.6	40.4
1–4 (%)	21.7	22.2	25.4	31.6
5–9 (%)	15.5	13.7	18.9	14.6
≥10 (%)	34.3	23.3	27.1	13.4
Polypharmacy (%)	49.7	37.0	46.0	23
Consultation primary care				
Total number of consultations (mean, SD)	9.4 (8.8)	10.2 (10.0)	8.1 (7.8)	8.1 (7.8)

CVD, cardiovascular disease; CV, cardiovascular; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVRM, cardiovascular risk management.

[a]Data on blood pressure were available in 75% of patients with CVD and in 65% of patients without CVD. Data on cholesterol were available in 63% of patients with CVD and in 54% of patients without CVD.

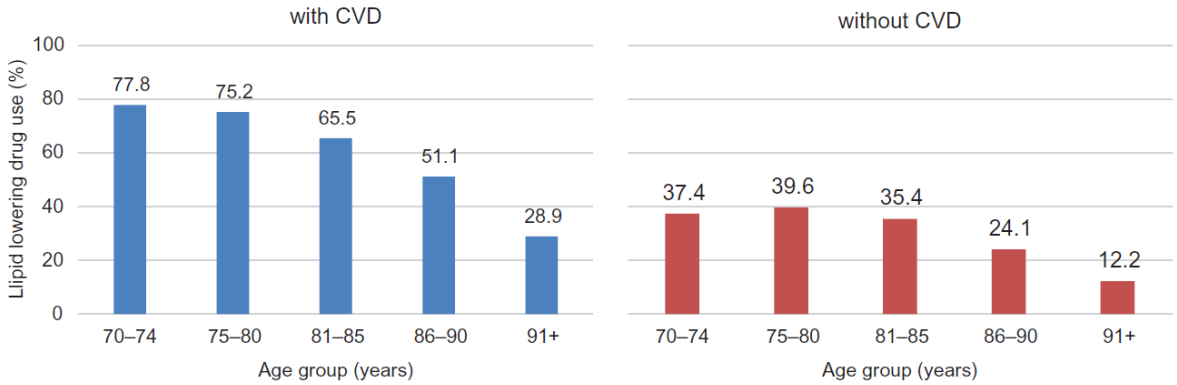

Figure 1. Use of lipid lowering drugs (%), according to age in older adults with CVD at baseline (n = 55,330), and without CVD at baseline (n = 188,998).

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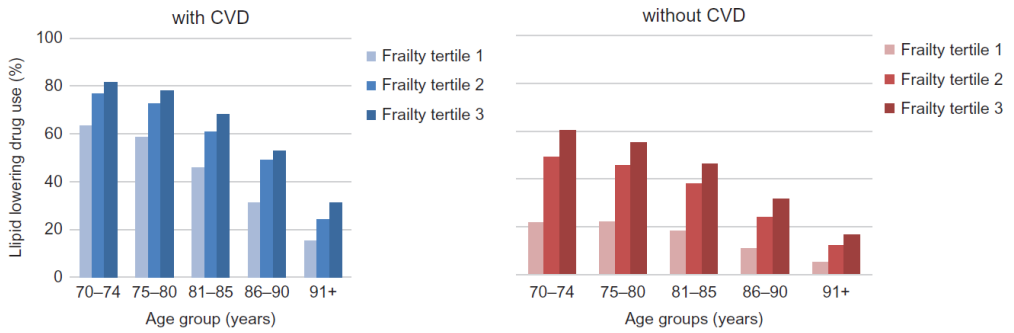

Figure 2. Use of lipid lowering drugs (%), according to age and frailty in older adults with CVD at baseline (n = 55,330), and without CVD at baseline (n = 188,998).

Supplemental data

Appendix 1 – Nivel- PCD data collection
Appendix 2 – Medication
Appendix 3 – (risk factors for) cardiovascular disease
Appendix 4 – Construction of the frailty index (FI)
Appendix 5 – Supplemental figure 1
Appendix 6 – Supplemental figure 2
Appendix 7 – Supplemental figure 3

Appendix 1 - Nivel- PCD data collection

General practitioners recorded medical information using the International Classification of Primary Care (ICPC)-1 coding system(1). For each patient, information on age, gender, physical examination, blood tests, morbidity, medication, and total number of primary care visits was extracted from the EHRs. For each patient, baseline was defined as the date of initial data registration.
This study has been approved according to the governance code of Nivel-PCD, under number NZR-00317.036. Dutch law allows the use of electronic health records for research purposes under certain conditions. According to this legislation, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (Dutch Civil Law, Article 7(2)).

Appendix 2- Medication

Data on prescriptions initiated by specialized doctors working in hospitals were only available if the refill prescription was written by the general practitioner. A great number of patients, especially after recently experiencing a cardiovascular event, receive their first lipid lowering drug prescription by other doctors than their primary care physician. Consequently, a delay between being prescribed a lipid lowering drug and receiving this as a refill prescription via a general practitioner existed in the database. To prevent an underestimation of the number of patients taking a lipid lowering drug, we defined ‘being prescribed a lipid lowering drug’ (yes/no) as ‘having at least one lipid lowering drug prescription during a patient’s entire period of follow-up’. To evaluate whether these drugs were giving in a primary or secondary preventive care setting, we evaluated whether patients using these drugs had been diagnosed with one or more atherosclerotic CVDs (see below) at baseline. For the assessment of polypharmacy and total number of drugs used at baseline, data during the first year of follow-up was used. Polypharmacy was defined as use of 5 or more different drugs (3).

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Antihypertensive drugs were classified as diuretics (ATC-code C03A-E), beta blockers (C07), calcium channel blockers (C08C), and drugs inhibiting the renin-angiotensin system (RAAS, C09). Drugs represented by ATC-code 'A10' and 'B01AC' were categorized as antidiabetic and antiplatelet drugs, respectively.

Appendix 3- (risk factors for) cardiovascular disease

Cardiovascular disease

Presence of one or more of the following atherosclerotic related CVDs (ICPC-code) at baseline was defined as 'having a CVD': angina pectoris (K74), acute myocardial infarction (K75), myocardial infarction >4 weeks ago (K76), transient ischemic attack (TIA, K89), stroke (K90), and peripheral artery disease (K92). An acute myocardial infarction and a TIA are categorized as transient CVDs in the Nivel database. Thus, data on the occurrence of these events are only available if a patient experienced the event during the period of data registration. Compared to angina pectoris, a TIA and peripheral vascular disease, an acute myocardial infarction and stroke are seen as compelling indications for lipid lowering drugs. For the assessment of total number of chronic disease at baseline, data on diseases classified as 'chronic' in the Nivel dataset were used.

Cardiovascular risk factors

For the assessment of blood pressure (mmHg), serum cholesterol levels (mmol/L), and Body Mass Index (BMI, kg/m2) the first available measurement during the first year after baseline was used. Blood pressure and cholesterol could have been measured before, during or after treatment with antihypertensive and lipid lowering drugs. Smoking prevalence was assessed using data on smoking status (yes/no) during the first year after baseline. Presence of diabetes, hypertension and hypercholesterolemia during the first year after baseline was based on ICPC-codes T90, K86/K87, and T93 respectively.

Appendix 4 – Construction of the frailty index (FI)

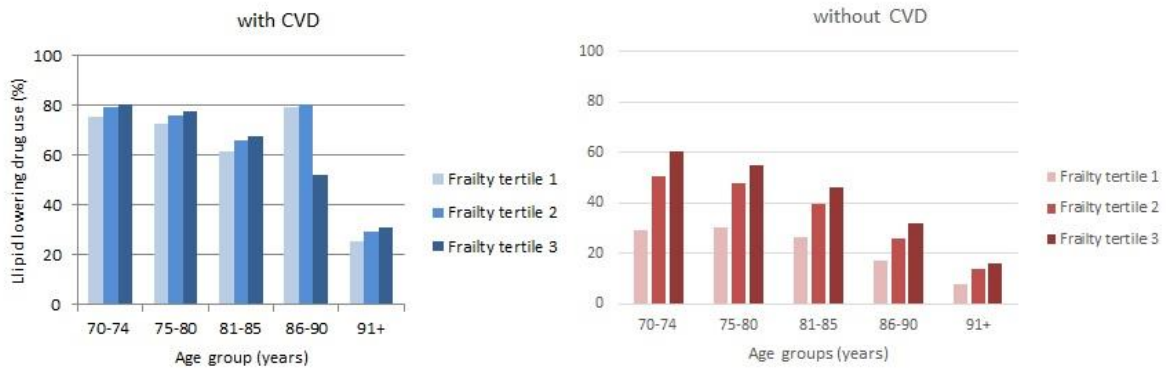
This FI is based on 140 ICPC-codes identifying 35 frailty deficits. Adding polypharmacy, defined as chronic use (≥3 prescriptions during 1 year) of 5 or more different drugs, sums up to a total of 36 deficits. ICPC-items received a positive score if they pertained to a 'chronic' disease (e.g. heart failure, osteoarthritis) or if they had occurred in the past year (e.g. depression, weight loss). For ease of interpretation, the summed positive scores (0-36) are converted to a scale ranging from 0-1 (e.g. 5 deficits produce a FI of 0.14). The construction of this FI is described in greater detail elsewhere(4). For the present study, we divided the total FI score into tertiles..

For this modified FI, the ICPC-codes identifying patients with an acute myocardial infarction, angina pectoris, stroke or TIA were excluded. With this, the total score of frailty deficits summed up to 34. Consequently, when calculating the total score on the FI the total number of deficits present was divided by 34 instead of 36.

Patients with (multiple risk factors for) CVD are regularly prescribed numerous preventive drugs such as lipid lowering drugs, (several) antihypertensive drugs, and platelet inhibiting drugs. Consequently, these patients are likely to be exposed to polypharmacy and therefore more likely to get a higher score on the Drubbel-frailty index. In order to evaluate the extent of this effect we performed additional sensitivity analyses in which we excluded the 'polypharmacy' deficit. Accordingly, we divided the total number of deficits by 35.

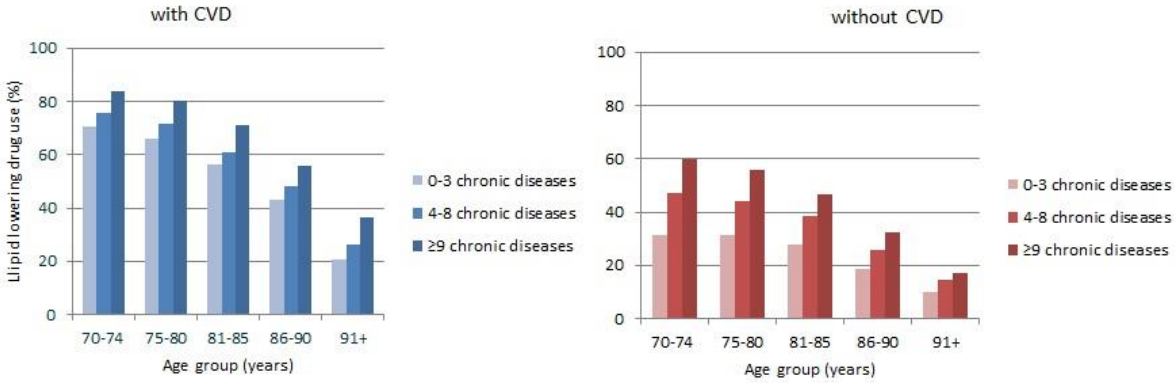
Kleipool, E.E.F., Nielen, M.M.J., Korevaar, J.C., Harskamp, R.E., Smulders, Y., Serné, E., Thijs, A., Peters, M.J.L., Muller, M. Prescription patterns of lipid lowering agents among older patients in general practice: an analysis from a national database in the Netherlands. Age and Ageing: 2019, 4, p. 577-582

Appendix 5 – Figure 1



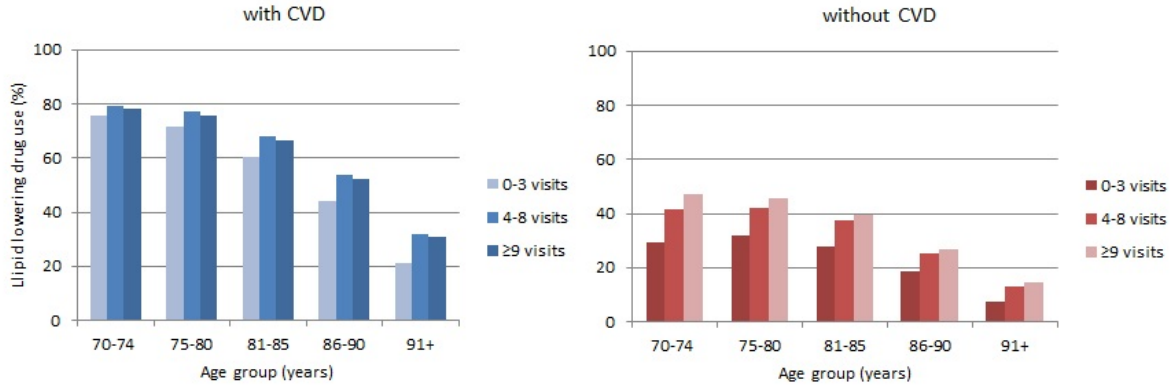
Use of lipid lowering drugs (%), according to frailty using a modified frailty index (excluding the CVD ICPC-codes also included in our definition of 'having preexisting CVD') in older adults with CVD at baseline (n=55,330), and without CVD at baseline (n=188,998).

Appendix 6 – Figure 2



Use of lipid lowering drugs (%), according to age and number of chronic diseases at baseline in older adults with CVD at baseline (n=55,330), and without CVD at baseline (n=188,998).

Appendix 7 – Figure 3



Use of lipid lowering drugs (%), according to age and number of primary care visits during the first year after baseline in older adults with CVD at baseline (n=55,330), and without CVD at baseline (n=188,998).

Kleipool, E.E.F., Nielen, M.M.J., Korevaar, J.C., Harskamp, R.E., Smulders, Y., Serné, E., Thijs, A., Peters, M.J.L., Muller, M. Prescription patterns of lipid lowering agents among older patients in general practice: an analysis from a national database in the Netherlands. Age and Ageing: 2019, 4, p. 577-582

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