Cardiovascular Diabetology

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Lipid-lowering therapy and LDL target attainment in type 2 diabetes: trends from the Italian Associations of Medical Diabetologists database

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Abstract

Background Hypercholesterolemia is a major cardiovascular risk factor, particularly in individuals with type 2 diabetes (T2DM), where cardiovascular events are more prevalent. Adherence to low-density lipoprotein cholesterol (LDL-c) targets remains suboptimal globally and in Italy. This study evaluates trends in LDL-c target achievement and lipid-lowering treatment with a stratification by cardiovascular risk among Italian patients with type 2 diabetes from 2019 to 2022.

Methods A cross-sectional analysis was conducted using the AMD Annals database, encompassing over 700,000 patients with T2DM. Patients were categorized by cardiovascular risk levels, LDL-c ranges and therapy types (statins, ezetimibe, PCSK9 inhibitors). Linear trends across the four years were evaluated.

Results The percentage of patients achieving LDL-c targets improved across all risk levels. In very high-risk patients, LDL-c < 55 mg/dL was achieved by 16.3% in 2019, increasing to 23.6% in 2022. High-risk patients achieving LDL-c < 70 mg/dL rose from 20.3 to 26.6% over the same period. Use of PCSK9 inhibitors, particularly in combination with statins, was associated with the highest target achievement rates, reaching 62% in very high-risk patients by 2022. We observed a reduction of moderate-intensity statins use in favor of combination therapies across the four years. Despite this, nearly one-third of patients still had LDL-c levels ≥ 100 mg/dL in 2022.

Conclusions While LDL-c management in Italian patients with T2DM has improved, significant gaps remain, particularly for very high-risk individuals. Expanding the use of advanced therapies like PCSK9 inhibitors and adhering more closely to guideline-based recommendations are critical to improve cardiovascular risk in this population.

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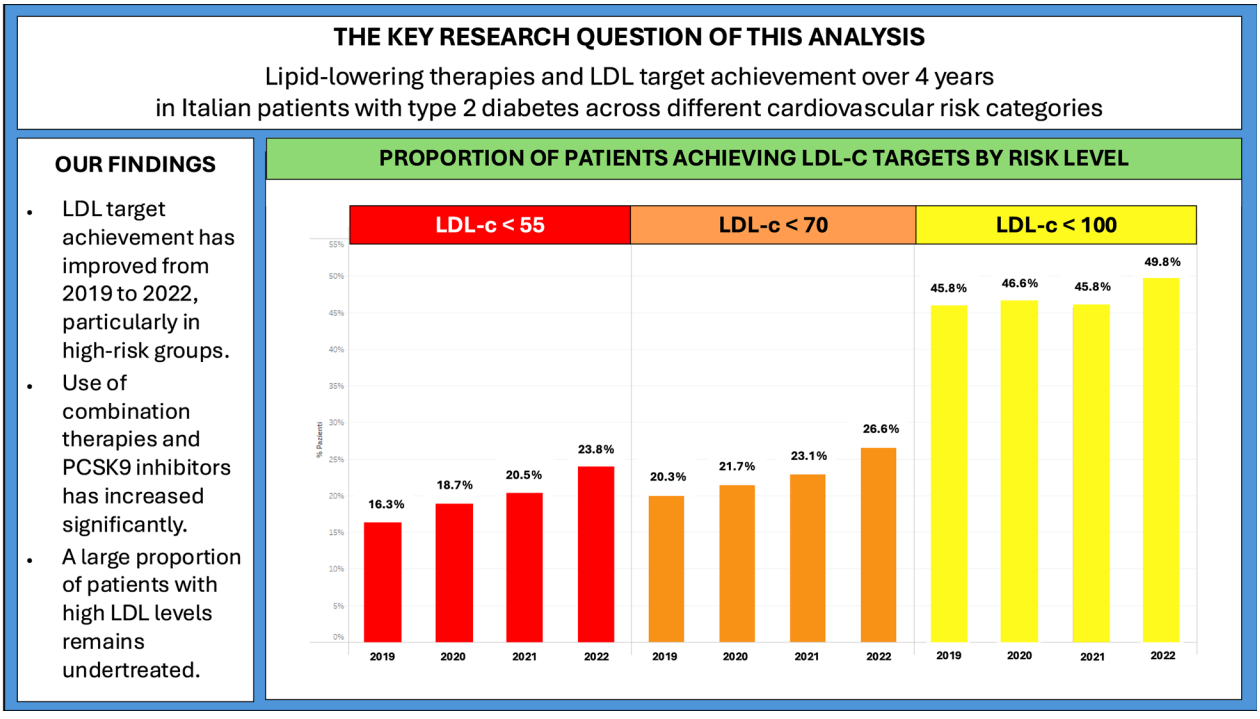
Keywords Type 2 diabetes mellitus, LDL cholesterol, Cardiovascular risk, Lipid-lowering therapy, Hypercholesterolemia, Statins, PCSK9 inhibitors

Graphical Abstract



Introduction

Cardiovascular disease (CVD) poses a substantial global health challenge, affecting approximately 32.2% of individuals with type 2 diabetes (T2DM) and remaining a leading cause of mortality in this population, with coronary artery disease (CAD) and stroke as primary contributors [1]. Hypercholesterolemia and hypertension are critical risk factors for atherosclerotic cardiovascular disease (ASCVD) in T2DM [2] due to underlying pathophysiological mechanisms including LDL cholesterol (LDL-C) damaging effects [3], with diabetes duration representing a crucial determinant of the risk [4]. As a result, epidemiological data indicate that about one third of people with type 2 diabetes are affected by CVD with great predominance of atherosclerotic disease [5]. The economic burden of ASCVD in individuals with T2DM is also substantial for direct and indirect costs linked to ASCVD that significantly exceed those of non-diabetic individuals, incurring in the United States an annual expenditure of approximately $37.3 billion [6]. Extensive evidence indicates that simultaneously addressing multiple cardiovascular risk factors can effectively prevent or delay the progression of ASCVD [7]. Nevertheless, despite established guidelines recommending specific LDL-C targets tailored to cardiovascular risk levels [8], a substantial proportion of patients with T2DM fail to achieve these targets [9, 10], resulting in elevated risk of severe cardiovascular complications [11].

Several large observational studies conducted across Europe have provided valuable insights into the real-world implementation of recent guidelines, consistently demonstrating suboptimal outcomes. The Da Vinci study, which analyzed data from 18 countries between 2017 and 2018, revealed that only 18% of very high-risk patients achieved their 2019 ESC/EAS LDL-C target, with the highest success rates observed among those receiving PCSK9 inhibitor-based combination therapy [12].

Similarly, the Santorini study examined lipid-lowering strategies in a cohort of over 9,000 patients at high and very high cardiovascular risk, across both primary and secondary care settings. The majority of patients were on lipid-lowering monotherapy, and, unsurprisingly, only 20% achieved their risk-based LDL-C targets [13]. In both studies approximately one third of the cohorts included patients with T2DM. In the 1-year follow-up of the Santorini study [14] improved outcomes were observed with greater utilization of combination therapy. However, despite this, no more than 31% of patients attained LDL-C levels within the target range.

These findings align with long-standing evidence from the EUROASPIRE survey program, which has consistently highlighted suboptimal lipid management over the years, despite multiple guideline updates. This persistent gap underscores the presence of clinical inertia, likely driven by limited awareness of actual cardiovascular risk among healthcare professionals [15].

In light of evolving epidemiology, the availability of new lipid-lowering therapies, updated treatment targets, and the variability in trends across different countries [9], ongoing monitoring of diabetes care quality has become increasingly imperative. The AMD (Associazione Medici Diabetologi) Annals initiative, which regularly assesses diabetes care trends in Italy [16], reports that only 21.4% of patients at high risk and 37.6% of patients at very high risk reach LDL-C levels below 70 mg/dl [17]. Recognizing the substantial challenge of lipid control among Italian patients with T2DM, this study aimed to evaluate lipid profiles, treatment strategies, and target achievements in different risk profiles, along with temporal trends over 4 years, from 2019 to 2022.

Materials and methods

Study design and data source

This cross-sectional study with temporal analysis utilized data from the AMD Annals database, which collects clinical information from 295 diabetes centers across Italy, representing approximately 50% of the country's diabetes clinics, comprising records of about 1,587,873 patients with type 2 diabetes from 2010 to 2022. The analysis focused on data from 2019 to 2022, encompassing a total of about 400,000 patients with at least one LDL-C measurement per year.

Eligibility criteria

The analysis was conducted independently for each of the years 2019, 2020, 2021, and 2022. Consequently, each patient could participate in the analysis for more than one year.

Inclusion criteria

(1) Patients with at least one clinical visit during the selected years. If multiple visits occurred within the same year, only the most recent visit (i.e., the one closest to December 31st) was considered for analysis; (2) Availability of LDL-C for the selected visit. If LDL-C values were unavailable for the selected visit, data from the most recent preceding visit with available LDL-C value were used; (3) For analyses requiring cardiovascular risk classification, patients were included only if, in addition to LDL-C levels, all other variables necessary for risk assessment were available at the selected visit. To mitigate the impact of missing data, no standardized risk calculator score was applied. Instead, cardiovascular risk stratification was performed based on the ADA 2023 Standards of Care [7] which largely aligns with the ESC/EAS guidelines [8]. Additionally, to enhance risk assessment within the very high-risk group, a CKD-based classification was incorporated according to the 2023 ESC Guidelines [18], ensuring a more comprehensive inclusion criterion. For further details, refer to Table 1.

Exclusion criteria

(1) Patients with autoimmune diabetes; (2) Patients with MODY (Maturity-Onset Diabetes of the Young); (3) Patients with gestational diabetes; (4) Patients with diabetes secondary to pancreatic disease; (5) Patients with

Table 1 Guideline-based risk assessment of type 2 diabetes study population

	ADA Standards of Care 2023 [7]	2019 ESC/EAS Guidelines [8]	2023 ESC Guidelines [18]
Very high	**Patients with Estabilished ASCVD***	**Patients with Established ASCVD** and/or **HF** and/or **Target organ damage** (microalbuminuria, retinopathy, or neuropathy) or at least three major risk factors	**Patients with Established ASCVD** and/or **Severe TOD**** and/or 10-year CVD risk ≥ 20% using SCORE2-Diabetes
High	**Patients ≥ 55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria) not fulfilling the very high-risk**	**Patients without target organ damage** (microalbuminuria, retinopathy, or neuropathy), with T2DM duration > 10 years or another additional risk factor	Patients not fulfilling the very high-risk criteria and a 10-year CVD risk 10 to < 20% using SCORE2-Diabetes
Moderate	**Patients not fulfilling the high and very high-risk criteria*****	Young patients (< 50 years) with T2DM duration < 10 years, without other risk factors	Patients not fulfilling the very high-risk criteria and a 10-year CVD risk 5 to < 10% using SCORE2-Diabetes

The criteria used for risk assessment are highlighted in bold for clarity

*Established ASCVD: Coronary Artery Disease defined as myocardial infarction history, angina, coronary artery stenosis and/or coronary revascularization; transient cerebral ischemic attack, ischemic stroke, carotid artery stenosis and/or carotid revascularization; peripheral artery disease and/or peripheral revascularization

**Severe TOD: eGFR < 45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR > 300 mg/g; stage A3)

***Authors' interpretation

ASCVD (Atherosclerotic Cardiovascular Disease), HF (Heart Failure), TOD (Target Organ Damage), CVD (Cardiovascular Disease), SCORE2-Diabetes (Systematic COronary Risk Evaluation 2 for Diabetes), T2DM (Type 2 Diabetes Mellitus)

inconsistent medical records preventing accurate evaluation of the study outcomes (including lack of specific treatment dosage).

Objectives of the analysis

The study was designed with the following three primary aims, analyzing data across the four years considered:

1. Analysis of average lipid profiles including LDL-C, triglycerides, and HDL cholesterol (HDL-C) levels, along with categorization of the population by cardiovascular risk (moderate, high, very high [8])
2. Assessment of the proportion of individuals receiving cholesterol-lowering therapies [19], and their distribution across cardiovascular risk categories.
3. Analysis of LDL-C target achievement across moderate, high, and very high-risk groups, and within specific subgroups, such as patients with coronary artery disease (CAD) or those with organ damage, defined as the presence of conditions like chronic kidney disease (CKD), heart failure, cerebrovascular disease (CeVD) or CAD.

Subgroups and sample sizes

The patient selection process and study design are summarized in Fig. 1. The initial cohorts drawn from the AMD Annals database consisted of 609,387 individuals with T2DM in 2019, 524,108 in 2020, 585,888 in 2021, and 650,188 in 2022. Following the identification of patients with available c-LDL data, the cohorts were narrowed to 470,712 in 2019, 394,475 in 2020, 464,765 in 2021, and 512,277 in 2022. Among these, the subgroups with sufficient data for cardiovascular risk stratification (moderate, high, very high) included 357,799 in 2019, 293,143 in 2020, 249,987 in 2021, and 389,312 in 2022.

Classification of treatments

According to lipid-lowering prescription, patients were classified into the following categories:

- Patients with T2DM treated with low to moderate-intensity statins (simvastatin 10 mg, pravastatin 10 or 20 mg, lovastatin 20 mg, fluvastatin 20 or 40 mg, atorvastatin 10 or 20 mg, rosuvastatin 5 or 10 mg), without ezetimibe or PCSK9 inhibitors
- Patients with T2DM treated with high-intensity statins (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg), without ezetimibe or PCSK9 inhibitors
- Patients treated with moderate-intensity statins + ezetimibe, without PCSK9 inhibitors
- Patients treated with high-intensity statins + ezetimibe, without PCSK9 inhibitors
- Patients treated with PCSK9i and statins, i.e., PCSK9 with any type of statin (with or without ezetimibe)
- Patients treated with PCSK9i without statins (with or without ezetimibe)
- Patients treated with statins without dosage (these are statins for which the dosages could not be traced). This group was included in the initial count of patients undergoing lipid-lowering therapy, but excluded from further in-depth analyses

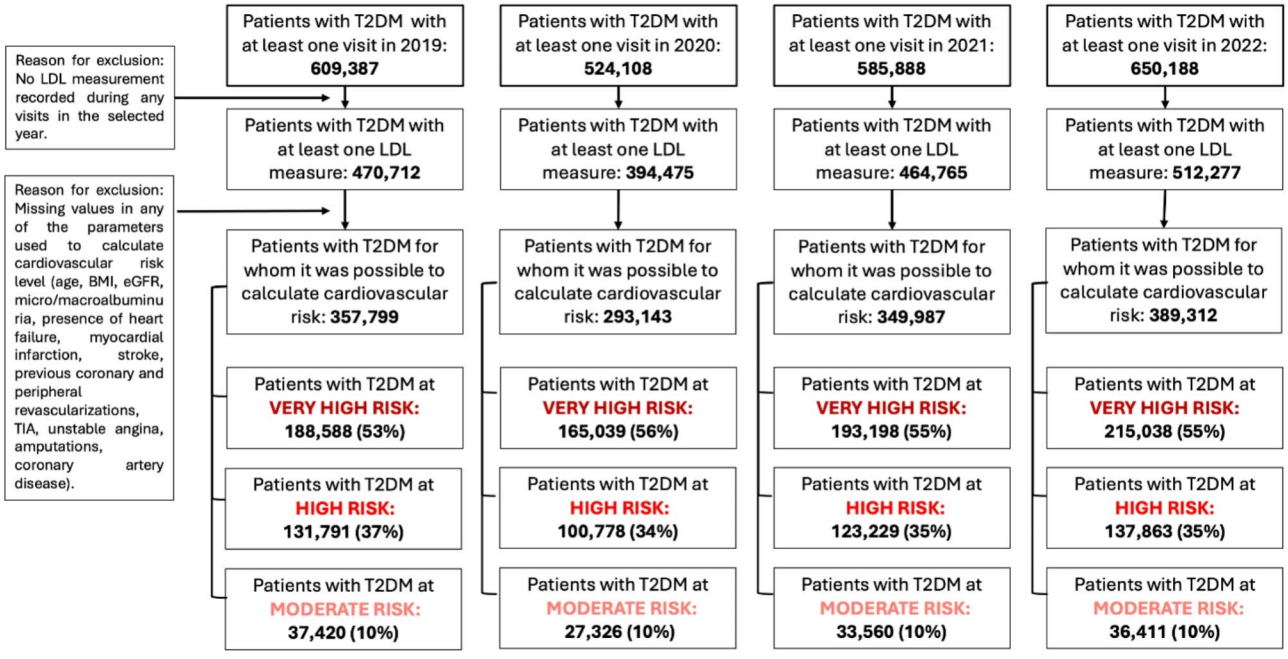


Fig. 1 Flowchart of patient selection process

In each of these groups, the use of omega-3 or fibrates was noted but not considered in the analysis.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were presented as counts and percentages. Trends across years were assessed using a linear regression model to calculate the *p*-value for trends (*p*-trend). Statistical significance was set at $p < 0.05$. All analyses were conducted using Tableau 2024.2, Excel MS 365 and Rulex 1.2.x.

Results

Lipid profile trends, cardiovascular risk categories and treatment coverages

The average LDL-C levels in patients with T2DM progressively improved from 91.3 ± 33.2 mg/dL in 2019 to 85.8 ± 34.1 mg/dL in 2022, while the reduction in triglyceride levels was less pronounced, and HDL-C levels remained stable throughout the four years (Fig. 2).

Figure 3 illustrates the distribution of patients with T2DM by cardiovascular risk level (moderate, high, and very high) over the years 2019 to 2022, alongside the proportion of patients receiving lipid-lowering therapy. Most patients with T2DM fall within the "very high-risk" category, consistently making up over half of the total population across the years. High-risk patients form the second-largest group, with moderate-risk patients being the smallest cohort, constituting less than 10% each year. There was a progressive increase in the percentage of patients receiving cholesterol-lowering therapies over the years, especially among very high-risk individuals (from 52.7% in 2019 to 55.2% in 2022). Therapy coverage for moderate- and high-risk patients remained lower, ranging from 36.7% to 42.9% and from 55.6 to 60.6%, respectively, compared to very high-risk patients.

The subgroup analysis by LDL-c ranges (< 55, 55–70, 70–100, 100–116, > 116 mg/dL) revealed a gradual improvement in LDL-c levels among patients with T2DM from 2019 to 2022 (Supplementary Fig. 1). The proportion of individuals achieving LDL-C levels < 55 mg/dL increased from 11.1% to 16.6%, while those in the 55–70 mg/dL range rose from 15.4% to 17.5%. Additionally, the percentage of patients with LDL-C levels ≥ 100 mg/dL declined from 36.4% to 31.2%.

A subgroup analysis of cardiovascular event prevalence in 2022, including myocardial infarction (MI), stroke, coronary revascularization, carotid revascularization, and peripheral revascularization, revealed distinct patterns across different patient groups.

Patients with coronary artery disease (CAD) only (59,544 cases) had the highest prevalence of cardiovascular events (36,929 cases), including MI (23,126 cases) and coronary revascularization (26,577 cases).

Patients with cerebrovascular disease (CeVD) only (20,344 cases) experienced a high incidence of strokes (19,370 cases), with a smaller subset undergoing carotid revascularization (511 cases), totaling 19,782 cardiovascular events.

In contrast, patients with peripheral artery disease (PAD) only (36,226 cases) had a lower overall event burden, primarily driven by peripheral revascularizations (2,216 cases). Patients with multiple cardiovascular diseases (30,938 cases) exhibited the highest cumulative burden of events (25,629 cases), emphasizing the compounded risk associated with overlapping conditions. Among this group, myocardial infarction (10,480 cases), stroke (13,092 cases), and various revascularization

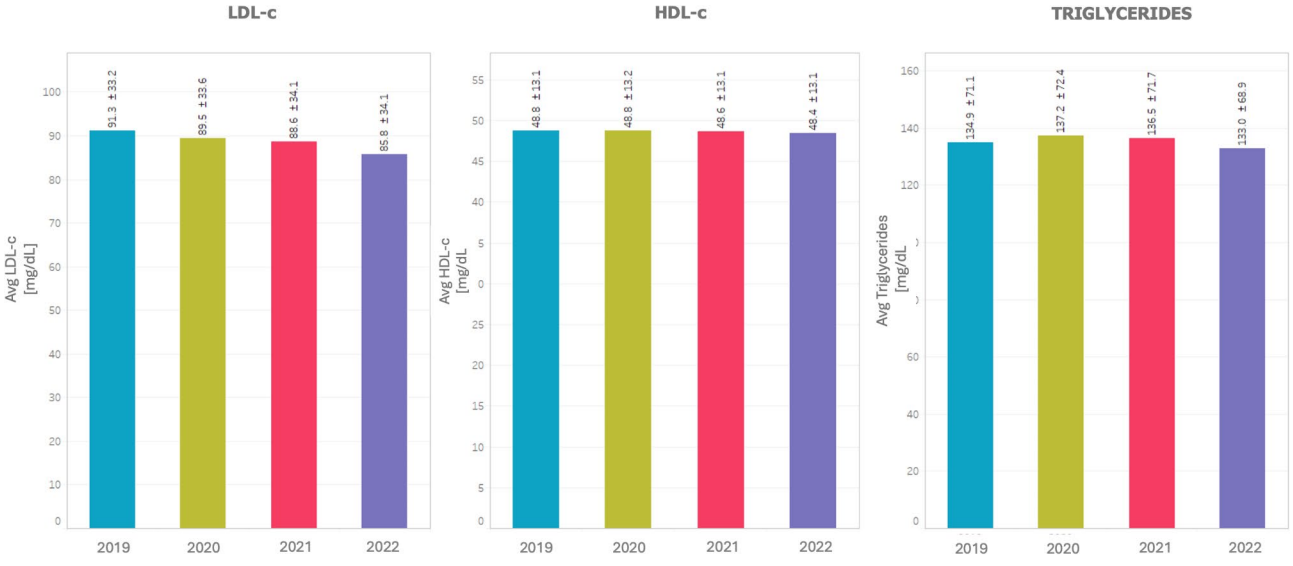


Fig. 2 Trends in lipid profiles (2019–2022). For all three variables—LDL, HDL, and triglycerides—the *p*-value for the trend over the 4-year period is < 0.01

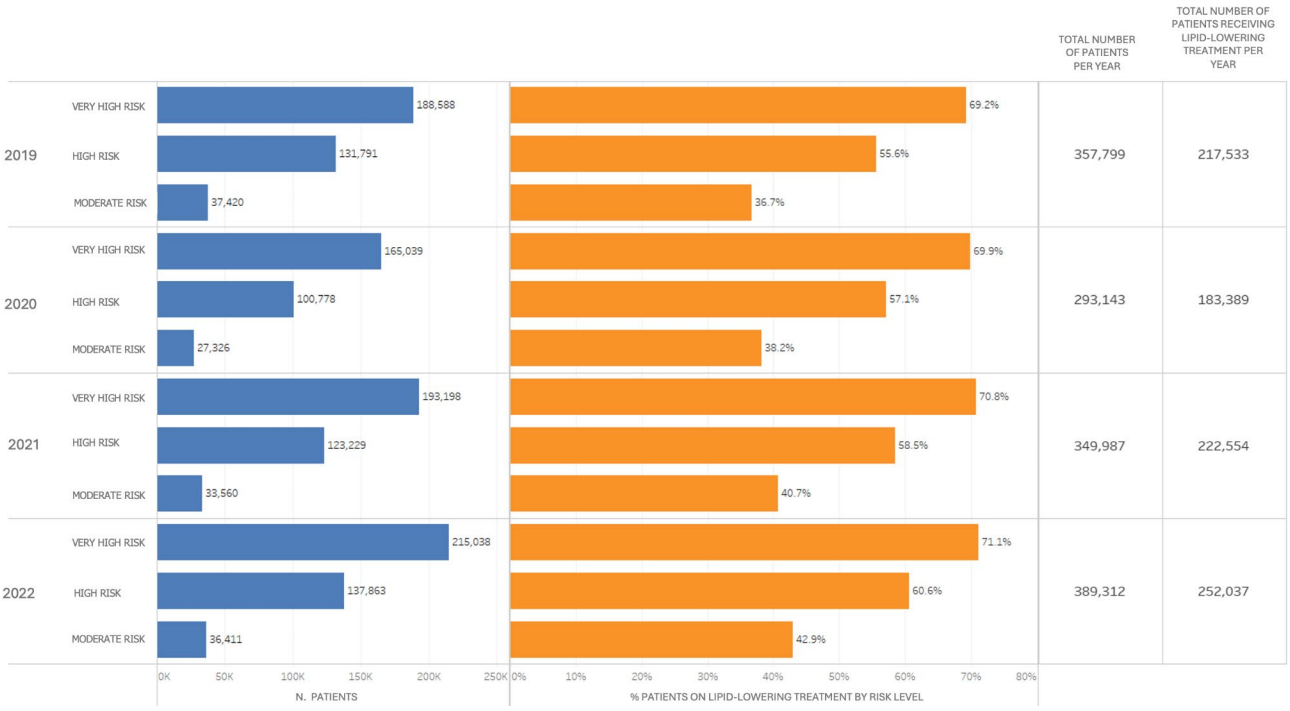


Fig. 3 Yearly distribution of patients with T2DM by cardiovascular risk level and treatment coverage. Trends were calculated for the change, between 2019 and 2022, within the three risk subgroups. The *p*-value for trend is < 0.01

procedures (coronary, carotid, and peripheral) were notably elevated (Supplementary Fig. 2).

Evolution of lipid-lowering therapy utilization

As far as therapy is concerned, for each year and for each LDL-c range, we analyzed the proportion of patients receiving cholesterol-lowering therapy (Supplementary Fig. 3).

Our results indicate a gradual increase in cholesterol-lowering therapy use, rising from 58.2% of patients in 2019 to 61.9% in 2022. Treatment is more prevalent among patients with lower LDL-C levels, with nearly 80% of those achieving LD-CC < 55 mg/dL receiving therapy. In contrast, only approximately 45% of patients with LDL-C levels > 100 mg/dL were treated. Alarmingly, 55% of individuals with LDL-C > 100 mg/dL did not receive any lipid-lowering therapy.

Table 2 details the distribution and trends in lipid-lowering therapies utilization. Moderate-intensity statins were the most frequently prescribed but decreased from 71% in 2019 to 60% in 2022, reflecting a shift toward combination therapies and advanced treatments. The use of ezetimibe increased substantially, particularly in combination with high-intensity statins, where usage rose from 2.4% to 6.5%, and nearly doubling with moderate-intensity statins (from 10 to 19%). High-intensity statins, despite their superior efficacy, remain underutilized compared to moderate-intensity statins. PCSK9 inhibitors saw a marked increase, quadrupling during the study period, although overall adoption remained low.

Target achievement across risk levels

Among very high-risk patients, the proportion meeting the LDL-C target of < 55 mg/dL rose from 16.3% in 2019 to 23.6% in 2022. For high-risk patients, the percentage achieving the LDL-C target of < 70 mg/dL increased from 20.3% in 2019 to 26.6% in 2022. In the moderate-risk group, target achievement rates (LDL-C < 100) were considerably higher, starting at 45.8% in 2019 and reaching 49.8% in 2022, with a modest improvement that was particularly evident in the last year (Fig. 4). For patients at high and very high cardiovascular risk, LDL-C target achievement was analyzed according to six therapy categories: high- and moderate-intensity statins, high- and moderate-intensity statins combined with ezetimibe, and PCSK9 inhibitors with or without statins. Tables 3 and 4 summarize the results for the very high- and high-risk groups, respectively.

In the very high-risk group (LDL-C target < 55 mg/dL), target achievement improved across all therapies over time. The highest success rates were seen with PCSK9 inhibitors combined with statins, followed by PCSK9 inhibitors alone, high-intensity statins plus ezetimibe, high-intensity statins, moderate-intensity statins plus ezetimibe, and moderate-intensity statins alone.

Similarly, in the high-risk group (LDL-C target < 70 mg/dL), target achievement also improved with all therapies.

Table 2 Distribution of all cholesterol therapies by year

	2019	2020	2021	2022	*p*-value
Total therapies in the year (n.)	217,533	183,389	222,554	252,037	
Treatment: high-intensity statins (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg), without ezetimibe or PCSK9 inhibitors					
n	30,155	25,695	29,475	31,456	
% Percentage of the total of all therapies for that year	13.86%	14.01%	13.24%	12.48%	< 0.01
Treatment: moderate-intensity statins (atorvastatin 10 or 20 mg, rosuvastatin 5 or 10 mg, or other statins), without ezetimibe or PCSK9 inhibitors					
n	154,655	125,046	144,032	150,961	
% Percentage of the total of all therapies for that year	71.09%	68.19%	64.72%	59.90%	< 0.01
Treatment: high-intensity statins + ezetimibe, without PCSK9 inhibitors					
n	5,208	6,502	11,080	16,110	
% Percentage of the total of all therapies for that year	2.39%	3.55%	4.98%	6.39%	< 0.01
Treatment: moderate-intensity statins + ezetimibe, without PCSK9 inhibitors					
n	22,866	21,895	32,426	47,296	
% Percentage of the total of all therapies for that year	10.51%	11.94%	14.57%	18.77%	< 0.01
Treatment: PCSK9i and statins, i.e., PCSK9 with any type of statin (with or without ezetimibe)					
n	56	77	159	263	
% Percentage of the total of all therapies for that year	0.03%	0.04%	0.07%	0.10%	< 0.01
Treatment: PCSK9i without statins (with or without ezetimibe)					
n	189	283	457	704	
% Percentage of the total of all therapies for that year	0.09%	0.15%	0.21%	0.28%	< 0.01
Treatment: statins without dosage* (these are statins for which the dosages could not be traced)					
n	4,404	3,891	4,925	5,247	
% Percentage of the total of all therapies for that year	2.02%	2.12%	2.21%	2.08%	< 0.01

N.B. In each of the treatment groups, the use of omega-3 or fibrates was noted but not considered in the analysis

*This group was included in the initial counts but excluded from further in-depth analyses

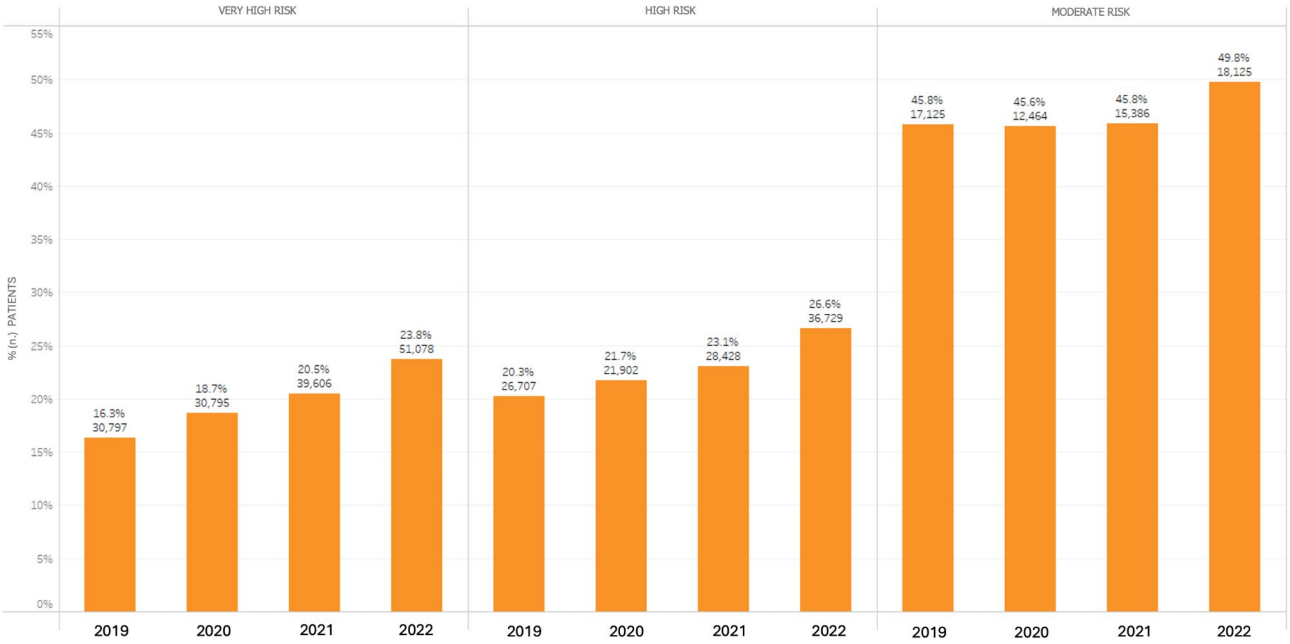


Fig. 4 Proportion of patients achieving LDL-c targets by risk level. The *p*-value for trend related each year during the 2019–2022 period is < 0.01 for all three risk levels

Table 3 LDL-C target achievement in very high-risk patients: analysis by therapy type and year

Very high-risk patients (LDL-C target < 55)	2019	2020	2021	2022	*p*-trend
Treatment: high-intensity statins (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg), without ezetimibe or PCSK9 inhibitors					
Total patients with this therapy over the four-year period	91,928				
Number and % of patients who achieve the < 55 LDL-C target	5,973 (25.2%)	5,827 (28.3%)	7,036 (30.4%)	8,190 (33.5%)	< 0.01
Treatment: moderate-intensity statins (atorvastatin 10 or 20 mg, rosuvastatin 5 or 10 mg, or other statins), without ezetimibe or PCSK9 inhibitors					
Total patients with this therapy over the four-year period	319,210				
Number and % of patients who achieve the < 55 LDL-C target	14,030 (16.6%)	13,148 (18.3%)	15,148 (18.8%)	17,160 (20.8%)	< 0.01
Treatment: high-intensity statins + ezetimibe, without PCSK9 inhibitors					
Total patients with this therapy over the four-year period	29,899				
Number and % of patients who achieve the < 55 LDL-C target	1,105 (27.5%)	1,828 (35.8%)	3,467 (40.6%)	5,765 (47.1%)	< 0.01
Treatment: moderate-intensity statins + ezetimibe, without PCSK9 inhibitors					
Total patients with this therapy over the four-year period	80,485				
Number and % of patients who achieve the < 55 LDL-c target	3,527 (23.1%)	3,927 (26.4%)	6,155 (29.4%)	9,703 (33.0%)	< 0.01
Treatment: PCSK9i and statins, i.e., PCSK9 with any type of statin (with or without ezetimibe)					
Total patients with this therapy over the four-year period	462				
Number and % of patients who achieve the < 55 LDL-C target	23 (46.6%)	30 (46.2%)	70 (54.7%)	135 (61.6%)	< 0.01
Treatment: PCSK9i without statins (with or without ezetimibe)					
Total patients with this therapy over the four-year period	1,245				
Number and % of patients who achieve the < 55 LDL-C target	66 (49.6%)	92 (43.4%)	138 (38.9%)	266 (48.8%)	n.s

N.B. In each of the treatment groups, the use of omega-3 or fibrates was noted but not considered in the analysis

Table 4 LDL-C target achievement in high-risk patients: analysis by therapy type and year

High-risk patients (LDL-C target < 70)	2019	2020	2021	2022	*p*-trend
Treatment: high-intensity statins (atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg), without ezetimibe or PCSK9 inhibitors					
Total patients with this therapy over the four-year period	21,445				
Number and % of patients who achieve the < 70 LDL-cCtarget	1,939 (35.0%)	1,676 (38.4%)	2,150 (39.2%)	2,586 (42.8%)	< 0.01
Treatment: moderate-intensity statins (atorvastatin 10 or 20 mg, rosuvastatin 5 or 10 mg, or other statins), without ezetimibe or PCSK9 inhibitors					
Total patients with this therapy over the four-year period	215,420				
Number and % of patients who achieve the < 70 LDL-C target	15,262 (25.9%)	12,203 (27.0%)	14,934 (27.9%)	17,915 (31.0%)	< 0.01
Treatment: high-intensity statins + ezetimibe, without PCSK9 inhibitors					
Total patients with this therapy over the four-year period	7,465				
Number and % of patients who achieve the < 70 LDL-C target	326 (33.3%)	450 (39.1%)	869 (41.4%)	1,531 (47.3%)	< 0.01
Treatment: moderate-intensity statins + ezetimibe, without PCSK9 inhibitors					
Total patients with this therapy over the four-year period	36.849				
Number and % of patients who achieve the < 70 LDL-C target	2,014 (31.2%)	1,965 (33.4%)	3,404 (35.5%)	5,883 (39.5%)	< 0.01
Treatment: PCSK9i and statins, i.e., PCSK9 with any type of statin (with or without ezetimibe)					
Total patients with this therapy over the four-year period	69				
Number and % of patients who achieve the < 70 LDL-C target	6 (60.0%)	4 60.0%)	16 (76.2%)	24 (61.6%)	n.s
Treatment: PCSK9i without statins (with or without ezetimibe)					
Total patients with this therapy over the four-year period	332				
Number and % of patients who achieve the < 70 LDL-C target	66 (49.6%)	92 (43.4%)	138 (38.9%)	266 (48.8%)	n.s

N.B. In each of the treatment groups, the use of omega-3 or fibrates was noted but not considered in the analysis

However, a clear upward trend is evident for both groups, with high-risk patients improving from 20.3% to 26.6% and very high-risk patients from 16.3% to 23.8%. Despite these improvements, none of the therapeutic strategies achieved optimal results.

Our analysis finally examined individuals with confirmed CAD (Fig. 5) and those with organ damage, defined as having one or more of the following comorbidities or complications: CKD, CAD, heart failure, or CeVD (Fig. 6). Among patients with T2DM and CAD, LDL-C target achievement was notably higher compared to the general T2DM population (23%–34% vs. 11%–17%) and individuals with very-high cardiovascular (CV) risk overall (16–24%). From 2019 to 2022, there was a clear improvement in LDL-C control within this group. The proportion of patients achieving LDL-C levels < 55 mg/dL increased from 23 to 34%, while those with LDL-C > 100 mg/dL declined from 19 to 14%. Similar trends but lower rates have been reported for patients with T2DM and organ damage with the proportion of patients achieving an LDL-C < 55 mg/dL improved significantly, increasing from 14.6% in 2019 to 21.1% in 2022. Overall, a significant proportion of patients continues to have LDL-C levels above recommended targets.

Discussion

Our retrospective study analyzed trends in lipid profiles and lipid-lowering treatment coverage in Italy between 2019 and 2022, leveraging the extensive AMD Annals database with a specific focus on LDL-C levels and target achievements. We evaluated the impact of different therapeutic approaches, including low- to high-intensity statins, ezetimibe, and PCSK9, in achieving LDL-C cholesterol targets, stratifying the analysis by cardiovascular risk levels and the presence of cardiovascular comorbidities. Our findings offer key insights into lipid management and treatment options in the Italian population with T2DM. We observed an improvement in average LDL-C levels over the study period, while triglyceride reductions were less pronounced and HDL-C levels remained stable. Overall, target achievement rates improved over the study period. These findings align with previous observations, such as the retrospective cohort study by Inglin et al. [20]. Despite this progress, our study shows that LDL-C target achievement remains suboptimal and decreases as risk level increases with less than one fifth of very high-risk individuals reaching the desired target in 2022. This is consistent with other recently published data by AMD Annals study group [16] reporting unsatisfying quality of care indicators.

Furthermore, we observed only a small increase in treatment coverage over the years. Disparities in therapy adoption were evident across different LDL-c ranges, with only about 45% of patients with LDL-C > 100 mg/dL receiving active treatment. On the other hand, when considering the cardiovascular risk category, approximately 80% of high-risk individuals received a treatment, without a significant increase over time. This seemingly

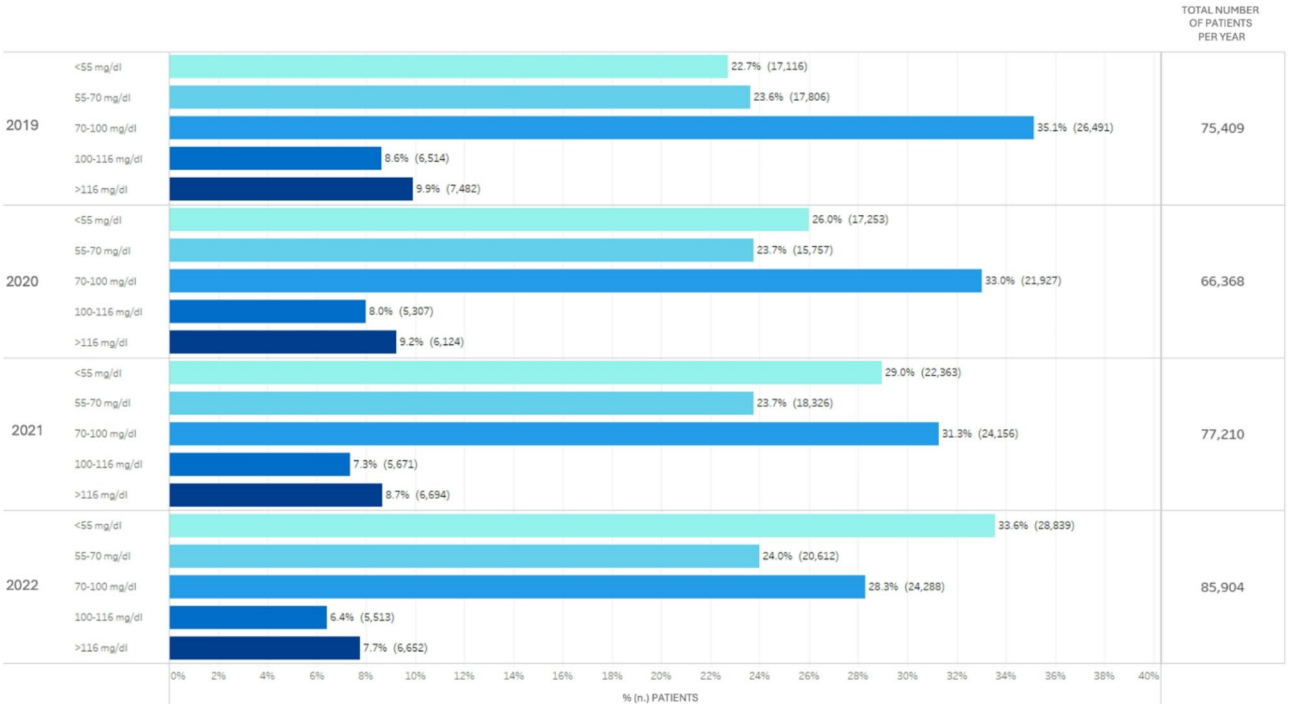


Fig. 5 Distribution over the years of patients with type 2 diabetes and CAD (target < 55 mg/dl), by LDL-C range. Percentages of patients in each LDL-C range for each year of the 2019–2022 period is significantly different, $p < 0.01$

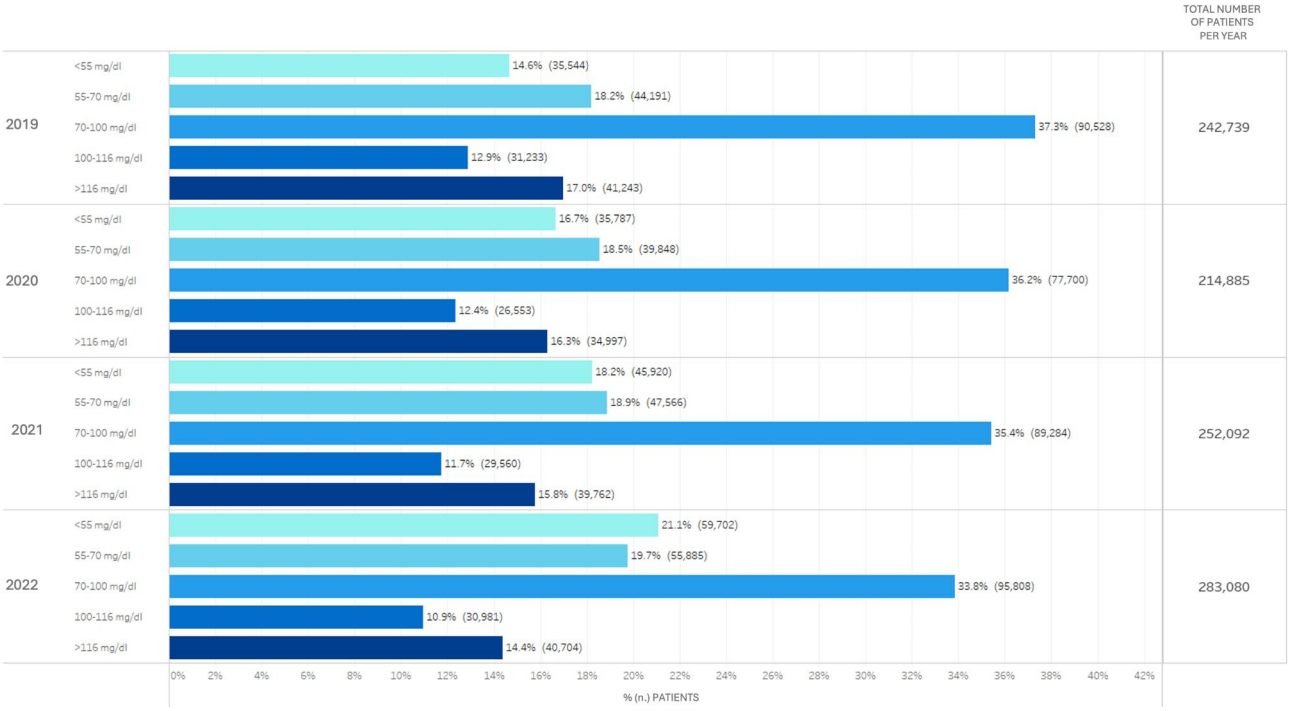


Fig. 6 Distribution over the years of patients with type 2 diabetes and organ damage (including one or more between CKD, CAD, heart failure, cerebrovascular disease; target < 55 mg/dl) by LDL-C range. Percentages of patients in each LDL-C range for each year of the 2019–2022 period is significantly different, $p < 0.01$

low percentage could be attributed to factors including potential misreporting of lipid-lowering therapy in the electronic medical record, patients achieving low LDL-C levels through lifestyle modifications alone, discrepancies in the timing of LDL-C measurement and treatment status assessment.

Regarding the proportion of patients classified as high and very high cardiovascular risk, some discrepancies emerge when comparing our findings with those of other large observational studies [21]. While our results align with a Spanish cohort of 373,185 patients with T2DM, in which 53.4% were categorized as very high risk [22], the study by Pintaudi et al. [23] reported a notably higher prevalence, with 78% of a similar population classified as very high risk.

These differences can be attributed to several factors, primarily variations in inclusion criteria and the use of different risk stratification guidelines as reference standards. Notably, a recent cross-sectional study analyzing 1,870,720 patients with type 2 diabetes across 30 provinces in China highlighted substantial regional variation in the prevalence of very high-risk patients, ranging from 60 to 75% [24].

Our findings confirm a critical gap in lipid management, especially in high-risk individuals and are partially contrasting with those reported in a registry study by Feng et al., including more than 130,000 patients, in which LDL-C target achievement was 43% in very-high risk subjects, with a 80% statin utilization in the whole study population [10]. These differences are further supported by the EUROASPIRE V survey, highlighting that primary prevention efforts remain underdeveloped in individuals at high cardiovascular risk [25].To our knowledge, our study provides the most up-to-date and comprehensive analysis of LDL-C target attainment in Italian patients with T2DM. Similar findings have also been documented in prior Italian real-world studies. In particular, the DARWIN-T2D Network of the Italian Diabetes Society evaluated lipid-lowering therapy patterns and LDL-c target attainment in a cohort of 63,000 patients from 2015 to 2016 [21]. Another Italian study focused on patients from the Tuscany region with a history of major adverse cardiac or cerebrovascular events (MACCE) and/or T2DM, providing region-specific insights into lipid management [26]. Internationally, the Santorini study [14] examined 9,600 patients, though it was not diabetes-specific, highlighting broader cardiovascular trends. Additionally, another international study [27] explored the implementation of ESC/EAS guidelines for LDL-c target achievement in patients with acute coronary syndrome, a highly specific population. Taken together, these studies underscore the ongoing challenges in lipid management and the variability in therapeutic strategies across different populations and healthcare settings. Our data emphasizes the urgent need for a more personalized approach to dyslipidemia management in

diabetic patients, as advocated by Banach et al. [28], to address the complex interplay of factors contributing to residual cardiovascular risk. In our cohort, the prevalence of cardiovascular disease, defined by the presence of CAD, CeVD, and PAD, remained alarmingly high. In 2022, 36% of patients were affected by CAD, with many cases associated with revascularization procedures and/or acute ischemic events.

Moreover, the present study highlights disparities in therapeutic approaches. Moderate-intensity statins remained the most prescribed therapy yet showing a declining trend while high-intensity statins, despite their proven efficacy, were underutilized. The combination of ezetimibe with moderate- or high-intensity statins increased nearly tripled from 2019 to 2022, but appears still low. This could be related to a lack of awareness of its added benefit, as previously reported in the IMPROVE-IT study [29] and possible unfamiliarity with the drug's safety profile. Similarly, the use of PCSK9i, particularly as monotherapy, grew considerably, likely reflecting their use in statin-intolerant patients. Notably, among very high-risk patients, PCSK9 inhibitors, particularly when combined with statins, were associated with the highest rates of success, with 62% of very high-risk patients reaching targets by 2022. This was followed by high-intensity statins combined with ezetimibe (47%) and high-intensity statins alone (34%). Similar trends were observed in high-risk patients. However, despite these promising results, the use of PCSK9i in Italy was limited during the study period due to recent regulatory approvals and high costs, factors that likely influenced our findings. Similarly, bempedoic acid and inclisiran were not included in our analysis as they were not routinely available in Italy. In line with other real world reports, although the improving trend in achieving LDL-c targets is evident, the success rate remains low in individuals with high and very high cardiovascular risk [17]. High-intensity statins, despite their superior efficacy, remain underutilized compared to moderate-intensity statins, representing a missed opportunity for better adherence to treatment guidelines [30]. Notably, while LDL-C mean values found in our cohort are consistent with those shown across 13 countries in CAPTURE study [5], the lipid lowering coverage in the present study appears to be lower, reflecting regional heterogeneity in treatment approaches. This adds to a cardiovascular risk profile heterogeneity between different countries, as previously reported [23]. Interestingly, among patients with T2DM and CAD, LDL-c target achievement rates were higher (23–34% over the years) compared to the general T2DM population (11–17%) and those with other major complications (e.g., chronic kidney disease, heart failure, or cerebrovascular disease). This may reflect greater awareness among healthcare providers of the heightened cardiovascular risk in CAD compared to other complications and point out the need for increased education of healthcare professionals regarding the importance of tight control in all high-risk groups of patients. Beyond patient adherence, several factors contribute to the challenges in achieving LDL-C targets. Clinical inertia, characterized by delayed therapy intensification, often hinders progress, especially in very high-risk patients. Additionally, statin intolerance, whether real or perceived, leads to suboptimal treatment coverage. Other barriers include provider unfamiliarity with updated guidelines, complex patient comorbidities that complicate therapy choices, and inadequate monitoring or follow-up, which can result in missed opportunities for intervention. Our study has some limitations that must be considered. First, the study's retrospective design and reliance on a database may limit the granularity of the findings, particularly regarding patient adherence and reasons for therapy selection. We acknowledge that our study population represents a highly selective group of patients with T2DM in Italy, excluding those managed exclusively by their general practitioners. This limitation suggests that LDL-C target achievement in the broader diabetic population may be even lower than reported. Additionally, cost and access barriers to advanced therapies, were not directly analyzed but likely contribute to the underutilization of PCSK9 inhibitors, especially as not all diabetes centers participating in AMD Annals had the authorization to prescribe PCSK9i. Moreover, the study's large sample size precluded longitudinal analysis, making it impossible to determine whether improvements in LDL-C attainment were due to individual patient progress or changes in the patient population. Finally, despite current European Atherosclerosis Society guidelines recommending Lp(a) assessment for comprehensive cardiovascular risk evaluation in dyslipidemia, this data was unavailable within the AMD Annals Database. Future research should prioritize interventions to improve adherence to lipid-lowering therapies, both per se and in comparison to strategies aimed to improve glycemic control, as well as strategies to enhance access to advanced treatments.

Conclusions

The coverage of lipid-lowering therapy in Italian diabetology centers is improving but remains insufficient to achieve metabolic targets and the necessary impact on cardiovascular outcomes. Significant disparities in therapy adoption persist across LDL-c ranges, underscoring the need for more aggressive intervention, particularly in patients with higher LDL-c levels who are often undertreated despite their elevated cardiovascular risk. The widespread implementation of high-intensity treatments is essential to meet recommended targets and optimize patient outcomes.

Abbreviations

AMD	Associazione Medici Diabetologi
ASCVD	Atherosclerotic cardiovascular disease
CAD	Coronary artery disease
CVD	Cardiovascular disease
CeVD	Cerebrovascular disease
CKD	Chronic kidney disease
HDL-c	High-density lipoprotein cholesterol
LDL-c	Low-density lipoprotein cholesterol
MI	Myocardial infarction
PAD	Peripheral artery disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
T2DM	Type 2 diabetes mellitus

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02648-1.

Supplementary Material 1

Supplementary Material 2

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AMD ANNALS Study Group. Participating centers (in alphabetical order by region) are listed in Supplementary Table 1.

Author contributions

A.R., P.P., F.B., L.M., N.M., W.B.: Conceptualized the study, supervised data analysis, and drafted the manuscript. A.R. R.Z., D.M., D.V., M.V., M.M., P.F.: Contributed to data analysis, interpretation, and critical revision of the manuscript. M.V., M.M.: Conducted the statistical analysis. R.Z., A.R., D.M: Provided data extraction and management. A.R., P.P., R.Z., D.M., P.S., A.O., P.F., E.S.: All authors read and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and all participating diabetes centers obtained the authorization of local Ethics Committees. All data were anonymized, and no direct patient involvement was required, ensuring compliance with ethical standards and data protection regulations.

Consent for publication

According to Italian Law 211/2003, no consent is required for epidemiological analysis regarding anonymous data.

Competing interests

The authors declare no competing interests.

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References

1. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17:83. https://doi.org/10.1186/s12933-018-0728-6.
2. Mooradian AD. Cardiovascular disease in type 2 diabetes mellitus: current management guidelines. Arch Intern Med. 2003;163:33. https://doi.org/10.1001/archinte.163.1.33.
3. Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020;41:2313–30.
4. Kim MK, Lee KN, Han K, Lee S-H. Diabetes duration, cholesterol levels, and risk of cardiovascular diseases in individuals with type 2 diabetes. J Clin Endocrinol Metab. 2024;109:e2317–23.
5. Mosenzon O, Alguwaihes A, Leon JLA, Bayram F, Darmon P, Davis TME, et al. CAPTURE: a multinational, cross-sectional study of cardiovascular disease prevalence in adults with type 2 diabetes across 13 countries. Cardiovasc Diabetol. 2021;20:154. https://doi.org/10.1186/s12933-021-01344-0.
6. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care. 2018;41:917–28.
7. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Cardiovascular disease and risk management: standards of care in diabetes—2023. Diabetes Care. 2023;46:S158–90.
8. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–88.
9. Khunti K, Ceriello A, Cos X, De Block C. Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 2018;137:137–48.
10. Feng L, Lam A, Carmody D, Lim CW, Tan G, Goh S-Y, et al. Trends in cardiovascular risk factors and treatment goals in patients with diabetes in Singapore-analysis of the SingHealth Diabetes Registry. PLoS ONE. 2021;16:e0259157. https://doi.org/10.1371/journal.pone.0259157.
11. Wong ND, Sattar N. Cardiovascular risk in diabetes mellitus: epidemiology, assessment and prevention. Nat Rev Cardiol. 2023;20:685–95.
12. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, et al. EU-Wi *d* e cross-section *a* l obser *v* at *i* o *n* al study of lipid-modifying therapy use in Se *c* ondary and Pr *i* mary care: the DA VINCI study. Eur J Prev Cardiol. 2021;28:1279–89.
13. Ray KK, Haq I, Bilitou A, Manu MC, Burden A, Aguiar C, et al. Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study. Lancet Reg Health Europe. 2023;29:100624.
14. Ray KK, Aguiar C, Arca M, Connolly DL, Eriksson M, Ferrières J, et al. Use of combination therapy is associated with improved LDL cholesterol management: 1-year follow-up results from the European observational SANTORINI study. Eur J Prev Cardiol. 2024;31:1792–803.
15. Santos RD. Inadequate control of atherosclerotic cardiovascular disease risk factors in Europe: EUROASPIRE repeats itself. Eur J Prev Cardiolog. 2019;26:820–3.

16. Russo G, De Cosmo S, Di Bartolo P, Lucisano G, Manicardi V, Nicolucci A, et al. The quality of care in type 1 and type 2 diabetes—A 2023 update of the AMD Annals initiative. Diabetes Res Clin Pract. 2024;213:111743.
17. Da Porto A, Candido R, Rocca A, Manicardi V, Nicolucci A, Miranda C, et al. Quality of care and clinical inertia in the management of cardiovascular risk factors in patients with type 1 and type 2 diabetes: data from AMD annals. J Endocrinol Invest. 2024;47:2595–602. https://doi.org/10.1007/s40618-024-02327-0.
18. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J. 2023;44:4043–140.
19. De Oliveira L, De Assis A, Giraldez V, Scudeler T, Soares P. Dyslipidemia: a narrative review on pharmacotherapy. Pharmaceuticals. 2024;17:289.
20. Inglin L, Lavikainen P, Jalkanen K, Laatikainen T. LDL-cholesterol trajectories and statin treatment in Finnish type 2 diabetes patients: a growth mixture model. Sci Rep. 2021;11:22603.
21. Morieri ML, Avogaro A, Fadini GP, The DARWIN-T2D Network of the Italian Diabetes Society. Cholesterol lowering therapies and achievement of targets for primary and secondary cardiovascular prevention in type 2 diabetes: unmet needs in a large population of outpatients at specialist clinics. Cardiovasc Diabetol. 2020;19:190.
22. Cebrián-Cuenca AM, Mata-Cases M, Franch-Nadal J, Mauricio D, Orozco-Beltrán D, Consuegra-Sánchez L. Half of patients with type 2 diabetes mellitus are at very high cardiovascular risk according to the ESC/EASD: data from a large Mediterranean population. Eur J Prev Cardiol. 2022;28:e32–4.
23. Pintaudi B, Scatena A, Piscitelli G, Frison V, Corrao S, Manicardi V, et al. Clinical profiles and quality of care of subjects with type 2 diabetes according to their cardiovascular risk: an observational, retrospective study. Cardiovasc Diabetol. 2021;20:59. https://doi.org/10.1186/s12933-021-01251-4.
24. Wang W, Qiao J, Zhang L, Zhang J, Luo J, Chen C, et al. Prevalence of very high cardiovascular disease risk in patients with type 2 diabetes mellitus: a population-based cross-sectional screening study. Diabetes Obes Metab. 2024;26:4251–60. https://doi.org/10.1111/dom.15763.
25. Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, et al. Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries. Eur J Prev Cardiol. 2021;28:370–9.
26. Berteotti M, Profili F, Nreu B, Casolo G, Zuppiroli A, Mannucci E, et al. LDL-cholesterol target levels achievement in high-risk patients: an (un)expected gender bias. Nutr Metab Cardiovasc Dis. 2024;34:145–52.
27. Laufs U, Catapano AL, De Caterina R, Schiele F, Sionis A, Zaman A, et al. The effect of the 2019 ESC/EAS dyslipidaemia guidelines on low-density lipoprotein cholesterol goal achievement in patients with acute coronary syndromes: The ACS EuroPath IV project. Vasc Pharmacol. 2023;148:107141.
28. Banach M, Surma S, Reiner Z, Katsiki N, Penson PE, Fras Z, et al. Personalized management of dyslipidemias in patients with diabetes—it is time for a new approach (2022). Cardiovasc Diabetol. 2022;21:263. https://doi.org/10.1186/s12933-022-01684-5.
29. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97. https://doi.org/10.1056/NEJMoa1410489.
30. Masi D, Zilich R, Candido R, Giancaterini A, Guaita G, Muselli M, et al. Uncovering predictors of lipid goal attainment in type 2 diabetes outpatients using logic learning machine: insights from the AMD annals and AMD Artificial Intelligence Study Group. JCM. 2023;12:4095.

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