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LDL-cholesterol target levels achievement in high-risk patients: An (un)expected gender bias

Martina Berteotti [a,*], Francesco Profili [b], Besmir Nreu [c], Giancarlo Casolo [d], Alfredo Zuppiroli [e], Edoardo Mannucci [a,c], Rossella Marcucci [a], Paolo Francesconi [b]

[a] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[b] Epidemiology Unit, Regional Health Agency (ARS) of Tuscany, Florence, Italy
[c] Diabetology Unit, Careggi university hospital, Florence, Italy
[d] Cardiology Unit, Versilia Hospital, Lido di Camaiore, Italy
[e] Former Department of Cardiology, Azienda Sanitaria di Firenze, Florence, Italy

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Abstract *Background and aims:* Lowering low-density lipoprotein cholesterol (LDL-C) is the cornerstone of cardiovascular disease prevention. Collection of epidemiological data is crucial for monitoring healthcare appropriateness. This analysis aimed to evaluate the proportion of high-risk patients who achieved guidelines recommended LDL-C goal, and explore the predictors of therapeutic failure, with a focus on the role of gender.
Methods and results: Health administrative and laboratory data from seven Local Health Districts in Tuscany were collected for residents aged ≥45 years with a history of major adverse cardiac or cerebrovascular event (MACCE) and/or type 2 diabetes mellitus (T2DM) from January 1, 2019, to January 1, 2021. The study aimed to assess the number of patients with optimal levels of LDL-C (<55 mg/dl for patients with MACCE and <70 mg/dl for patients with T2DM without MACCE). A cohort of 174 200 individuals (55% males) was analyzed and it was found that 11.6% of them achieved the target LDL-C levels. Female gender was identified as an independent predictor of LDL-C target underattainment in patients with MACCE with or without T2DM, after adjusting for age, cardiovascular risk factors, comorbidities, and district area (adjusted-IRR 0.58 ± 0.01; $p < 0.001$). This result was consistent in subjects without lipid-lowering therapies (adjusted-IRR 0.56 ± 0.01; $p < 0.001$).
Conclusion: In an unselected cohort of high-risk individuals, females have a significantly lower probability of reaching LDL-C recommended targets. These results emphasize the need for action to implement education for clinicians and patients and to establish clinical care pathways for high-risk patients, with a special focus on women.

* Corresponding author. Largo Brambilla, 3, Florence, 50134, Italy.
E-mail address: martina.berteotti@unifi.it (M. Berteotti).

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1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is one of the leading causes of mortality and morbidity worldwide [1]. In the latest decades ASCVD risk factors have been clearly identified and addressed by international guidelines both in primary and secondary prevention [2,3]. Among these risk factors, low-density lipoprotein cholesterol (LDL-C) is considered the primary causal and modifiable one. There is a dose-dependent log−linear relationship between LDL-C levels and cardiovascular (CV) events, and, conversely, lowering LDL-C is highly effective and safe with no evidence of a threshold and irrespective of the drug(s) used to achieve such reduction [4–7]. As the benefit of lowering LDL-C depends on the absolute risk of ASCVD, guidelines have identified specific risk categories with relative recommended target for prevention [2,8,9]. Patients with clinically ascertained ASCVD carry the highest risk of recurrent CV events, and should be treated aggressively in order to achieve LDL-C levels $\leq$55 mg/dl and a reduction of at least 50% from baseline. Type 2 diabetes mellitus (T2DM) is another independent CV risk factor, increasing risk of ASCVD by about two-fold on average [10]. Unless accompanied by concomitant ASCVD or severe target organ damage (characterizing patients at the absolute highest risk), or in young patients ($<$50 years) with DM duration $<$10 years and no other risk factors (moderate risk), most diabetic patients are included in the high-risk category, with an LDL-C goal of $\leq$70 mg/dl and a reduction of at least 50% from baseline [2].

Despite recent developments in risk prediction and treatments, guideline recommendations are often disattended in clinical practice [11]. This issue appears to be even more significant in women. Several studies have indicated that women are less likely to be assessed for CV risk factors and receive appropriate preventive medications [12–17]. In light of this, real-world data play a crucial role in assessing the adherence to guidelines recommendations, with the aim of monitoring the need to improve current practices for managing (very) high-risk patients.

Therefore, by retrospectively analyzing administrative data from Tuscany, we sought to investigate the proportion of patients with ASCVD and/or T2DM who achieved target LDL-C levels. Additionally, we aimed to identify possible independent predictors of LDL-C attainment with a particular focus on the role of gender.

2. Methods

2.1. Study population

Target population was composed of all residents in Tuscany Region aged 45+ years and still living from January 1st 2019 to January 1st 2021, with previous T2DM diagnosis or MACCE. Only people with at least one determination of LDL-C in the index year were considered. Data were available for the following health districts: Empolese Valdelsa-Valdarno, Prato, Aretina-Casentino-Valtiberina, Versilia, Amiata Grossetana-Colline metallifere, Siena, Apuane, Lunigiana, Valdarno, Amiata-Val d'Orcia-Valdichiana, Valdichiana aretina, Val d'Elsa, Colline dell'Albegna. These areas represent 45.2% of the whole population of Tuscany.

2.2. Data sources

All drugs, hospital discharges and socio-demographic data were retrieved from administrative health databases of Tuscany region. Laboratory measurements performed for LDL-C were retrieved from the regional laboratories. Results of laboratory measurements were provided to Tuscan Regional Health Agency (ARS) by local public health facilities; these data were collected for healthcare planning and improvement purpose. All these databases were linked by a universal anonymous identification code (Iduni), unique for each Tuscan inhabitant.

Age class, gender, health district of residence, socioeconomic deprivation Index of the area of residence, other comorbidities (chronic kidney disease-CKD, atrial fibrillation, hypertension, heart failure), were considered as further putative moderators of adherence to guidelines.

The socioeconomic deprivation Index is a composite measure of neighborhood socioeconomic disadvantage which uses poverty, education, housing and employment indicators to characterize census-based regions.

2.3. Stratifying characteristics

Target population was divided by previous T2DM diagnosis or MACCE and by lipid lowering therapy (LLT). Previous diagnosis of T2DM was extracted using a validated algorithm, including subjects with any one of the following: a diagnosis of T2DM on a hospital discharge record; disease-specific exemptions from copayment to health care; at least two prescriptions of drugs for T2DM within six months [18]. Prior cardiovascular events (MACCE) were defined by a diagnosis of angina, heart failure, myocardial infarction, other ischemic heart diseases, cardiac arrest, stroke, or transient ischemic attack and/or procedures of percutaneous angioplasty or coronary by-pass in hospital discharge records. Data on prescriptions of LLT (statins, ezetimibe, combination of two drugs) were retrieved from drugs database (see supplementary material for ICD9-CM and ATC codes). Such data include drug-dispensing records in a total or partial reimbursement regimen. Patients on LLT were defined as $\geq$75% coverage of treatment days over the previous 6 months of LDL-C exam.

2.4. Outcomes

The outcome of interest of the study was the proportion of patients with LDL-C at target: LDL-C $<$55 mg/dl for patients with previous MACCE, LDL-C$<$70 mg/dl for patients with diabetes without MACCE [9]. LDL-C values were considered at target when they were in the mentioned thresholds in all tests performed during the year.

2.5. Statistical analysis

Descriptive analyses data were summarized for the overall population and separately by gender. A multivariate Poisson regression model was used to detect the association between gender and LDL-C target. Incidence rate ratios and 95% confidence intervals (C.I.) of LDL-C at target were performed. The analysis was stratified in patients receiving (or not receiving) LLT and in patients with T2DM, MACCE, or both. Analyses were performed using the Stata/SE 14.2 software.

3. Results

In the 2019–2020 biennium 1 727 029 individuals aged 45 years and older from selected Tuscany districts were identified. Among them 328 747 (19.0%) reported a diagnosis of T2DM and/or previous MACCE. The final analyzed cohort, for whom at least one LDL-C measurement was available, consisted of 174 200 individuals (mean age 72.2 ± 10.6 years): 76 734 individuals had T2DM (44.0%), 65 878 had experienced at least one MACCE (37.8%) and the remaining subjects had both T2DM and a history of MACCE (18.3%).

Overall, most patients did not receive any LLT (89 840, 51.6%), despite only 22.7% of them having LDL-C values at the target level. Among those on LLT, most individuals received statins alone (43.8%), while ezetimibe or combined therapy was found in less than 4% of patients regardless of gender. LDL-C target attainment was more common among treated patients (18.6% vs. 5.1%, $p < 0.001$) and among patients with T2DM (13.5% in the T2DM group, 15%, in the T2DM and MACCE group, 6.9% in the MACCE group, $p < 0.001$), supplementary Table 1 and graphical abstract.

Hypertension and CKD were more frequently reported among patients on LLT (91.3% vs. 80.5%, $p < 0.001$; 20.7% vs 18.9%, $p < 0.001$, respectively). Similarly, these conditions were more prevalent among patients who achieved LDL-C targets compared to those who did not (90.1% vs 85.2%, $p < 0.001$ and 26.2 vs 18.9%, $p < 0.001$, respectively), supplementary Table 1.

Women accounted for 45.1% of the cohort and were older than men (proportion over 75 years old 50.5% vs 40.1%, $p < 0.001$). Additionally, CKD and T2DM without MACCE history were more common among women (23.2% vs 16.9%, $p < 0.001$ and 51.4% vs. 38%, $p < 0.001$ respectively). On the other hand, the majority of men included in the analysis had a history of MACCE and were in secondary prevention. Women were less likely to be prescribed any LLT, and the attainment of LDL-C target levels was significantly lower compared to men (8.8% vs. 14.0%, $p < 0.001$), Table 1. This reduced proportion of women achieving target levels was confirmed in each risk category (Fig. 1).

Tables 2 and 3 show the results of multivariable Poisson regression analysis for LDL-C target level attainment in patients on LLT (48.4% of the entire cohort) and untreated subjects, respectively.

After adjusting for age, district area, CV risk factors and comorbidities, female gender was the only independent variable associated with a significantly lower probability of achieving LDL-C target levels in every risk category, regardless of LLT status: overall adjusted IRR 0.58, 95% C.I. 0.55–0.62, $p < 0.001$ in treated individuals and overall adjusted IRR 0.56, 95% C.I. 0.54–0.58, $p < 0.001$ in untreated subjects. Conversely, in the T2DM group, increasing age and the presence of comorbities such as hypertension and CKD were independently associated with a higher likelihood of achieving the LDL-C goal.

Table 1 Baseline characteristics of the studied cohort for gender.

Covariate	Level	Overall (174 200)		Men (95 557)		Women (78 643)		p-value
		n	%	n	%	n	%	
Age (years old)	45–54	11 675	6.7	6765	7.1	4910	6.2	<0.001
	55–64	29 126	16.7	17 907	18.7	11 219	14.3	
	65–74	55 286	31.7	32 497	34.0	22 789	29.0	
	75–84	57 348	32.9	29 941	31.3	27 407	34.8	
	85+	20 765	11.9	8447	8.8	12 318	15.7	
Comorbidities	Chronic kidney disease	34 364	14.1	16 128	16.9	18 236	23.2	<0.001
	Heart failure	31 805	18.3	17 874	18.7	13 931	17.7	<0.001
	Atrial fibrillation	14 885	8.5	8376	8.8	6509	8.3	<0.001
	Hypertension	149 342	85.7	81 804	85.6	67 538	85.9	0.107
Intervention groups	T2DM	76 734	44.0	36 305	38.0	40 429	51.4	<0.001
	MACCE	65 878	37.8	39 832	41.7	26 046	33.1	
	T2DM and MACCE	31 588	18.1	19 420	20.3	12 168	15.5	
Target LDL-C achieved	Yes	20 274	11.6	13 334	14.0	6940	8.8	<0.001
Lipid lowering therapy	None	89 840	51.6	45 734	47.9	44 106	56.1	<0.001
	Statin	76 183	43.7	44 870	47.0	31 313	39.8	<0.001
	Ezetimibe	5985	3.4	3794	4.0	2191	2.8	<0.001
	Statin + ezetimibe	6621	3.8	4199	4.4	2422	3.1	<0.001
Socio-economic deprivation	Low	24 910	14.3	14 160	14.8	10 750	13.7	<0.001
	Intermediate	120 065	68.9	65 889	69.0	54 176	68.9	
	High	29 225	16.8	15 508	16.2	13 717	17.4	

Abbreviations: MACCE, major adverse cardiac or cerebrovascular event; T2DM, type 2 diabetes mellitus; LDL-C, low density lipoprotein cholesterol.

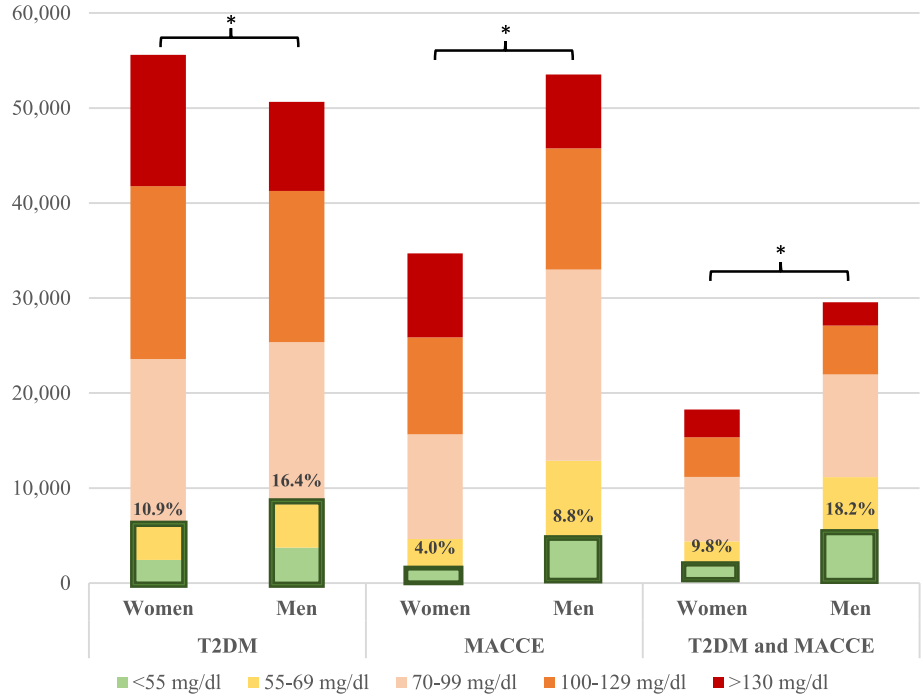

Figure 1 LDL-C values according to risk category and gender groups. Squares ad percentages indicate the proportion of subjects who achieved LDL-C recommended target (<70 mg/dl in patients with T2DM group and <55 mg/dl in those with MACCE with or without T2DM). Abbreviations: MACCE, major adverse cardiac or cerebrovascular event; T2DM, type 2 diabetes mellitus; LDL-C, low density lipoprotein cholesterol. $*p < 0.001$.

4. Discussion

The main findings of the present analysis, conducted in a real-world population of patients at high and very high CVD risk, can be summarized as follows.

1) LLT was significantly underutilized in patients with T2DM and/or a history of MACCE, with less than 50% of patients receiving at least one drug, primarily statin alone.
2) The recommended LDL-C goals outlined in the 2019 ESC guidelines were achieved by only a minority of individuals (11.6%), and the lowest rate of goal attainment was observed among patients with a history of MACCE without T2DM.

Table 2 Multivariable Poisson regression analysis for LDL-C target levels attainment in patients on lipid lowering therapy. Incidence rate ratio of LDL-C target levels with 95% confidence intervals.

Covariates	T2DM2			MACCE			T2DM and MACCE		
	IRR	95% C.I.	p-value	IRR	95% C.I.	p-value	IRR	95% C.I.	p-value
Gender									
Male	Ref.			Ref.			Ref.		
Female	0.61	0.57–0.65	<0.001	0.47	0.41–0.55	<0.001	0.59	0.52–0.67	<0.001
Age (years old)									
45–54	Ref.			Ref.			Ref.		
55–64	1.32	1.09–1.60	0.004	1.02	0.72–1.47	0.877	1.68	0.95–2.97	0.076
65–74	1.36	1.13–1.62	0.001	0.98	0.70–1.37	0.911	1.64	0.94–2.85	0.079
75–84	1.44	1.20–1.73	<0.001	0.83	0.59–1.17	0.284	1.51	0.87–2.62	0.145
≥85	1.68	1.35–2.08	<0.001	1.31	0.91–1.87	0.143	1.84	1.04–3.24	0.036
Comorbidities									
Hypertension	1.20	1.09–1.34	<0.001	1.67	1.16–2.40	0.006	1.48	0.95–2.31	0.086
Chronic kidney disease	1.12	1.01–1.24	0.025	1.22	1.02–1.46	0.025	1.05	0.91–1.20	0.499
Heart failure	0.86	0.64–1.14	0.291	1.11	0.96–1.28	0.148	1.09	0.96–1.23	0.184
Atrial Fibrillation	1.17	0.99–1.37	0.058	1.33	1.10–1.61	0.003	1.35	1.14–1.60	0.001
Socio-economic deprivation									
Low	Ref.			Ref.			Ref.		
Intermediate	1.04	0.94–1.15	0.419	1.03	0.86–1.23	0.735	1.03	0.87–1.23	0.722
High	1.02	0.90–1.16	0.756	0.93	0.74–1.18	0.555	1.01	0.87–1.32	0.530

Abbreviations: MACCE, major adverse cardiac or cerebrovascular event; T2DM, type 2 diabetes mellitus; LDL-C, low density lipoprotein cholesterol; IRR, Incidence Rate Ratio; C.I., confidence interval.

Table 3 Multivariable Poisson regression analysis for LDL-C target levels attainment in patients without any lipid lowering therapy. Incidence rate ratio of LDL-C target levels with 95% confidence intervals.

Covariates	DMT2			MACCE			DMT2 and MACCE		
	IRR	95% C.I.	p-value	IRR	95% C.I.	p-value	IRR	95% C.I.	p-value
Gender									
Male	Ref.			Ref.			Ref.		
Female	0.63	0.60–0.66	<0.001	0.43	0.40–0.47	<0.001	0.55	0.51–0.59	<0.001
Age (years old)									
45–54	Ref.			Ref.			Ref.		
55–64	1.12	1.01–1.24	0.030	0.95	0.80–1.13	0.560	1.10	0.89–1.35	0.379
65–74	1.19	1.08–1.31	<0.001	1.01	0.87–1.19	0.835	0.98	0.80–1.19	0.843
75–84	1.20	1.08–1.32	<0.001	0.97	0.83–1.13	0.686	0.92	0.76–1.13	0.434
≥85	1.15	1.01–1.30	0.030	1.17	0.99–1.39	0.064	0.82	0.67–1.03	0.085
Comorbidities									
Hypertension	1.26	1.18–1.34	<0.001	1.49	1.27–1.74	<0.001	1.46	1.16–1.84	0.001
Chronic kidney disease	1.08	1.01–1.16	0.029	1.07	0.97–1.17	0.184	0.99	0.91–1.06	0.711
Heart failure	1.05	0.89–1.24	0.568	0.95	0.88–1.02	0.154	0.97	0.90–1.04	0.330
Atrial Fibrillation	1.16	1.05–1.29	0.004	0.96	0.87–1.06	0.400	1.05	0.95–1.16	0.353
Socio-economic deprivation									
Low	Ref.			Ref.			Ref.		
Intermediate	1.01	0.94–1.08	0.838	1.03	0.93–1.13	0.595	0.94	0.86–1.04	0.230
High	1.01	0.93–1.10	0.810	1.10	0.98–1.23	0.095	1.00	0.89–1.12	0.950

Abbreviations: MACCE, major adverse cardiac or cerebrovascular event; T2DM, type 2 diabetes mellitus; LDL-C, low density lipoprotein cholesterol; IRR, Incidence Rate Ratio; C.I., confidence interval.

3) LLT prescription rates were particularly low in women, and female gender was identified as the only independent variable associated with a significantly lower probability of achieving LDL-C target levels in every risk category, both among treated and untreated subjects.

Despite the strong and independent role of LDL-C in the pathogenesis of CVD and the body of evidence confirming the benefit and safety of aggressive LDL-C reduction, our findings reveal a significant underutilization of LLT and a subsequent failure to achieve optimal LDL-C goals. These results are consistent with several other real-world studies. The EUROASPIRE V survey, that collected data from 7824 patients across 27 European countries at least 6 months after hospitalization for a coronary event, reported that less than 30% of individuals achieved LDL-C levels at or below 70 mg/dl, despite approximately 84% of patients receiving LLT [19]. Similarly, recent registries from the United States have shown that over 50% of patient in secondary prevention are not receiving any LLT [20,21], and nearly 80% of individuals with ASCVD have LDL-C levels exceeding 70 mg/dl [22]. A Korean nationwide cohort study encompassing 5049 post myocardial infarction patients, reported that only 22.1% of individuals achieved their LDL-C goals. Among them, a reduced adjusted hazard of MACCE was observed (HR: 0.63, p = 0.041) compared to non-achievers [23]. This unsatisfactory outcome has also been documented in Italian registries, such as the EFFECTUS, which reported that only 5.8% of patients in secondary prevention achieved LDL-C levels at or below 70 mg/d.

In the present study, we set an even more ambitious LDL-C target of ≤55 mg/dl, as recommended by the latest guidelines [2,9]. Notably, our registry collected data from the biennium 2019–2020, so a considerable number of subject may not have been treated according to lower target proposed by the 2019 ESC/EAS guidelines [9]. This factor could partially explain why only 6.9% of patients with history of MACCE without T2DM achieved the LDL-C target. However, by assuming an LDL-C goal of 70 mg/dl, the proportion of LDL-C attainment would have been 19.9%, which is comparable to the findings of most of the previously reported registries. Indeed, in the DA VINCI study, which included 5888 patients, a slightly higher proportion of patients (18%) met 2019 ESC guidelines LDL-C target in secondary prevention [24]. However, it is important to note that the DA VINCI study was a prospective observational registry, and a considerably higher number of subjects receiving combination therapy was documented (9% compared to 1.3% in our registry).

One of the main responsible of the inadequate LDL-C control is the underuse of LLT. Real-world data shown that most patients are not receiving any LLT, and even when it is prescribed, the titration is largely suboptimal, both in primary and secondary prevention [25–30]. However, the failure to achieve LDL-C threshold despite high-intensity statin therapy has also been reported in other observational studies [31,32], which suggest that factors other than medication usage, such as poor adherence to therapy or limited prescription of second-line LLT, may be involved in the suboptimal LDL-C control, as reviewed elsewhere [33].

However, regardless CV risk category, female gender emerged as strongest independent predictor of failure to achieve LDL-C targets. This gender disparity has been consistently observed in several previous registries [13–17,34–36]. Importantly, this finding was consistent regardless of background LLT, indicating a bias in both the inadequate prescription and titration of LLT in women.

One possible explanation for the undertreatment of women is the delay in CV risk assessment and CV risk factor management [12,13,17]. Despite what is commonly perceived, latest European statistics have documented that absolute numbers of women living with and dying from ASCVD exceed those of men [37]. Importantly, despite women being traditionally underrepresented in statins trials [38], there is enough evidence to confirm an equal CV benefit from LDL-C reduction [39–41]. Moreover, women have been shown to display a 20% higher risk of short-term mortality after acute coronary syndrome compared to men [42–44], emphasizing the importance of aggressive risk factor management. It is therefore of paramount importance not to deny or delay LLT in women based on a misperception of their CV risk.

Another finding of the present study was the higher attainment of LDL-C targets in patients whit T2DM, both in primary and secondary prevention, compared to patients with a history of MACCE alone. T2DM has already been reported as an independent determinant for achieving LDL-C targets [45,46]. One possible explanation for this finding is the more structured follow-up and specialized care that T2DM patients often receive, particularly in outpatient clinics. This kind of organization has been proven to reduce mortality and improve CV outcomes [47,48]. Similar findings have been described in Australian registries, where patients who visited a general practitioner after a hospitalization for ischemic heart disease or had a chronic disease management plan had a lower risk of CVD emergency readmission [49]. Interestingly, we also found that increasing age and comorbidities were independent predictors of LDL-C target attainment, especially in the T2DM subgroup of patients. Younger age has already been associated with statin underprescription and poorer LDL-C control, especially in women [12–14]. These data depict the picture of an erroneously perceived “low-risk patient”, whereas the presence of T2DM itself requires adequate LDL-C optimization.

On the other side, even if a higher level of socioeconomic deprivation was described in women, it was not independently associated with the risk of LDL-C goal underattainment. Accordingly, a Chinese registry found that sex disparities in LLT were more prominent in rural residents in primary prevention, but not in secondary prevention. Furthermore, education level was not associated with the gender difference in LLT [14]. These observations suggest that factors other than socioeconomic status, such as healthcare system biases and physician unawareness of women’s CV risk, may play a significant role in the underutilization of LLT and suboptimal LDL-C management in women.

The present registry has some limitations. Firstly, data were collected by linking health administrative and laboratory records, which limited the availability of detailed information about medical history, statin therapy potency and adherence to LLT. However, the study aimed to provide an overview of real-world LDL-C target level attainment, which was confirmed to be suboptimal, regardless of the background therapy. Besides, the lack of available lipid profiles before treatment prevented the calculation of whether a 50% reduction in LDL-C levels was achieved. This missing information could have resulted in an overestimation of LDL-C target attainment, further emphasizing the unsatisfactory findings observed in the study.

Another limitation is the absence of data on the use of proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i). Given the low LDL-C attainment observed in the study, it can be hypothesized that only a limited proportion of patients were receiving second-line LLT. It has been shown that adherence to PCSK9i is higher compared to statins, and these therapies have been demonstrated to improve patients’ quality of life [50,51]. Additionally, the recent introduction of inclisiran in the treatment armamentarium for patients who are statin intolerant or have above-target LDL-C levels provides another potential option to improve LDL-C target attainment [52].

Finally, we were not able to better refine CV risk category of T2DM patients based on the presence of comorbidities, target organ damage and DM duration. This limitation may have resulted in the underestimation of risk for some patients and, consequently, the overestimation of LDL-C goal achievement. Conversely, the proportion of patients who could have been classified as moderate risk (with a less stringent recommended LDL-C target) is likely to be minimal, given the high prevalence of hypertension (>85%) and the fact that less than 6% of patients were younger than 50 years old. Therefore, the considerations regarding the improved management of T2DM patients should be regarded as hypothesis-generating, as no specific information regarding this issue was available in the study.

In conclusion, the present analysis, performed on a cohort of more than 174 000 high to very-risk individuals, highlights the ongoing problem of inadequate achievement of LDL-C targets in clinical practice. In particular, women still have the highest risk of being undertreated according to guidelines recommendations irrespectively from their risk category and background therapy. These results call for action aimed to: 1) education for the general population and patients with a history of MACCE; 2) increasing awareness among healthcare professionals regarding the importance of gender-tailored lipid-lowering therapy; 3) improvements in clinical pathways, from admission to recovery and follow-up, that should prioritize the appropriate use of LLT, taking into account gender differences.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.09.023.

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