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ORIGINAL ARTICLE

Evaluation of biochemical and economic outcomes in patients treated with PCSK9 inhibitors in a real clinical practice setting

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ABSTRACT

BACKGROUND: PCSK9 inhibitors (PCSK9i) in combination with high-dose statins can reduce LDL-cholesterol (LDL-C) levels by 50-60% over statin monotherapy. This analysis investigated biochemical (LDL-C reduction) and economic outcomes in Italian patients treated with PCSK9i or potentially eligible but untreated.

METHODS: Administrative databases of healthcare institutions covering around 5 million residents were used to identify patients with PCSK9i prescriptions or potentially eligible-untreated patients between 2017 and Oct-2022. Outcomes were assessed during follow-up in cohorts balanced for baseline covariates by propensity score matching (PSM).

RESULTS: After PSM-balancing, 2649 treated and 2649 potentially eligible-untreated patients were included: mean age 64.4-64.7 years, 70-68% males, 92-93% with hypertension, 24-25% with diabetes, and 87% with previous atherosclerotic/cardiovascular events. During follow-up, PCSK9i-treated patients *versus* untreated/eligible showed a reduction of LDL-C levels (68.9±43.9 *vs.* 100.4±34.6 mg/dL, P<0.0001), hospitalization rates for heart attack (4.5% *vs.* 6.8%, P=0.0069), heart failure (4.5% *vs.* 6.6%, P=0.010), and lower all-cause mortality (3.2% *vs.* 9.5%, P<0.0001). The multivariate Cox model confirmed that eligible-untreated patients had a more than doubled mortality risk compared to the PCSK9i-treated ones (HR: 2.291, 95%CI: 1.651-3.178, P<0.0001). Although mean annualized total healthcare costs were higher in PCSK9i-treated *versus* untreated/eligible patients (€6745 *vs.* €4343, P<0.0001), because of the higher drug costs, PCSK9i therapy was associated with reduced expenses for hospitalizations (€1113 *vs.* €1687, P<0.0001) and specialist outpatient services (€386 *vs.* €787, P<0.0001).

CONCLUSIONS: The real-world analysis suggests that therapy with PCSK9i resulted in reduced LDL-C levels, lower mortality rates and cost savings for hospitalizations and specialist services.

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KEY WORDS: Cardiovascular diseases; Costs and cost analysis; Cholesterol, LDL; PCSK9 inhibitors.

The control of low-density lipoprotein cholesterol (LDL-C) through lipid-lowering therapy represents a landmark of cardiovascular prevention.[1] The guidelines of the European Societies of Cardiology and Atherosclerosis (ESC/EAS) released in 2019 have further decreased the recommended target levels of LDL-C, especially in patients at high and very high cardiovascular risk.[2] Statins remain the most commonly used entry therapy for patients with dyslipidemia.[2] However, evidence has shown an unsatisfying relative risk reduction after statin treatment of around 30%; the remaining 70% which is commonly referred as "residual risk" or "persistent risk".[3, 4] Therefore, a current open question is whether other treatment options can lead to greater LDL-C reductions thus increasing the chances of lipid target attainment.

The advent of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) unveiled a new phase in the treatment of hypercholesterolemia.[5] The mechanism of action of these drugs was described more than one decade ago and is based on the inhibition of the PCSK9 enzyme, involved in the breakdown of hepatic LDL receptors and typically upregulated by statins. The inhibition of PCSK9 allows a more effective hepatic uptake of LDL, resulting in a decrease in circulating LDL-C levels up to 50%.[5] Multiple randomized clinical trials (RCTs) for PCSK9i have demonstrated their clinical benefits on various domains of patients' lipid profiles, in turn resulting in better cardiovascular and mortality outcomes.[6-16] A recently published systematic literature review and meta-analysis comprehensively browsed PubMed, Web of Science, Scopus, and Cochrane CENTRAL to summarize the results of RCTs comparing PCSK9i *versus* placebo.[17] After the selection of 21 studies corresponding to a total of 24,732 patients, the meta-analysis reported significant improvements associated with PCSK9i over placebo in terms of biochemical parameters, namely LDL-C, total cholesterol, triglycerides, lipoprotein(a) and Apo-B. Besides, the results of safety outcomes revealed with lower likelihood of myocardial infarction (OR: 0.87) and cerebrovascular events (OR: 0.71) in patients treated with PCSK9i.[17]

The positive data from clinical research provided the necessary regulatory evidence for the approval of PCSK9i by agencies such as Food and Drug Administration (FDA)[18] and the European Medicines Agency (EMA),[19, 20] and put the basis of clinical guidelines for the use of these therapies in different patient populations.[2, 21]

In June 2022, the Italian Medicines Agency (AIFA) updated the LDL-C threshold values from 100 to 70 mg/dL for the prescription of PCSK9is in patients ≤80 years in secondary prevention.[22]

The promising results from clinical research have been substantiated by data form from the real clinical practice. In Italy, the recent findings of the AT-TARGET-IT registry indicated that early initiation of PCSK9i proprotein in patients with acute coronary syndrome (strike early strike strong strategy) was successful in increasing the percentage of patients reaching the LDL-C target of <55 mg/dL[23] and in achieving all the clinical endpoints, in terms of reduced rates of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and ischemia-driven revascularization.[23]

Nonetheless, real-world evidence (RWE) from two contemporary nationwide registries of patients with stable coronary artery disease highlighted how a significant proportion of patients who meet the ESC/EAS and AIFA eligibility criteria for PCSK9i therapy are still untreated.[24]

The present analysis aimed to evaluate biochemical outcomes, in terms of LDL cholesterol reduction, and the healthcare resource utilization and costs covered by the Italian National Health System (NHS) in patients treated with PCSK9i and in those potentially eligible for PCSK9i therapy but not treated.

Materials and methods

Data source

A retrospective observational analysis was performed using the administrative flows of a pool of Italian Local Health Units (LHUs) covering approximately 5 million health-assisted residents. Administrative databases are large data warehouses of healthcare resources/services supplied and reimbursed by the Italian National

Healthcare Service (NHS). The following databases were used for this analysis: beneficiaries' database for patients' demographics, pharmaceutical database for data on drug prescriptions with their Anatomical Therapeutic Chemical (ATC) code, hospitalization database for the hospital discharge diagnoses classified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), exemption database for active payment waiver codes associated with specific disease diagnoses, and outpatient specialist service database for data on specialist visits, diagnostic procedures and laboratory tests. Moreover, data from the laboratory test database were linked to the other administrative databases.

To ensure patients' privacy, an anonymous univocal numerical code was assigned to each participating subject, in full compliance with the European General Data Protection Regulation (GDPR) (2016/679). This code also allowed the electronic linkage between the different databases. All the results were reported in an aggregated form, to make it impossible to identify patients, either directly or indirectly. Informed consent was waived in line with the pronouncement of the Data Privacy Guarantor Authority, General Authorization for personal data treatment for scientific research purposes – n.9/2014. The analysis was approved by the ethics committees of the healthcare units involved.

Study design and selection criteria

From 2017 to October 2022, the analysis included all patients with at least one prescription for PCSK9i or those potentially eligible for treatment but not treated (herein referred as "PCSK9i-untreated/eligible"). The users of PCSK9i were identified through the prescriptions of evolocumab (ATC code C10AX13) or alirocumab (ATC code C10AX14). The date of inclusion (index-date) was that of the start of therapy with PCSK9is. Besides, the PCSK9i-untreated/eligible patients were selected among those who had at least one measurement of LDL-C during the inclusion period and at least 1 year of data availability before the index-date (last available LDL-C test). The eligibility to PCSK9i was established along with AIFA reimbursability criteria that apply to patients in primary prevention (without cardiovascular events during all the available characterization period), patients with familial hypercholesterolemia, and patients in secondary prevention (with at least one cardiovascular event during all the available characterization period).

In detail, the AIFA indications for evolocumab were the following: 1) primary prevention in patients aged ≤80 years with homozygous familial hypercholesterolemia; 2) primary prevention in patients aged ≤80 years with heterozygous familial hypercholesterolemia and LDL-C levels ≥130 mg/dL despite treatment for at least 6 months with a high potency statin at the maximum tolerated dose + ezetimibe or with proven intolerance to statins and/or ezetimibe; 3) secondary prevention in patients aged ≤80 years with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia or mixed dyslipidemia with LDL-C levels ≥70 mg/dL despite treatment for at least 6 months with a high-potency statin at the maximum tolerated dose + ezetimibe or after a single LDL-C measurement in case of recent acute myocardial infarction (AMI) in the last 12 months or multiple cardiovascular events or with demonstrated intolerance to statins and/or ezetimibe.

The AIFA indications for alirocumab were the following: 1) primary prevention in patients aged ≤80 years with heterozygous familial hypercholesterolemia and LDL-C levels ≥130 mg/dL despite treatment for at least 6 months with a high potency statin at the maximum tolerated dose + ezetimibe or with demonstrated intolerance to statins and/or ezetimibe; 2) secondary prevention in patients aged ≤80 years with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia or mixed dyslipidemia and LDL-C levels ≥70 mg/dL despite treatment for at least 6 months with a high potency statin at the highest tolerated dose + ezetimibe or after a single LDL-C measurement in case of recent AMI (last 12 months) or multiple cardiovascular events or with demonstrated intolerance to statins and/or ezetimibe.

The methodological details used to ascertain the presence of familial hypercholesterolemia, or the occurrence of cardiovascular events are

provided in Supplementary Digital Material 1, Supplementary Table I, Supplementary Table II, Supplementary Table III. The PCSK9i-untreated/eligible patients were selected in the presence of the following conditions: statin use, identified by the ATC codes C10AA, C10BA, C10BX in the 6 months before the index-date; adherence to statins, considered as a proportion of days covered (PDC) at least 60% in the 6 months before the index-date; ezetimibe use, identified by the ATC codes C10AX09, C10BA02, C10BA05, C10BA06, C10BA10, C10BA11, C10BA12 in the 6 months before the index-date; intolerance to statins, identified by the presence of at least two different statins in the 12 months before the index-date. The PDC method was used to o estimate adherence, based on the proportion of days when a patient has access to a medication over a given observation timespan, as previously described.[25]

The characterization period was the whole period of data availability (at least 1 year) before the index-date, and the follow-up was all the available period after the index-date. Patients with no continuous inclusion during the study, for instance those who moved to another region, were excluded from the analysis.

Patients' baseline characteristics

For all the patients included, the demographic characteristics were collected at index-date, specifically age and gender distribution expressed as percentage of male subjects. During the characterization period, the general clinical status was investigated using the Charlson comorbidity index[26] which assigns a score to 19 weighted concomitant diseases, searched through drug treatments and hospitalizations in the 12 months preceding inclusion. Moreover, the following comorbidities were also recorded: hypertension, diabetes, atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), chronic pulmonary disease, cancer, peptic ulcer disease, and congestive heart failure (CHF). These conditions were identified by means of hospitalization discharge diagnoses, drug prescriptions, and/or exemption codes detailed in Supplementary Digital Material 2, Supplementary Table IV.

Analysis of biochemical and economic outcomes

During all available follow-up, biochemical outcomes were assessed in PCSK9i-treated and PCSK9i-untreated/eligible patients by evaluating the last C-LDL determination recorded in the database. Moreover, the number and percentage of patients with at least one hospitalization and with the following diagnoses (at any level) were reported: AMI (ICD-9-CM code 410-411); percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) (procedures 36.X, 00.6); heart failure (HF, ICD-9-CM code 428); cerebrovascular events (ICD-9-CM codes 430-438), and all-cause mortality. During the whole follow-up, the mean annualized direct healthcare costs per patient were estimated in PCSK9i-treated and in PCSK9i-untreated/eligible patients, relating to pharmaceutical prescriptions, hospitalizations and outpatient specialist services according to the prices established by the Italian NHS for the healthcare providers or to regional tariffs.

Statistical analysis

Continuous variables are reported as the mean±standard deviation (SD), and categorical variables as frequencies and percentages. To assess whether PCSK9i-treated and PCSK9i-untreated/eligible patients were comparable or not for the baseline characteristics, the standardized mean difference (SMD) was calculated for baseline variables. SMD<0.2 was considered an adequate balance for a variable between the groups.[27] Propensity score matching (PSM) with a 1:1 ratio was used to balance the groups considering the following potential confounders: age, gender, Charlson comorbidity index, PCSK9i treatment, diabetes, hypertension, ASCVD, and CHF.

A Cox proportional hazard model was developed to analyze the probability of mortality event onset among treatment groups, adjusted for baseline variables and CKD which resulted unbalanced across PSM-matched cohorts. Lastly, a generalized linear model (GLM) was applied as a multivariate approach to identify predictors of healthcare costs among treatment groups.[28] In cost analysis, outliers, *i.e.* those costs exceeding

more than 3 times the SD over the mean value, were excluded. A P value <0.05 was considered statistically significant and all the analyses were performed using Stata SE version 17.0 (StataCorp, College Station, TX, USA).

Results

The analysis identified 4359 PCSK9i-treated and 4020 PCSK9i-untreated/eligible patients. After balancing the groups for the baseline covariate through PSM, 2649 PCSK9i-treated patients were compared with 2649 PCSK9i-untreated/eligible patients (Table I). PCSK9i-treated and PCSK9i-untreated/eligible patients were aged respectively 64.4 and 64.7 years, there was a preponderance of male subjects (70-68%) and the most frequent comorbidities were hypertension (92-93%), atherosclerotic and cardiovascular diseases (86.6-86.9%) and diabetes (24-25%). The PCSK9i-treated patients compared to the PCSK9i-untreated/eligible showed a lower rate of cerebrovascular disease (14.0 *vs.* 23.1%, SMD=0.235), and CKD (4.9 *vs.* 14.9%, SMD=0.348).

The levels of LDL-C, cardiovascular-related hospitalizations and mortality rates were then compared across groups during all available follow-up (on average 2.9 years and 3.2 years, respectively). As detailed in Table II, PCSK9i-treated patients had significantly lower LDL-C levels compared to the untreated/eligible ones (68.9 *vs.* 100.4 mg/dL, P<0.0001). Despite the low number of hospitalizations recorded and the limited length of follow-up (<3 years), PCSK9i-treated displayed a significantly lower rate of hospitalization for AMI (4.4% *vs.* 6.8%, P=0.0069), for HF (4.4% *vs.* 6.6%, P=0.0100), and for cerebrovascular events (4.1% *vs.* 6.4%, P=0.0049), together with a reduced mortality rate (3.2% *vs.* 9.5%, P<0.0001). Cox regression model to predict the occurrence of outcomes, after PSM balancing, revealed that PCSK9i-untreated/eligible patients had an increased mortality risk

TABLE I.—*Baseline demographic and clinical characteristics of patients PCSK9i-treated and PCSK9i-untreated/eligible patients after PSM.*

	PCSK9i-treated (N.=2649)	PCSK9i-untreated/eligible (N.=2649)	SMD
Male gender, N. (%)	1851 (69.9%)	1804 (68.1%)	0.038
Age at index-date, years, mean±SD	64.4±9.4	65.7±9.4	0.177
Age at index-date, years, median	65.0	67.0	-
Age groups			
<50 years, N. (%)	205 (7.7%)	180 (6.8%)	0.036
51-60 years, N. (%)	678 (25.6%)	572 (21.6%)	0.094
61-70 years, N. (%)	987 (37.3%)	950 (35.9%)	0.029
71-80 years, N. (%)	740 (27.9%)	947 (35.7%)	0.168
>80 years, N. (%)	39 (1.5%)	0 (0%)	0.243
Charlson Comorbidity Index, mean±SD	0.9±1.0	0.9±1.1	0.017
Charlson Comorbidity Index=0, N. (%)	1121 (42.3%)	1236 (46.7%)	0.087
Charlson Comorbidity Index=1, N. (%)	981 (37.0%)	910 (34.4%)	0.056
Charlson Comorbidity Index ≥ 2, N. (%)	547 (20.6%)	503 (19.0%)	0.064
Comorbidities			
Hypertension, N. (%)	2443 (92.2%)	2474 (93.4%)	0.045
Diabetes, N. (%)	633 (23.9%)	664 (25.1%)	0.027
ACVSC, N. (%)	2294 (86.6%)	2302 (86.9%)	0.009
AMI, N. (%)	1434 (54.1%)	1197 (45.2%)	0.179
Cerebrovascular disease, N. (%)	372 (14.0%)	613 (23.1%)	0.235*
CHF, N. (%)	307 (11.6%)	318 (12.0%)	0.013
Chronic pulmonary disease, N. (%)	68 (2.6%)	110 (4.2%)	0.089
CKD, N. (%)	129 (4.9%)	395 (14.9%)	0.348*
Rheumatologic disease, N. (%)	710 (26.8%)	792 (29.9%)	0.069
Cancer, N. (%)	292 (11.0%)	330 (12.5%)	0.045

AMI: acute myocardial infarction; ASCVD: atherosclerotic cardiovascular disease; CHF: congestive heart failure; CKD: chronic kidney disease; PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitors; PSM: propensity score matching; SD: standard deviation; SMD: standardized mean difference.
*SMD values ≥0.2, indicating unbalanced variables between the groups.

TABLE II.—*Biochemical outcomes, cardiovascular-related hospitalizations and mortality in PSM-balanced cohorts of patients PCSK9i-treated and PCSK9i-untreated/eligible patients.*

	PCSK9i-treated (N.=1543)	PCSK9i-untreated/eligible (N.=1595)	P
LDL-C (last test), mg/dL, mean±SD	68.9±43.9	100.4±34.6	<0.0001*
AMI, N. (%)	70 (4.5%)	109 (6.8%)	0.0069*
PCI/CABG, N. (%)	94 (6.1%)	116 (7.3%)	0.2107
HF, N. (%)	69 (4.5%)	106 (6.6%)	0.0100*
Cerebrovascular events, N. (%)	63 (4.1%)	102 (6.4%)	0.0049*
Mortality, N. (%)	49 (3.2%)	152 (9.5%)	<0.0001*
Follow-up length, years, mean±SD	2.9±1.3	3.2±1.8	

AMI: acute myocardial infarction; CABG: coronary artery bypass graft surgery; HF: heart failure; LDL-C: low-density lipoprotein cholesterol; PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitors; PCI: percutaneous coronary intervention; PSM: propensity score matching; SD: standard deviation. *Statistically significant.

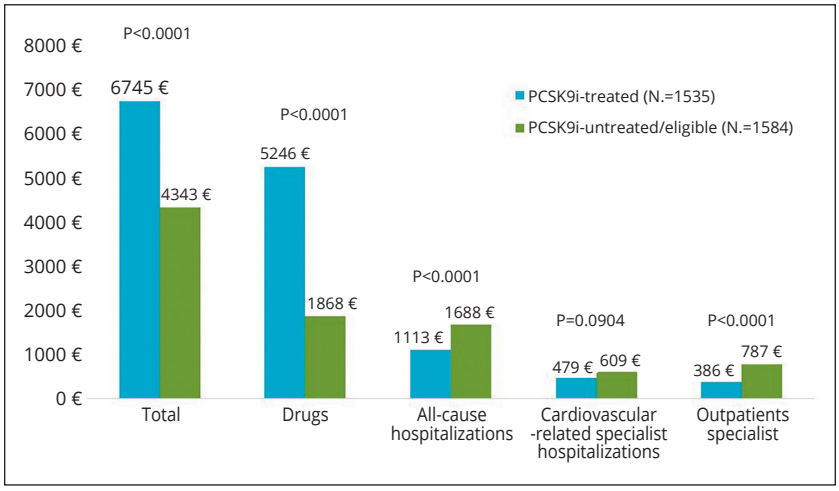

Figure 1.—Annual healthcare direct costs per patient during the follow-up in PCSK9i-treated and PCSK9i-untreated/eligible patients. Significant P values are highlighted in bold.

compared to the PCSK9i-treated patients with an HR 2.291 (95%CI 1.651-3.178, P<0.0001). Concerning the other outcomes, a comparable risk was found between the two cohorts, probably due to the relatively short follow-up period of less than 3 years.

The analysis of the annualized direct costs per patient during all available follow-up (Figure 1) showed that PCSK9i-treated patients were characterized by higher overall costs compared to PCSK9i-untreated/eligible patients (€ 6745±7937 *vs.* € 4343±9082, P<0.0001), mainly driven by drug expenses (€ 5245±7243 *vs.* 1868±6933, P<0.0001), in front of reduced costs for all-cause hospitalizations (€ 1113±2847 *vs.* € 1687±3754, P<0.0001), cardiovascular-related hospitalizations (€ 479±1971 *vs.* € 609±2326, P=0.0904, NS), and outpatient specialist services (€ 386±721 *vs.* € 787±3122, €, P<0.0001).

The GLM to identify the potential predictors of mean annualized costs (excluding PCSK9i drug cost) after PSM balancing revealed that PCSK9i-untreated/eligible patients were associated with a healthcare cost increase of +2084€/patient per year with respect to PCSK9i-treated patients. Other variables, such as the comorbidity index and CKD were also predictive of cost increase (Supplementary Digital Material 3: Supplementary Table V).

Discussion

The present observational analysis, carried out in a setting of Italian real clinical practice, compared the biochemical and economic outcomes between a cohort of patients with hypercholesterolemia treated with PCSK9-i and a matched cohort of patients who met the eligibility criteria to receive PCSK9-i, recently updated by AIFA,[22] but still untreated.[29]

The assessment of demographic variables confirmed that the included population was around 65 years of age with a slight predominance of male gender, in agreement with previous national and international evidence.[30, 31] The relatively old age of our patients might be feasibly explained by the criteria of PCSK9-i eligibility and reimbursement that apply to patients with a previous history of failure or intolerance to statins traditionally used as first therapy in most patients with dyslipidemia.[10, 29] Moreover, the absence of clinically relevant drug-drug interactions of PCSK9i with other drugs might represent a further advantage in elderly subjects that often require polypharmacy regimens.[31]

The analysis of biochemical and clinical endpoints suggested a more marked reduction of LDL-C levels, a lower likelihood of AMI, HF and cerebrovascular disease, together with a reduced mortality rate in patients with an ongoing PCSK9i treatment compared to those who met the eligibility criteria to therapy but still untreated. The successful reduction of LDL-C after PCSK9i is largely consistent with the results of several RCTs.[6-16] Since 2014, two phase 3 placebo-controlled 3 RCTs, the GAUSS-2 trial (Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin intolerant Subjects) and the MENDEL-2 (Monoclonal antibody against PCSK9 to reduce Elevated LDL-C in subjects currently Not receiving Drug therapy for Easing Lipid levels-2) demonstrated the efficacy and safety of evolocumab in reducing LDL-C levels over placebo.[6, 7] Successively, the ODYSSEY outcomes trials[10-12, 16] reported that in patients with a recent acute coronary syndrome followed up to 5 years, alirocumab therapy resulted in more than halved LDL-C levels in 4 months, and in markedly reduced rates of major adverse cardiovascular events (MACE), and mortality.

More recently, the FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial demonstrated that treatment with evolocumab added to a previous statin therapy lowered LDL-C levels to a median of 30 mg/dL within 48 weeks, and reduced the risk of cardiovascular events, such as heart attack and stroke, in high-risk patients.[14] A secondary analysis of the FOURIER trial found a direct relationship between achieved LDL-C levels at 4 weeks and related cardiovascular outcomes (primary composite endpoint: cardiovascular death, AMI, stroke, coronary revascularisation, or unstable angina; secondary composite endpoint: cardiovascular death, AMI, or stroke).[15]

RWE data further corroborated the biochemical and clinical benefits of PCSK9i emerged from clinical trials. The recent Italian multicenter real-world study AT-TARGET-IT confirmed that the use of PCSK9i was effective for the achievement of lipid targets in patients with high and very high cardiovascular risk, mostly due to the better adherence and persistence compared to statin therapy.[23] Another study by Piccinni *et al.* on the administrative database of the Tuscany region during one year of observation reported that the prescription attitude of clinicians PCSK9i is below the expectations, but users of PCSK9i in monotherapy showed a high adherence and persistence.[32]

The effect of PCSK9i treatment on cardiovascular morbidity and mortality deserves a more in-depth clarification. Plenty of outcome research and long-term clinical trials are currently focused on the role of PCSK9i therapy on cardiovascular risk in patients with dyslipidemia. Our data on the positive rebounds of the PCSK9is in reducing the rates of cardiovascular/cerebrovascular hospitalizations and deaths, although promising and largely consistent with previous data, should be anyhow interpreted with caution, considering the relatively short follow-up below 3 years and the included population that was burdened by several cardiovascular comorbidities. Moreover, differently than the two mentioned Italian studies, we did not consider drug utilization in terms of adherence and persistence because this was not among the study aims.

Lastly, cost analysis revealed that the higher costs associated with the elevated prices of PCSK9i compared to statins were partly counterbalanced by significant reductions in expenditures for hospitalizations and specialist services. Previous cost-effectiveness analyses in other countries suggested that PCSK9i added to standard lipid-lowering treatment should be contextualized in the specific population at increased risk

for MACE. PCSK9is have been deemed as a cost-effective option in patients with familial hypercholesterolemia, ASCVD, or other risky conditions.[33-36]

This real-world analysis opens the way to further long-term studies useful to enlarge our awareness of drug access and public healthcare sustainability of PCSK9is. It is conceivable that, if confirmed, the positive data of PCSK9is on LDL-C target achievement as well as reduction of cardiovascular morbidity and mortality might have the potential to yield cost savings deriving from cardiovascular risk management.

One novelty of this study is due to the contextual analysis of the biochemical and economic outcomes of PCSK9i use in a routine clinical practice setting, as similar evidence, especially in Italy is currently scanty. Another strength is represented by the large sample size of an unselected population in real-life settings, thus comprising patients generally underrepresented in RCTs.

Limitations of the study

Some of this study limitations should be mentioned. The findings of the current analysis derive from data of a subset of health-assisted individuals representing a sample of the Italian population. However, the administrative databases report incomplete information on comorbidities and other potential confounders (such as the role of smoking habit, blood pressure control, and obesity), thus limiting the evaluation of their impact on the present results. Since the comorbidities analysed were addressed based on available data before inclusion (using a proxy of diagnosis, such as the use of disease-specific medications and/or disease-related hospitalizations), there might be incomplete capture of these variables among patients. The comparative analysis between the two cohorts was performed by balancing them with a PSM approach: despite PSM represents a valuable methodology to abate non-randomization bias in observational analyses, it was based on the covariates extracted from the databases and evaluated at baseline. Some factors not traceable from the administrative databases were not included, thus the influence of these unknown/unmeasured confounders could not be considered (the lack of a priori randomization in observational analyses generates data not powered as those which could be derived from randomized trials). Lastly, inclisiran was not included in our analysis, since it was approved for reimbursement in Italy in October 2022, after the closure of our inclusion period.[37]

Conclusions

In conclusion, despite some limitations related to the impossibility of extracting certain clinical variables from the databases, these data generated from real clinical practice seem to suggest that, in patients with a severe cardiovascular profile, PCSK9i therapy would result in a greater reduction in C-LDL levels, mortality, and containment of the consumption of resources and direct healthcare costs, especially in terms of hospitalizations and specialist services (Supplementary Digital Material 4: Supplementary Figure 1).

Key messages

- PCSK9 inhibitors (PCSK9i) in combination with high-dose statins can reduce LDL-cholesterol levels by 50-60% compared to statins alone, but a significant proportion of patients potentially eligible to PCSK9i therapy are still untreated.
- This real-world analysis confirmed that PCSK9i-treated patients had a more marked reduction of LDL-cholesterol, resulting in lower rates of cardiovascular-related hospitalizations and all-cause mortality.
- Although PCSK9i are a more expensive option than statins, their use might provide cost savings, especially for hospitalizations and specialist services.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Melania Dovizio: conceptualization, supervision, original draft preparation, reviewing; Marta Nugnes: original draft preparation, and editing; Biagio Iacolare, Carmela Nappi, Stefania Saragoni: data analysis, and methodology; Margherita Andretta, Antonietta Barbieri, Fausto Bartolini, Gianmarco Chinellato, Mariarosaria Cillo, Stefania Dell'Orco, Stefano Grego, Antonella Lavalle, Cataldo Procacci, Davide Re: data collection, data curation; Luca Degli Esposti: conceptualization, methodology, supervision. All authors read and approved the final version of the manuscript.

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Supplementary data

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