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Statin utilization and lipid goal attainment in high or very-high cardiovascular risk patients: Insights from Italian general practice

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ABSTRACT

Background and aims: Statin utilization and lipid goal achievement were estimated in a large sample of Italian patients at high/very-high cardiovascular (CV) risk.

Methods: Patients aged ≥18 years with a valid low-density lipoprotein cholesterol (LDL-C) measurement in 2015 were selected from the IMS Health Real World Data database; non-high-density lipoprotein cholesterol (non-HDL-C) was assessed in those with available total cholesterol measurements. Index dates were defined as the last valid lipid measurement in 2015. Patients were hierarchically classified into mutually exclusive risk categories: heterozygous familial hypercholesterolemia (primary and secondary prevention), atherosclerotic CV disease (including recent acute coronary syndrome [ACS], chronic coronary heart disease, stroke, and peripheral arterial disease), and diabetes mellitus (DM) alone. Statin and non-statin lipid-modifying therapy (LMT) use, and European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guideline-recommended goal attainment, were assessed.

Results: Among 66,158 patients meeting selection criteria, the overall rate of LMT prescriptions was 53.3%, including 7.7% on high-intensity statin therapy. Statin use was highest for recent ACS and lowest for DM alone. LDL-C goal attainment was 16.0% for <1.8 mmol/l and 45.0% for <2.5 mmol/l; 24.3% reached non-HDL-C <2.6 mmol/l and 52.2% were at <3.3 mmol/l. Goal achievement was greatest with high-intensity statin use.

Conclusions: Statin use in this cohort was consistent with previous reports in Italian patients at high/very-high CV risk, and low relative to statin use in other European countries. The low rate of ESC/EAS lipid goal attainment observed was consistent with outcomes of other European studies.

1. Introduction

Despite recent decreases in cardiovascular (CV) mortality, CV disease (CVD) continues to account for most deaths in Italy (~38%), with ischemic heart disease and stroke, in particular, remaining major public health issues (ranking high among causes of years of life lost, causing 6% and 3%, respectively, of the total) [1,2]. Age-standardized 2012 mortality rates for coronary heart disease (CHD) in Italy were 148.0 per 100,000 for men and 82.7 per 100,000 for women [1]. Decreasing low-density lipoprotein cholesterol (LDL-C) with statin therapy has been demonstrated to reduce mortality and improve CV outcomes significantly, both among populations with established CVD and in primary prevention

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groups [3–7]. Moreover, many Italians have high lipid levels; e.g., in one observational study representative of the general Italian adult population aged 40–79, the proportion with hypercholesterolemia was 55.6% [8]. Statins offer demonstrated benefits: randomized controlled trials show that each 1 mmol/l (39 mg/dl) reduction in LDL-C effects a consistent ~22% reduction in CV events across varying CV risk profiles, clinical and demographic characteristics, and baseline LDL-C levels [3]. Furthermore, CV outcomes benefits are greater with high- *versus* moderate-intensity statin therapy [9–11], and statins have been widely shown to be well tolerated and safe [3,12,13]. Nevertheless, in Europe, including Italy, statins remain markedly underutilized relative to other countries and regions, and LDL-C reductions fall notably short of clinical guidelines [14–16].

Statins are recommended by both the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) and Italian guidelines as first-line pharmacological treatment of hypercholesterolemia. When the present study was conducted, the 2011 ESC/EAS cholesterol treatment guidelines were in place, which recommended that patients with very-high CV risk (defined as established CVD, type 1 or 2 diabetes mellitus [DM] with end organ damage, moderate-to-severe chronic kidney disease [CKD], or a 10-year Systematic COronary Risk Evaluation [SCORE] risk ≥10%) achieve an LDL-C treatment goal of <1.8 mmol/l (<70 mg/dl) or, when this goal cannot be achieved, a ≥50% reduction from baseline LDL-C [17]. For patients with high CV risk (defined as markedly elevated single risk factors, or a 10-year risk SCORE ≥5% to <10%) the LDL-C treatment goal was <2.5 mmol/l (<100 mg/dl) [17]. To estimate CV risk, the 2011 ESC/EAS guidelines also recommended measurement of non-high-density lipoprotein cholesterol (non-HDL-C), particularly in patients with DM, metabolic syndrome, or CKD [17], with non-HDL-C targets of <2.6 mmol/l and <3.3 mmol/l (<100 mg/dl and <127 mg/dl) for patients at very-high and high CV risk, respectively. Since the completion of the data extraction for the present study, updated (2016) ESC/EAS guidelines have been released, with minimal differences regarding statin recommendations and related thresholds [18]. The ESC/EAS guidelines affirm that thresholds can be achieved with statin monotherapy in the majority of patients with an elevated CV risk. The Italian national guidelines are also closely aligned, recommending statins for individuals who have already experienced a CV event, including peripheral arterial disease (PAD), with an LDL-C goal of <70 mg/dl, and for those with familial dyslipidemias, DM, CKD, or a 10-year risk SCORE ≥5%, with an LDL-C goal of <100 mg/dl [19].

Despite demonstrated statin benefits, the CV burden in Italy remains high, and the literature describing statin utilization and lipid goal attainment in Italian patients with established CVD is limited [20–22]. The present study assessed real-world evidence of lipid-modifying therapy (LMT) utilization in Italy in 2015 compared with the 2011 ESC/EAS guidelines in place at the time. Using de-identified data from a large sample of primary care electronic medical records (EMRs), LMT utilization and achievement of LDL-C and non-HDL-C ESC/EAS guideline targets are described, within each of the following indications: heterozygous familial hypercholesterolemia (HeFH); atherosclerotic cardiovascular disease (ASCVD), including recent acute coronary syndrome (ACS), chronic CHD, stroke and PAD; and DM.

2. Patients and methods

2.1. Database and cohort selection

A retrospective observational study of a cross-section of Italian patients at high or very-high CV risk was conducted using the IMS Health Real World Database. This database included anonymized EMRs of ~750,000 patients from routine clinical practices of approximately 700 Italian general practitioners (GPs) in 2015. De-identified data pertain to EMRs completed by physicians during patient office visits. This primary care database represents over 2% of the Italian adult population. Validation studies, comparing the information in this database with that available from the Italian Office of National Statistics and other sources in Italy, have demonstrated that the database population is representative of the general population in Italy with respect to age and sex distribution, and the prevalence of chronic conditions such as hypertension, chronic obstructive pulmonary disease, and DM. Prescription volume for selected drug classes, including non-steroidal anti-inflammatory drugs, and psychotropic, alimentary tract, and cardiovascular medicines, is also comparable to national statistic usage [23].

Inclusion criteria were: a valid LDL-C measurement in 2015 (the last 2015 LDL-C measurement was designated as the index date); ≥18 years of age; and ≥1 high/very-high CV risk condition as defined by the 2011 ESC/EAS guidelines [17]. At least 2 years of continuous enrollment in the database before the index date were required to classify patients, and to assess current LMT and prior LMT for patients not currently prescribed treatment.

2.2. Determination of ASCVD and non-ASCVD categories

Six high/very-high CV risk mutually exclusive groups were defined in the pre-index period, using the following hierarchy: 1) clinically diagnosed HeFH (defined as ≥4 points on the Dutch Lipid Clinic Network diagnostic criteria [DLCNDC; Supplemental Table 1], as a reflection of the 87.6% of patients with DLCNDC scores ≥4 to <6); [24] 2) recent ACS (myocardial infarction [MI] or unstable angina requiring hospitalization within the 12 months before the index date); 3) chronic CHD (history of MI, stable or unstable angina, coronary revascularization, or another CHD diagnosis); 4) stroke (including transient ischemic attack); 5) PAD (peripheral vascular disease by non-coronary atherosclerotic disease, abdominal aortic aneurysm, and carotid artery stenosis); and 6) DM (all severities, including both type 1 DM and type 2 DM). Groups were identified using GP-recorded diagnosis codes per the International Classification of Diseases, Ninth Revision (ICD-9; Supplemental Table 2).

Patients with the hierarchical conditions recent ACS, chronic CHD, stroke, and PAD are jointly referred to as 'ASCVD', while data for patients with DM alone (referred to as 'non-ASCVD') and patients with HeFH (comprising both HeFH patients under primary prevention and HeFH patients under secondary CV prevention), are presented separately.

2.3. Determination of LMT treatment

Current LMT treatment was assumed if, for a recorded prescription of any length, there was evidence of supply on or within 30 days before the index date. Patients not "currently treated" but with evidence of supply for an LMT prescription >30 days before the index date were considered to have a history of LMT treatment (Fig. 1). Patients not currently treated and without history of LMT on the index date or during the 2 years before the index date were considered to have no evidence of LMT treatment.

LMTs were classified as statin or non-statin LMT. Statin therapy, alone or in combination with non-statin LMT, was stratified as either high intensity (atorvastatin 40 mg–80 mg or rosuvastatin 20 mg–40 mg) or low to moderate intensity (all other statins and doses). Non-statin LMT included ezetimibe, niacin (nicotinic acid), fibrates (gemfibrozil, fenofibrate, fenofibric acid, ciprofibrate, and

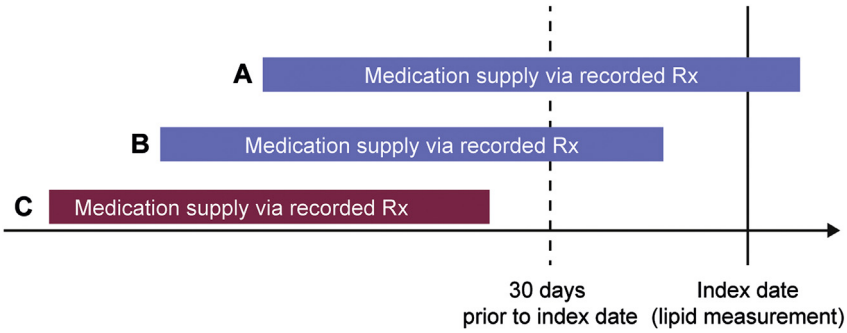

Fig. 1. Lipid-modifying therapy prescription status as of the index date.
Reproduced with permission from Steen et al. [50]. Blue bars representing scenarios A and B (medication supply via recorded Rx on or within 30 days prior to the index date) define the patient as being treated as of the index date. The red bar representing scenario C (medication supply via recorded Rx more than 30 days prior to the index date) defines the patient as not being treated as of the index date. Rx, prescription. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

bezafibrate), and bile acid sequestrants (cholestyramine, colesevelam, and colestipol).

2.4. Determination of LDL-C and non-HDL-C levels

Achievement of 2011 ESC/EAS lipid goals for high and very-high CV risk; i.e., LDL-C <2.5 mmol/l and <1.8 mmol/l, and non-HDL-C <2.6 mmol/l and <3.3 mmol/l, respectively, was assessed. The current LMT and lipid values were assessed concurrently (i.e., overlapping with or actually on the index date), to ensure that lipid levels best reflected the impact of the current treatment regimen.

2.5. Statistical analysis

Descriptive statistical analyses were conducted for this study. Demographic, clinical, and medication characteristics, LMT utilization, and achieved lipid levels were described via proportions and mean ± standard deviation (SD), as appropriate. All analyses were conducted with SAS® V.9.4.

3. Results

The inclusion criteria were met by 66,158 patients (Fig. 2), comprising 2081 (3.1%) with clinically diagnosed HeFH, 36,120 (54.6%) with ASCVD, and 27,957 (42.3%) with DM alone. Among the hierarchical ASCVD subcategories, recent ACS was identified for 736 patients (1.1%), chronic CHD for 19,622 (29.7%), stroke for 9721 (14.7%), and PAD for 6041 (9.1%). The mean age was 70.7 years and 59.5% were male (Table 1).

3.1. LMT utilization in 2015

In total, 53.3% of patients were prescribed LMT, and 51.0% were prescribed statin therapy (7.7% high-intensity statins, 43.3% low-to-moderate intensity statins, and 2.3% non-statin LMT; Table 2). Statins were mostly prescribed as monotherapy (96.7% with high-intensity and 93.1% low-to-moderate intensity statin). Approximately 2.8% of patients on high-intensity and 6.5% on low-to-moderate intensity statins had concomitant ezetimibe prescriptions.

3.1.1. ASCVD population

Approximately 61.1% of patients with ASCVD were prescribed LMT and 58.9% were prescribed statins. Among the ASCVD hierarchical risk categories, patients with a recent ACS had the highest

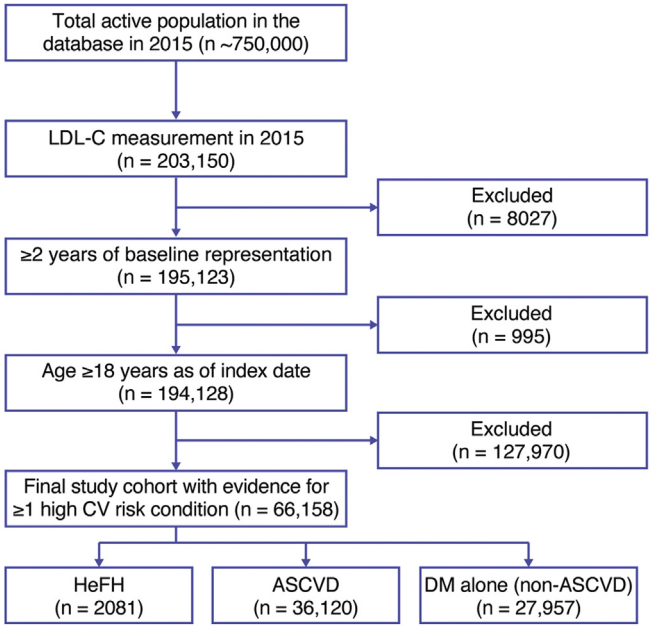

Fig. 2. Italian cohort selection.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

prescription rates for any statin and for high-intensity statin, followed by CHD, stroke, and PAD (Table 2).

Among patients with ASCVD treated with non-statin LMT monotherapy, ezetimibe was most commonly prescribed among patients with recent ACS, and decreasingly so for patients with CHD, stroke, and PAD (Table 2). LMT non-treatment rates are also shown in Table 2.

3.1.2. DM alone (non-ASCVD population)

Among patients with DM alone, 42.4% were prescribed LMT and 39.9% were prescribed statins. Only 2.4% had prescriptions for high-intensity statins, and only 24.2% of those treated with non-statin LMT received ezetimibe (Table 2). In total, 57.5% had no evidence of LMT use on the index date, of whom 68.3% also had no indication of having had prescriptions for LMT within the 2 years before.

3.1.3. HeFH patients

In total, 64.7% of HeFH patients were prescribed LMT and 62.5%

Table 1
Baseline characteristics for the overall study cohort and hierarchical CV risk subgroups.

	Total cohort N = 66,158	ASCVD n = 36,120				DM alone n = 27,957	HeFH[a] n = 2081
		Recent ACS n = 736	Chronic CHD n = 19,622	Stroke n = 9721	PAD n = 6041		
Demographic characteristics							
Age, years, mean (SD)	70.7 (11.3)	67.4 (12.8)	72.8 (10.3)	73.4 (9.4)	72.7 (10.4)	68.4 (11.9)	63.9 (12.6)
Male, %	59.5	41.7	49.2	64.7	62.1	62.9	76.0
Prevalent CV risk conditions, %							
HeFH	3.1	0	0	0	0	0	100
Recent ACS	1.1	100	0	0	0	0	0.3
Chronic CHD	30.7	57.6	100	0	0	0	13.9
Stroke/TIA	19.5	10.7	14.7	100	0	0	9.7
PAD	15.8	11.1	14.4	13.7	100	0	8.5
DM	62.5	28.0	39.0	33.5	31.9	100	17.5
Comorbidities of interest, %							
Hypertension	76.3	69.4	76.5	81.7	76.1	75.6	60.7
History of CHF[b]	5.9	7.1	10.8	4.3	4.7	3.5	2.5
Dementia[b]	1.5	0.5	1.8	1.6	1.7	1.3	1.0
COPD[b]	16.7	16.6	20.6	17.8	21.7	12.9	11.0
Musculoskeletal pain	89.3	84.1	90.1	91.7	93.3	87.3	88.0
Moderate/severe liver disease[b]	0.3	0.4	0.2	0.2	0.4	0.4	0
Concomitant medications, %							
Beta-blockers	50.3	80.0	77.2	41.6	38.0	37.5	36.3
ACEIs/ARBs	77.1	83.8	86.0	77.1	71.8	73.3	56.6
Clopidogrel	13.2	31.3	32.3	8.9	7.9	2.4	5.7

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; ASCVD; atherosclerotic cardiovascular disease; CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; PAD, peripheral arterial disease; SD, standard deviation; TIA, transient ischemic attack.
[a] HeFH includes primary prevention HeFH patients (no ASCVD) and secondary prevention HeFH patients (with ASCVD).
[b] Based on Quan-Charlson comorbidity scale components.

Table 2
Use of LMT overall and by hierarchical disease categories.

%	Total cohort N = 66,158	ASCVD n = 36,120				DM alone n = 27,957	HeFH[a] n = 2081
		Recent ACS n = 736	Chronic CHD n = 19,622	Stroke n = 9721	PAD n = 6041		
High-intensity statin	7.7	56.1	15.9	5.5	3.6	2.4	6.7
Monotherapy	96.7	97.8	96.3	97.9	95.8	97	95.7
Plus ezetimibe	2.8	1.9	3.3	1.7	1.9	2.4	2.9
Plus other non-statin LMT	0.5	0.2	0.4	0.4	2.3	0.6	1.4
Low-to-moderate intensity statin	43.3	26.6	49.8	49.4	36.7	37.5	55.8
Monotherapy	93.1	87.2	90.5	94.4	95.3	95.3	87.2
Plus ezetimibe	6.5	12.2	9.3	5.2	4.4	4.2	12.7
Plus other non-statin LMT	0.4	0.5	0.3	0.3	0.3	0.5	0.1
Nonstatin LMT only	2.3	1.9	2.5	2.2	1.6	2.5	2.2
Ezetimibe	41.0	92.9	58.5	45.2	35.7	24.2	91.3
Other LMT	59.0	7.1	41.5	54.8	64.3	75.8	8.7
Evidence of prior LMT	18.3	7.5	17.4	19.0	17.8	18.2	28.1
High-intensity statin	11.8	54.4	22.6	7.5	7.2	6.0	17.1
Low-to-moderate intensity statin	83.4	43.5	74.5	89.4	88.3	86.4	82.3
Nonstatin LMT	4.9	1.8	2.8	3.4	4.6	7.6	0.6
No evidence of prior LMT	28.4	7.9	14.5	24.0	40.3	39.3	7.2

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; LMT, lipid-modifying therapy; PAD, peripheral arterial disease.
Numbers in the gray bars denote absolute percentages, and add up to 100% vertically. Numbers in the white bars are relative percentages of the absolute percentages in the gray bars. ASCVD subgroups represent hierarchical categorization.
[a] HeFH includes primary prevention HeFH patients (no ASCVD) and secondary prevention HeFH patients (with ASCVD).

were prescribed statins (Table 2). Ezetimibe was the most common non-statin LMT, prescribed in 91.3% of patients with HeFH receiving non-statin LMT treatment. Regarding prior treatment for HeFH, 20.3% of HeFH patients without current LMT also had no evidence of treatment in the 2-year period before the index date.

3.2. ESC/EAS-recommended lipid goal achievement

In the overall cohort, mean (SD) LDL-C was 2.7 (1.0) mmol/l, and 16.0% and 45.0% achieved guideline-recommended LDL-C goals of <1.8 mmol/l and <2.5 mmol/l, respectively. Mean (SD) non-HDL-C

was 3.4 (1.1) mmol/l, with 24.3% achieving the <2.6 mmol/l threshold and 52.2% achieving the <3.3 mmol/l threshold.

As expected, observed goal achievement was higher with high-intensity than with low-to-moderate intensity statins (34.1% vs 23.0% for LDL-C <1.8 mmol/l and 69.9% vs 61.3% for LDL-C <2.5 mmol/l; Table 3). Correspondingly, mean LDL-C and non-HDL-C levels were lower for patients treated with high-intensity versus low-to-moderate intensity statins (Supplemental Table 3). Mean LDL-C and non-HDL-C levels were 2.9 mmol/l and 3.7 mmol/l for patients receiving non-statin LMT and 3.1 mmol/l and 3.7 mmol/l, respectively, among patients untreated on the index date.

3.2.1. ASCVD population

Among all ASCVD risk conditions, mean LDL-C was lowest for patients with recent ACS (2.1 mmol/l), followed by CHD (2.5 mmol/l), stroke (2.8 mmol/l), and PAD (2.9 mmol/l). The recent ACS group also had the highest proportion of LDL-C goal achievers (42.7% for <1.8 mmol/l and 76.2% for <2.5 mmol/l), followed by CHD (22.7% and 56.3%), stroke (12.7% and 40.8%), and PAD (11.1% and 36.0%).

Mean non-HDL-C level was 2.6 mmol/l in the recent ACS group, 3.1 mmol/l in the CHD group, 3.4 mmol/l for stroke, and 3.5 mmol/l for PAD. As with LDL-C, achievement of non-HDL-C goals was highest among patients with recent ACS (55.1% for <2.6 mmol/l and 80.1% for <3.3 mmol/l), followed by CHD (32.9% and 62.3%) and stroke (21.4% and 50.3%), and was lowest among PAD patients (18.3% and 45.6%).

Higher LDL-C and non-HDL-C goal achievement occurred with more intensive statin treatment consistently across all ASCVD hierarchical categories (Table 3).

3.2.2. DM alone (non-ASCVD population)

Among patients with DM alone, mean LDL-C was 2.7 mmol/l, with 14.0% achieving LDL-C <1.8 mmol/l and 42.9% achieving LDL-C <2.5 mmol/l. Mean non-HDL-C was 3.4 mmol/l, and non-HDL-C goals were attained by 21.3% of patients for <2.6 mmol/l and 49.9% for <3.3 mmol/l.

LDL-C goal achievement of <2.5 mmol/l was similar among DM patients receiving high-intensity and low-to-moderate intensity statins; and likewise for non-HDL-C <3.3 mmol/l threshold achievement (Table 3).

3.2.3. HeFH patients

Among patients with clinically diagnosed HeFH, mean LDL-C was 5.4 mmol/l, with less than 1% of patients achieving LDL-C <1.8 mmol/l and <2.5 mmol/l. Mean non-HDL-C was 5.9 mmol/l, and proportions achieving non-HDL-C goals were likewise small (1.1% and 2.3% for <2.6 mmol/l and <3.3 mmol/l, respectively). Due to these low goal achievement rates, no differences by LMT use were observed (Table 3).

Table 3
Achievement of lipid goals by CV risk category and treatment type.

%	Total cohort N = 66,158	ASCVD n = 36,120				DM alone n = 27,957	HeFH[a] n = 2081
		Recent ACS n = 736	Chronic CHD n = 19,622	Stroke n = 9721	PAD n = 6041		
LDL-C<1.8 mmol/l	**n = 10,573**	**n = 314**	**n = 4451**	**n = 1234**	**n = 670**	**n = 3902**	**n = 2**
High-intensity statin[b]	34.1	52.3	36.1	24.9	29.6	29.6	0
Low-to-moderate intensity statin[b]	23.0	37.8	28.0	18.7	18.0	23.7	0.2
Nonstatin LMT only	10.0	7.1	12.5	5.2	8.2	10.7	0
No LMT at index date	6.8	20.4	8.4	4.7	5.6	7.1	0
LDL-C<2.5 mmol/l	**n = 29,756**	**n = 561**	**n = 11,044**	**n = 3969**	**n = 2176**	**n = 12,004**	**n = 2**
High-intensity statin[b]	69.9	87.1	73.5	63.8	64.3	63.7	0
Low-to-moderate intensity statin[b]	61.3	75.5	68.3	56.4	55.5	64.8	0.2
Nonstatin LMT only	32.8	28.6	39.2	23.8	27.6	34.0	0
No LMT at index date	26.3	43.4	30.2	20.8	22.2	28.2	0
LDL-C≥2.5 mmol/l	**n =36,402**	**n = 175**	**n = 8578**	**n = 5752**	**n = 3865**	**n = 15,953**	**n = 2079**
High-intensity statin[b]	30.1	12.8	26.5	36.2	35.6	36.3	100
Low-to-moderate intensity statin[b]	38.7	24.5	31.7	43.6	44.5	35.2	99.8
Nonstatin LMT only	67.2	71.4	60.8	76.2	72.4	34.0	100
No LMT at index date	73.7	56.6	69.8	79.2	77.8	28.2	100
%	Total cohort N=61,336[c]	ASCVD n = 33,510				DM alone n=26,065[c]	HeFH[a] n=1,761[c]
		Recent ACS n=668[c]	Chronic CHD n=18,218[c]	Stroke n=9001[c]	PAD n=5623[c]		
Non-HDL-C <2.6 mmol/l	**n = 14,891**	**n = 368**	**n = 5992**	**n = 1928**	**n = 1027**	**n = 5557**	**n = 19**
High-intensity statin[b]	44.4	63.9	46.7	34.1	38.0	39.8	3.4
Low-to-moderate intensity statin[b]	34.6	52.0	40.5	31.1	28.9	34.9	0.8
Nonstatin LMT only	12.7	7.1	17.9	9.2	5.6	11.9	0
No LMT at index date	12.1	34.3	15.3	9.5	10.7	12.1	1.1
Non-HDL-C<3.3 mmol/l	**n = 32,012**	**n = 535**	**n = 11,349**	**n = 4528**	**n = 2562**	**n = 12,997**	**n = 41**
High-intensity statin[b]	74.2	89.4	77.2	69.2	66.0	70.6	3.4
Low-to-moderate intensity statin[b]	68.6	77.1	74.5	66.4	65.5	71.1	2.2
Nonstatin LMT only	36.3	35.7	39.7	30.8	36.0	37.8	0
No LMT at index date	34.3	56.9	37.6	30.5	32.0	35.7	2.5

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV. cardiovascular; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LMT, lipid-modifying therapy; non-HDL-C, non-high-density lipoprotein cholesterol; PAD, peripheral arterial disease.

[a] HeFH includes primary prevention HeFH patients (no ASCVD) and secondary prevention HeFH patients (with ASCVD).

[b] Statins in monotherapy and combination therapy.

[c] Non-HDL-C measurements were missing for a portion of each CV risk group.

4. Discussion

Both the 2014 Italian national guidelines [19] and the ESC/EAS guidelines [17,18] recommend that all patients at CV risk should receive the highest-intensity statin needed to reach their target LDL-C levels. This current study, conducted in a general practice population in Italy at high or very-high risk for ASCVD events using a large primary care EMR database, sought to provide additional evidence regarding LMT utilization and lipid goal attainment in Italy. Relative to other European countries, we observed low percentages of Italian patients who received any LMT (53.3%) while being at high or very-high risk of CV events, thus confirming that Italy remains a comparatively low user of statins despite comparable CV risks. Another observation of the present study was the low percentage of high-intensity statin users (7.7%), even for individuals classified as affected by severe genetic hypercholesterolemia (e.g. HeFH) or in those at very-high CV risk. A possible explanation may be related to the fact that the 2014 Italian national guidelines strongly recommend use of low-to-moderate intensity statin versus high-intensity statin as first prescription in untreated patients.

Historically, overall statin use in Italy has grown significantly over the past decade, including a nearly two-fold increase from 2004 to 2010 [25], irrespective of a restriction of reimbursement to only high CV risk patients (defined as a ≥20% 10-year risk of a first CV event, according to the CV risk chart of the *Istituto Superiore di Sanità* [26], or established ASCVD or DM) by the Italian Medicine Agency (*Agenzia Italiana del Farmaco*) in 2004 [27]. However, in their 2013 analysis of health metrics, the Organisation for Economic Co-operation and Development (OECD) found that Italy ranked fifth-lowest among 23 member countries in terms of defined daily dose of LMT per 1000 population, but 13th highest among 34 countries and above the OECD average for hospital discharges for circulatory diseases per 1000 population. Italy is also 21st and 11th for highest mortality among 33 countries related to ischemic heart disease and cerebrovascular disease, respectively [28].

In the present study, the highest rate of statin use was associated with patients with a recent history of ACS (82.7%), and this is consistent with previous publications [29,30]. Fewer ACS patients in our study received high-intensity statins (56.1%) than those in the studies by Maggioni et al. (84.9%) [29] and Degli Esposti et al. (86.0%) [30], even though, with the patent for atorvastatin having expired in November 2011, statins have since become much cheaper for health services.

The proportion of CHD patients prescribed statins in our study in 2015 (65.7%) was consistent with prescription rates after hospital discharge in three earlier post-MI study cohorts [21,31–33]. A subanalysis of PAD statistics in the multinational Prevalence of peripheral Arterial disease in subjects with moderate CVD risk, with No overt vascular Diseases nOR diAbetes mellitus (PANDORA) study (2011) [34] showed very-low (6.5%) statin use in the Italian PAD cohort compared with our finding of 40.3%.

The percentage of patients with DM prescribed statins in our study (39.9%) has shown no change since a 2008 study by Modesti et al. evaluating eight Italian primary care practices [35], which predated the 2011 ESC/EAS guidelines, and in which only a third of patients were prescribed statins. Despite the demonstrated benefit of statins in DM patients, the post-MI study by Monaldi et al. [31] found that the presence of DM significantly reduced the likelihood of statin treatment both in hospital and at follow-up.

The aforementioned recommendation of the 2014 Italian national guidelines for use of low-to-moderate statin as first prescription might have contributed to the continuing low level of lipid goal attainment observed in this cohort of Italian patients at high or very-high CV risk. Overall, 55.0% were not at the less stringent ESC/EAS high CV risk LDL-C goal of <2.5 mmol/l; despite the greater probability of goal achievement with increasing statin intensity, 30.1% of patients taking high-intensity statins failed to achieve the high CV risk LDL-C target and 65.9% failed to achieve the very-high risk target (<1.8 mmol/l). This is one of the few studies [36] that measures non-HDL-C goal achievement in an Italian cohort. Overall, 52.2% had non-HDL-C levels <3.3 mmol/l (ESC/EAS high CV risk target) and 24.3% had non-HDL-C levels <2.6 mmol/l (very-high CV risk target).

Similar studies have been conducted in other European countries. The Spanish SAFEHEART Registry study found that 11.2% of familial hypercholesterolemia patients achieved LDL-C <2.5 mmol/l despite 71.8% of patients being on maximal LMT; this number increased to 22.4% over the 5-year follow-up [37]. In studies by Pijlman et al. (Netherlands) [38] and Béliard et al. (France) [39], LDL-C <2.5 mmol/l was achieved in 20.9% and 10.4% of HeFH patients, respectively. In the latter study, the rate of goal achievement with maximal LMT was 18.8%.

Our study's results are consistent with evidence of ESC/EAS goal achievement seen in European statin data [15,16,40,41]. The Dyslipidemia International Study (DYSIS) [40], which evaluated LDL-C goal achievement in European (n = 31,773) and Chinese (n = 25,317) patients treated with statins, identified by EAS/ESC criteria as being at very-high CV risk, found a 35.2% rate of goal achievement (<1.8 mmol/l) among the European cohort. Goal achievement in EUROASPIRE IV (study data collected in 2014–2015) in all patients (86.0% on statins) was 19.3% for LDL-C <1.8 mmol/l and 57.8% for <2.5 mmol/l [41]. Achievement for the high-intensity and low-to-moderate intensity statin groups were 26.6% and 17.5%, respectively, for LDL-C <1.8 mmol/l and 67.9% and 59.4%, respectively, for LDL-C <2.5 mmol/l.

Statin underutilization is a multifactorial issue. For example, reimbursement policy decisions have previously impacted consumption of statins in Italy, as demonstrated by Damiani et al. [42]. As emphasized by an Italian intersociety position paper and in several Italian studies, adherence is another fundamental element of underutilization [43]. Statin intensity was identified by Maggioni et al. [29] as a factor in adherence in a population of patients with both ACS and DM. Adherence, defined by Maggioni et al. as the correct daily dosage at 1-year follow-up, was increased with high-intensity statin use versus low-to-moderate intensity statins (67.1% vs 38.9%). However, since the data source in our study relies largely on prescriptions, it was not possible to assess adherence in a systematic manner.

Strategies to maximize statin use in high CV risk patients are critical to achieve the greatest possible reduction of CV outcomes. Statins and non-statin LMT should be optimized to attain lipid goals, such as those outlined in the ESC/EAS and other guidelines [17]. Combination therapy with statins and ezetimibe was shown in the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study to reduce CV events in patients with a recent ACS to a greater degree than statin alone [5]. New classes of LMT are also emerging as therapeutic options in patients at high CV risk. The European Medicines Agency has approved the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors alirocumab and evolocumab, which have been shown to lower LDL-C by 50%–70% [44]; PCSK9 inhibitors have subsequently shown cardiovascular benefits [45,46].

4.1. Limitations

As the study evaluated patients in primary care, results may not be generalizable to high or very-high CV risk patients being treated by a specialist. Secondly, the use of LMT was based on prescriptions in the IMS Health Real World Data database, with which it is not

possible to capture patient compliance. Thus, patients identified as receiving LMT may not have been taking the prescribed treatment, or taking it as prescribed. Thirdly, patient data were provided voluntarily by GPs. GPs may have reached variable diagnoses, which could have underestimated or misclassified patients in some subgroups. Fourth, legitimate reasons for statin non-prescription, such as intolerance or contraindication, were not identified. Finally, patients were selected based on the availability of a lipid measurement, which might not be representative of the total population of Italian patients at high or very-high CV risk.

Sex disparities in LMT utilization and achievement of lipid goals have been reported across a number of observational studies [41,47,48], despite the similar efficacy of statins in men and women observed in randomized clinical trials [49]. No sub-analyses by sex were performed for the current dataset, thus this may also be considered a limitation of this study.

4.2. Conclusions

In summary, this large study shows that there continues to be underutilization of LMTs among patients with high or very-high CV risk in Italy, despite the demonstrated efficacy of statins in this population. Optimal statin utilization, the addition of other LMTs (such as ezetimibe and PCSK9 inhibitors), and patient adherence programs may be expected to improve lipid goal achievement and reduction in CV risk in this population. Such a shift towards better lipid control in these individuals at high or very-high CV risk has the potential to result in notable population health and pharmacoeconomic benefits.

Conflict of interest

Drs Fanelli and Paizis are employees of Sanofi Italy. At the time of this study, Dr Gorcyca was an employee of Sanofi US, Dr Tomic was an employee of Sanofi Italy, and Dr Ansell was an employee of IMS Health. Dr Iorga is an employee of Regeneron Pharmaceuticals, Inc. Dr Arca received honoraria for consultancy/lectures from Regeneron Pharmaceuticals, Inc., Sanofi, Amgen, Mylan, AstraZeneca, MSD, and Pfizer, and research grants from Amgen, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, and Boehringer Ingelheim. Dr Averna received honoraria for participation in advisory boards and sponsored lectures from Amgen, Aegerion, Alexion, AstraZeneca, Chiesi, Mediolanum, MSD, Sanofi, and Pfizer. Dr Maggioni served on the scientific committees of studies sponsored by Novartis, Cardiorentis, and Bayer. Dr Catapano received research grants to his institution from Amgen, AstraZeneca, Daiichi-Sankyo, Genentech/F. Hoffman La Roche, GlaxoSmithKline, Merck, Regeneron Pharmaceuticals, Inc., Sanofi, and Sigma Tau; and received honoraria for consultancy/lectures from Aegerion, Amgen, Boehringer Ingelheim, Doc Generici, Genzyme/Ionis, Merck, Pfizer, Roche, Sanofi, and Sigma Tau.

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Author contributions

K.G. and S.I. contributed to the concept and design of the study. D.A. was responsible for data acquisition. All authors were involved in the evaluation and interpretation of the results and the reviewing and approval of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.02.024.

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