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Sex-differences in factors and outcomes associated with adherence to statin therapy in primary care: need for customisation strategies

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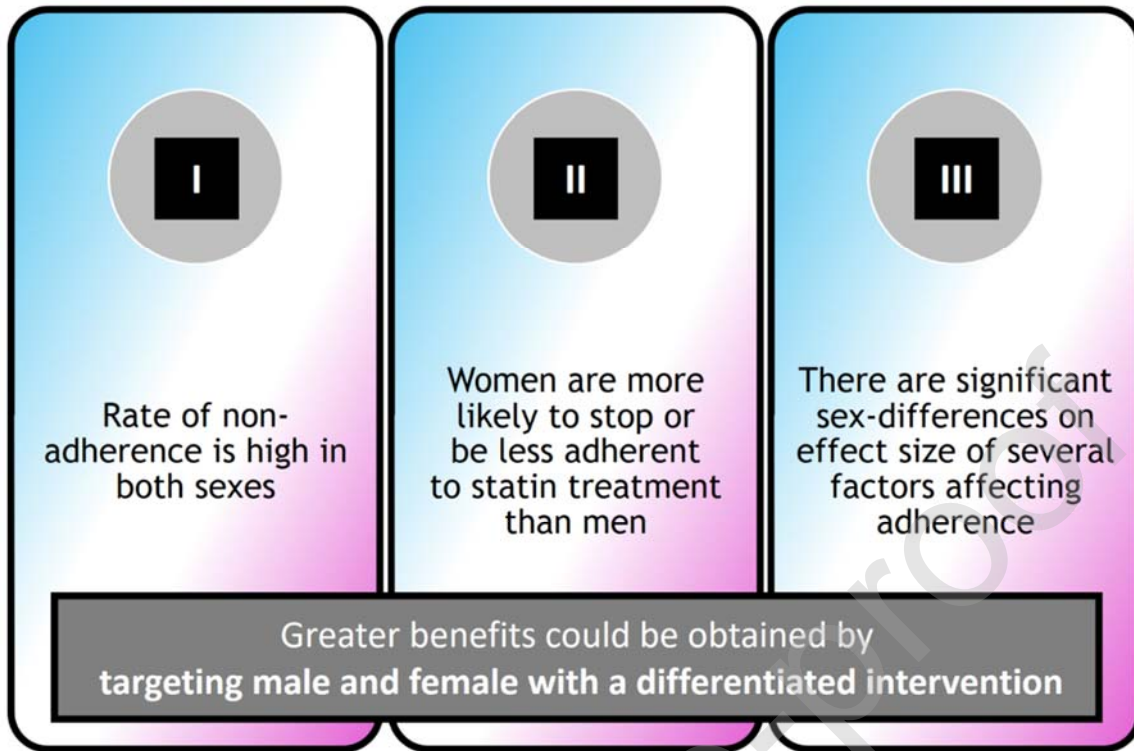

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Graphical abstract

I — Rate of non-adherence is high in both sexes

II — Women are more likely to stop or be less adherent to statin treatment than men

III — There are significant sex-differences on effect size of several factors affecting adherence

Greater benefits could be obtained by **targeting male and female with a differentiated intervention**

ABSTRACT

Despite the invaluable efficacy of statins, adherence to therapy is extremely poor in clinical practice. Improvement interventions should be as personalized as possible, but it is necessary to know factors that most influence adherence, and sex seems to be a key determinant. Thus, we aimed at exploring potential areas of sex-differences in statin adherence in a real-world population. For this purpose, we assessed adherence (as proportion of days covered) on a wide cohort of new statin users aged >40 years, and we evaluated its association with several covariates through sex-stratified log-binomial regression models. In addition, to compare also the benefits of optimal statin adherence in primary prevention of cardiovascular disease between men and women, we implemented sex-stratified Cox proportional hazard models.

Our study showed that women are more likely to stop or be less adherent to statin treatment than men. Moreover, we observed significant sex-differences on effect size of several factors associated with adherence that should be taken into consideration for the management of patients. Finally, we observed no significant difference between men and women regarding statin efficacy in terms of reduction of incident

hospitalization for ischemic heart disease and/or non-haemorrhagic cerebrovascular disease.

These results invoke the responsibility of physicians to a prompt and personalized intervention. Physicians should consider routine screening for non-adherence in their clinical practice, target patients at higher risk of non-adherence, and improved motivation and communication.

Key Words: Statins; Adherence; Gender-medicine; Administrative database

1. Background

Statins are cholesterol-lowering drugs whose efficacy in reducing cardiovascular (CV) morbidity and mortality are one of the most remarkable successes of clinical CV medicine.[1-4] However, adherence to statin therapy is extremely poor in clinical practice.[5-8] Medication non-adherence usually refers to whether patients fail to take the medication as directed (dose and frequency of regimen) and/or discontinue it prematurely [9]. It is a growing concern to clinicians, healthcare systems, and other stakeholders,[10] because of its high prevalence and its association with adverse outcomes and higher costs of care.[11]

Among the theories used to explore patient adherence to therapeutic regimens, one of the most commonly used is a patient-centred approach,[12, 13] in which the representations of illness (e.g., potential impact of the illness, symptoms experienced, illness controllability by treatment) made by patients guide their behaviour and performance with therapy. This approach can be strongly influenced by sex.[14] Although some evidence has suggested a gender difference in the extent of adherence to some chronic treatments, including the lipid-lowering therapy,[14] whether predictors of statin non-adherence may differ between sex has not been fully investigated.[14, 15] Furthermore, even if the association between good adherence to therapy and efficacy in terms of reduction of CV events is established,[16] whether the extent of this association is the same in men and women has been poorly addressed.[17] Thus, we aimed at exploring potential areas of sex-differences in statin adherence in the clinical practice, and at comparing the benefit gained by having an optimal statin adherence, in terms of hospitalization for ischemic heart disease and/or non-haemorrhagic cerebrovascular disease saved, between men and women.

2. Methods

2.1. Data source and cohort selection

This study used administrative databases of Lombardy region (data availability 2000-2012), the most populated region in Italy (more than 10 million people, one-sixth of Italy's population). See **Supplementary material** for further details.

The target population consisted of subjects with age >40 years, who have received a first prescription for statin medication (ATC C10AA) between January 1, 2002 and December 31, 2007. We defined the index date as the date of the first prescription fill for any statin in the study period. Patients were required to not have prior statin prescription in a two-year period before the index date, to select only incident users. Patients were also required to have 1 year of enrolment after the index date to allow complete adherence evaluation at 1-year of follow-up.

2.2. Assessing adherence to statins

Exposure to statins was inferred from the presence of prescriptions for any drugs belonging to the ATC class C10AA in the prescription database and was estimated by assuming a treatment schedule of one tablet per day. Adherence was measured through proportion of days covered (PDC), calculated as the ratio between the number of days covered by medication and the total number of days in follow-up. In the case of an early refill for the same drug (same statin at the same dosage), the start of this prescription was shifted after the end of the previous one. In the case of an early refill for a different dose or a different statin, this prescription was considered as a change in therapy and the previous one was truncated. See **Supplementary material** for detailed explanation.

PDC ranges from 0 to 1, with 1 corresponding to 100% medication adherence. We defined a threshold for optimal adherence at 80% (PDC >0.80), which is a conventional threshold deemed necessary to obtain adequate therapeutic efficacy. [18]

For the analysis of persistence, treatment discontinuation was defined as a gap of at least 30 days between the end of a prescription coverage and the beginning of the following one. As already reported in literature,[19-22] the gap was chosen to represent a period between doses that would lead to a decline in therapeutic effectiveness [23] and because it is the mean pharmaceutical dispensation duration for statin packages in Italy. A sensitivity analysis where treatment discontinuation was defined as a gap of at

least 60 days was also performed. The date of the end of the coverage of the last prescription before interruption was taken as the date of discontinuation. Persistence was defined as the lack of any discontinuation during follow-up.

2.3. Covariates assessment

A number of patient characteristics were captured from administrative databases and used as covariates. These characteristics were as follows: sex, age (at the time of the index date, divided into decades), comorbidity status based on Charlson Comorbidity Index (CCI, in a 2-year period before the index date),[24] hospitalization for hepatic (ICD-9 codes 570-573, V42.7) or renal disease (ICD-9 580-589, V42.0, V45.1), and hospitalization for CV events (ischemic heart disease [ICD-9 codes 410-414], non-haemorrhagic cerebrovascular disease [ICD-9 codes 433-435, 437.0, 437.1]; all hospitalizations assessed in a 2-year period before the index date). The index statin was also classified as being high potency (rosuvastatin 10-20-40 mg, atorvastatin 20-40-80 mg, simvastatin 40 mg) or medium/low potency (simvastatin 10-20 mg, pravastatin 20-40 mg, lovastatin 20-40-80 mg, fluvastatin 40-80 mg, atorvastatin 10 mg, rosuvastatin 5 mg).[25] The information on use of antidiabetic (ATC A10B), antihypertensive (ATC C02, C03, C07, C08, C09),antithrombotic (ATC B01A), and antidepressant (ATC N06A) treatments in a 2-year period before the index date were also retrieved, as well as the total number of drugs prescribed in 1-year period before the index date.

2.4. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical data as number and percentage. Imbalances between sexes were assessed through standardized mean differences for binary, categorical and continuous covariates. Equipoise was considered to be reached when the between-group comparison of covariates above mentioned had an absolute value of <0.1.[26]

Adherence was assessed at one year, i.e. all patients were followed-up for 365 days from the index date. Sex-stratified log-binomial regression models were fitted to estimate relative risks (RR) and 95% confidence intervals [95%CI] for the association between optimal adherence (PDC >0.80), and several covariates included age, number and type of co-medications at baseline, first statin potency, previous CV hospitalization, previous hospitalization for liver or kidney disease, and CCI (evaluated in the two years preceding the index date).

As secondary objective, we aimed at comparing the benefits of optimal statin adherence in primary prevention of cardiovascular disease (CVD) between men and women, two matched cohorts were defined as follows. After exclusion of patients with hospitalization for CV events before the index date and/or during the first year of follow-up, for each woman of the cohort, one man randomly selected from the same cohort was matched by age (±3) at cohort entry and 1-year PDC value (±0.10) as proxy of the patient's attitude to the statin treatment in the first year of follow-up. The selected cohorts were then followed-up from the index date until the date of hospitalization for an ischemic heart disease and/or non-haemorrhagic cerebrovascular disease, end of membership in the database (i.e., emigration), end of database coverage (31/12/2012), or death, whichever occurred first. All statin prescriptions dispensed to the matched cohort members during this period of observation were identified. The adherence was assessed as PDC, and classified as low (≤0.40), intermediate (0.41 to 0.80), and high (>0.80) based on PDC values. Sex-stratified Cox proportional hazard models were fitted to estimate adjusted hazard ratios (HR) with corresponding 95% confidence interval (95%CI) for hospitalization for CV events associated with statin adherence. Because drug exposure may vary over time, adherence categories were included in the model as time-dependent variables, thereby accounting for their cumulative and varying nature.[27]
Data processing was performed by SAS (Statistical Analysis System) software version 9.4 (SAS. Institute, Inc. Cary, North Carolina), and two-tailed $p<0.05$ was considered for statistical significance in all analyses.

3. Results

3.1. Description of the cohort
A total of 303,383 men and 310,271 women aged >40, incident users of statins in the period 2002-2007, were enrolled in the study. Baseline characteristics of selected cohort are shown in **Table 1**. Compared to women, men were younger (62.9±10.6 vs 65.7±10.8) but showed a higher prevalence of antithrombotic treatment (49.66% vs 37.55%), and of comorbidities (higher percentages for CCI equal to 1 and for CCI ≥2). Men also showed higher prevalence of hospitalization for CV events previous to the index date than women (24.25% vs 10.64%). Prescriptions of antidepressant drugs were more common among women than men (19.79% vs 10.57%). The percentage of subjects with at least 10 prescribed drugs in the two years before the cohort entry was higher for women than

men (45.78% vs 35.76%). As first statin, simvastatin was the most frequently prescribed both for men and women (34.60% and 34.20%, respectively), followed by atorvastatin (32.76% and 30.50%, respectively); about 35% of men and 31% for women were firstly prescribed with a high potency statin.

3.2. Adherence and persistence to statin therapy

The average number of statin prescriptions filled in the first year of treatment was higher in men than in women (5.2±4.24 vs 4.5±4.0; **Table 2**). About 29% of men and 34% of women had only one statin prescription during the first year of follow-up. On average, the 1-year PDC was 0.48 (±0.35) for men and 0.41 (±0.32) for women; a similar difference was seen excluding patients with only one prescription (mean PDC 0.64±0.29 and 0.57±0.28, respectively) but also selecting only men and women with a previous cardiovascular event (mean PDC 0.69±0.31 and 0.63±0.33, respectively). In men and women, the proportion of patients with a PDC >0.80 at 1-year was about 27% and 19%, respectively (**Table 2**).

Evaluating adherence distribution according to age (**Figure 1**), average PDC was significantly higher for males in all age decades (p<0.001 for all decades) up to 81-90 years, even if the differences between the two sexes become smaller as the age increases, becoming not significantly different for subjects over 90 years. Nevertheless, the proportion of subjects with PDC >0.80 was higher for males only up to the age of 70, since the proportion was later reversed in favour of the female sex.

Sex-specific trends by months of the proportion of adherent patients are shown in **Figure 2**. For both sexes, the proportion of patients with optimal adherence sharply falls during the first five months (p<0.001), to 33% in men and to 25% in women. Afterwards, trends remained approximately stable afterwards, although still decreasing. Overall, men and women significantly differed for the trend in adherence (test for coincidence, p-value <0.001). The same analysis with the exclusion of subjects with only one prescription showed an overlapping trend, only settled at values on average 10 percentage points higher for both women and men each month, up to 1-year proportion of adherent subjects equal to 28% in women and 38% in men.

Regarding the analysis of persistence, 23.08% of male patients showed a continued use of medications, while the proportion was significantly lower in the female group (15.76%); on average, a continuous therapy lasted just under five months (136±136 days) and four months (121±124 days) for men and women, respectively (**Table 2**). The

percentage of persistent individuals was higher using a permissible gap of 60 days, but it was still significantly different between men and women (35.53% vs 27.14%, respectively).

3.3. Factors associated with adherence to statin therapy

The results of the application of the sex-stratified log-binomial regression models for the risk of optimal adherence (PDC >0.80) are reported in **Figure 3**. The model confirmed the role of age and concomitant medications as predictors of adherence. Compared to patients aged 51-60 years, younger and older (>70 years old) patients were less likely to be adherent to the statin treatment. Specifically, among subjects in the former class (41-50 years old), the likelihood of adherence was lower in women than men (tests of homogeneity for sex differences, p <0.0001). Also a past hospitalization for liver disease and receiving an antidepressant treatment before the index date were significantly associated with a low probability of optimal adherence for both sex, with a stronger and significant effect in women just in case of past hospitalization for liver disease (p <0.0001). Conversely, patients treated with high potency statins, or other cardiovascular drugs, with previous CV hospitalization, or more generally, with a severe health status based on CCI, were more likely to be adherent, with higher RR for men in case of high potency statins, presence of antihypertensive or antithrombotic treatment, and higher RR for women in case of antidiabetic treatment, and past hospitalization for CV events (all p <0.0001). Taking into account subjects with at least 10 prescribed drugs at baseline, we observed that women were more likely to be adherent to the statin treatment, while men with polypharmacy were at risk of not being adherent to the statin treatment, with a significant test of homogeneity for sex difference (p <0.0001).

3.4. Statin adherence and incidence of hospitalization for CV events

To evaluate the association between time-varying cumulative adherence and incidence of hospitalization for CV events, two matched cohorts of 175,069 men and 175,069 women (ratio 1:1, with matching variables equally distributed among sexes) free from CVD at cohort entry was enrolled (baseline characteristics in **Supplementary Table 1**). Within this cohort, we identified 13,143 (7.51%) women and 24,923 (14.24%) men with a hospitalization for ischemic heart disease and/or non-haemorrhagic cerebrovascular disease during the follow-up.

As shown in **Table 3**, compared with women and men with a PDC ≤0.40, respectively, we found a significant risk reduction of hospitalisation for CV events with 0.41≤ PDC ≤0.80 (HR 0.857 [0.826-0.890] for women and HR 0.891 [0.868-0.915] for men) and with PDC >0.80 (HR 0.812 [0.761-0.866] for women and HR 0.785 [0.751-0.820] for men). Tests of homogeneity for sex-differences did not show significant differences among these estimates.

4. Discussion

4.1. Principal findings

This study explored sex-differences in adherence among new statin users in the primary care setting. Our results showed that (i) the rate of non-adherence is high in both sexes, (ii) women are more likely to stop or be less adherent to statin treatment than men, (iii) there are significant sex-differences on effect size of several factors associated with adherence, and (iv) the risk reduction of incident hospitalization for CV events with increasing adherence shows no significant difference between men and women regarding statin efficacy.

4.2. Sex and statin adherence

The higher rate of non-adherence in women found in our cohort is in accordance with previous studies and consistent among different patient groups or different treatments.[28-30] In an observational study evaluating sex-differences in medication adherence of a large population of commercially insured US adults,[31] female patients were consistently less likely to be adherent with their diabetes medications, cholesterol medications, blood pressure medications, and antiplatelet medications compared with male patients, despite women tended to be more proactive in obtaining preventive care and treatment for medical conditions. In a retrospective cohort study of US adults who initiated statins in 2007–2014,[32] male sex was consistently shown to be associated with higher likelihood of high statin adherence and persistence. In a meta-analysis of 22 cohort studies,[33] eighteen studies examined sex as a predictor of adherence, and the majority of these showed that women were less likely to be adherent to statins. Another meta-analysis of 53 studies [34] showed that compared with men, women had a 10% greater odds of non-adherence.

4.3. Sex-specific differences in the predictors of non-adherence

The reasons for disparities between women and men in prescribed medications and adherence to them may relate to sex-specific factors.[14, 35] In general, from the patient's perspective, issues such as satisfaction, health beliefs, naïve illness theories, and preferences for health care can all influence intentional non-adherence. Women may face different expectations and priorities that affect the attention they pay to maintaining their own health.[36] Moreover, men experienced less depression and anxiety and a more active problem-oriented and solving approach, all factors affect self-care activity. Women instead, despite better knowledge of diseases, reported lower satisfaction with social support and lower quality of life.[37-40]

Confirming that, our study has shown that some factors traditionally associated with higher or lower adherence to therapy have a different impact in the two sexes.

We found a U-shape association between age and adherence for both sexes, an evidence already known from literature,[33] with younger and older subjects showing a lower adherence compared with individuals in the middle age. Prevalence of optimal adherence was significantly higher for males aged 41-70 years than for females of that age, but this relationship reversed later in life, though the mean PDC was higher for men in each age decade. The observation that younger people were less adherent than older individuals is consistent with the concept that people who perceive themselves to be at low risk for serious sequelae from hyperlipidaemia are more likely to be non-adherent.[41, 42] This is probably more impactful for women, who have a better health condition and a lower prevalence of cardiovascular risk factors than men of the same age.[43, 44] Concerning elderly, the lower adherence pattern, confirmed by literature[45, 46], is probably consequent to comorbidities, polypharmacy, and cognitive dysfunction that commonly characterize this sub-sample of the population, and mainly the male population. With increasing age, and after menopause, women develop a greater awareness of their health status, especially if this becomes more severe, [43, 47] and become more proactive and engaged in seeking, gaining and discussing health-related issues,[48] which probably encourages them to be more compliant to treatment than men. Analogous considerations may explain the evidence that, compared with men, probability of optimal adherence was higher for women with previous CV hospitalization. Similarly, as the number of concomitantly administered drugs increases, the likelihood of being adherent increases in women, who are more likely to be adherent to the treatment if more than 10 drugs have been prescribed at the index date, while in men

more than 10 drugs prescribed at the index date significantly reduced the likelihood of optimal adherence. Also the presence of antidiabetic therapy increased the probability of optimal adherence more in women than in men (+29% in women vs +14% in men). As the prescriptions for these drugs are to be considered as a proxy not only for the pathological state, but also for the attempt to control disease through a specific therapy, this again could suggest that in women with a compromised clinical condition, efforts toward a proactive self-management are greater. Otherwise, the increase in the probability of optimal adherence with concomitant treatment with antihypertensive or antithrombotic drugs was more evident in men then in women; we can suppose that these therapies do not imply significant changes in lifestyle and self-management (as antidiabetic treatment), and they result in a higher adherence (especially in men) simply by favouring the 'passive' habit of taking a chronic therapy.

Our study also found that men had a slightly higher probability to be adherent to statin treatment than women if they received a high-intensity statin as first statin prescribed (+22% vs +19%). The increase in adherence observed for both sexes with the use of high-intensity statins may depend on the fact that the prescription reflects a more severe clinical condition. Nevertheless, the reason for a smaller RR in women could be that female patients experience more side effects from their medications.[49] Unpleasant side effects are a common reason for discontinuing medications, so higher rates of side effects in female patients [50] could contribute to lower rates of adherence.

4.4. Sex difference in the association between statin adherence and hospitalization for CV events

Whether statin therapy is as effective in women as in men is debated, especially for primary prevention. The CTT Collaboration, in a meta-analysis using individual participant data from 174 000 participants in 27 randomised trials,[51] have been able to demonstrate conclusively that among women and men the effects of statin therapy on major vascular events and mortality were similar. This is true not only among high-risk populations with established CVD, but also when statin therapy was used for the primary prevention of CVD. In attempt to confirm whether women benefit to the same extent as do men from statin therapy for the primary prevention also in the primary care setting, we defined two matched cohorts of men and women without hospitalization for CV events before the index date. Our study detected an approximately 19% and 21% decrease in the risk of hospitalization for ischemic heart disease and/or non-

haemorrhagic cerebrovascular disease among women and men with optimal adherence to statins (PDC >0.80) when they were compared with poor adherence subjects (PDC ≤0.40), with no evidence of a sex-different efficacy of the statin treatment. The observation that the reduction of hospitalization for CV events is secondary to good adherence to statins regardless of the sex of the patient is confirmed by studies that failed to highlight differences between men and women in terms of statin efficacy/effectiveness.[52, 53]

4.5. Impact on clinical practice

The evidence of sex-based differences in factors influencing adherence can support improvement strategies, and in particular those that can be implemented by the doctor in a personalized way, for example through communication or practical approaches,[54, 55] although the effectiveness of interventions aimed at improving adherence is still debated.[56] For example, our study showed that, compared to subjects aged 51-60 years, younger patients have a lower probability of being adherent, especially if women. This suggests physician to pay a special attention to young female patients who are prescribed statins. In this subgroup, it may be necessary to model communication processes, emphasizing the need for treatment and highlighting the risks associated with a lack of control of hypercholesterolemia. Still, the increased risk of non-adherence associated with hospitalizations for liver causes in the female population, perhaps indicating a greater fear of side effects associated with treatment in women, could suggest to the doctor who prescribes a statin to a woman to devote time in describing the risk-benefit profile of the drug, informing her of the true extent of the adverse effects and of their possible management. On the other hand, the concomitant poly-therapy seems to negatively influence adherence only in the male population. In this case, the use of tools that help the patient to follow complex therapeutic regimes (such as pill boxes or written schemes indicating drugs, doses and timing of assumption) or solutions that simplify these regimes (such as the use of fix dose combinations when available) are to be preferred in male patients.

4.6. Strengths and limitations

Whilst administrative databases may constitute a fundamental source of readily available and relatively inexpensive large amounts of good quality data (demographic, clinical, economic) referring to the general population, the use of administrative

registry as data source may result in several limitations. First, adherence and persistence were derived from drug prescriptions: though widely used,[57] this method is based on several assumptions, such as the correspondence between prescription refill and medicine intake, and between the prescribed number of pills and days covered.[58] Nevertheless, the definition of the PDC index is likely to have allowed us to evaluate the prescriptive sequence with an approach closer to the real-life habit of patients. Second, we lack information regarding the reason for discontinuation of statin therapy, clinically appropriate in same cases.[59-61] Third, our data did not allow us to explore other potential predictors of non-adherence, such as cholesterol levels, life style habits (e.g. smoking), or socioeconomic factors (for example income, educational level, or marital status),[62] as these covariates are not recorded in administrative databases. Notably, among socioeconomic factors, the impact of income is probably smaller in the Italian context,[63] also because statin therapy is fully reimbursed by the National Health System.

5. Conclusions

Our findings support the need for physicians, pharmacists, and other health care professionals to address adherence in all patients taking statins, also considering that the association between optimal adherence and hospitalisation for CV events CV risk reduction was confirmed in both sexes. Moreover, the identification of sex-differences in the role of influencing factors confirms the existence of different mechanisms underlying the attitude of the two sexes towards pharmacological therapy, suggesting that greater benefits could be obtained by targeting male and female patients with a differentiated intervention, for example in men through a simplification of the therapeutic regimen and in women through a more emphatic communication.

Ethical approval

In Italy, retrospective studies using administrative databases do not require Ethics Committee (EC) protocol approval nor notification, therefore we did not request approval from the EC, nor consult with the EC to receive a formal written waiver.

Conflict of interest

EO, MTB, MC, ET, LM and FR report no disclosures. ALC received research funding and/or honoraria for advisory boards, consultancy or speaker bureau from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Mediolanum, Merck or MSD, Pfizer, Recordati, Rottapharm, Sanofi-Regeneron, Sigma-Tau. GC received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry of Education, University and Research (MIUR). He took part in a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN, and BMS). He also received honoraria as member of Advisory Board from Roche.

Author contributions

MC, EO, and FR were responsible for the study concept and design. EO and MTB did the analysis. ET, GC, LM, and ALC contributed to the interpretation of the results. MC and EO wrote the manuscript and all authors critically revised for important intellectual content and approved the final manuscript.

Legends to the Figures

Figure 1. Mean Daily Possession Ratio (PDC) and proportion of adherent patients (PDC >0.80) with statin medications at 1 year, according to sex and age decades.

Student's t-test and Chi-square tests were used to compare mean PDC and proportion of adherent patients (PDC >0.80) by age decades between men and women. Significant differences are reported in the figure (*).

The lines represent mean PDC values (y-axis on the left). The bars represent the proportion of patients with optimal adherence (PDC >0.80; y-axis on the right)
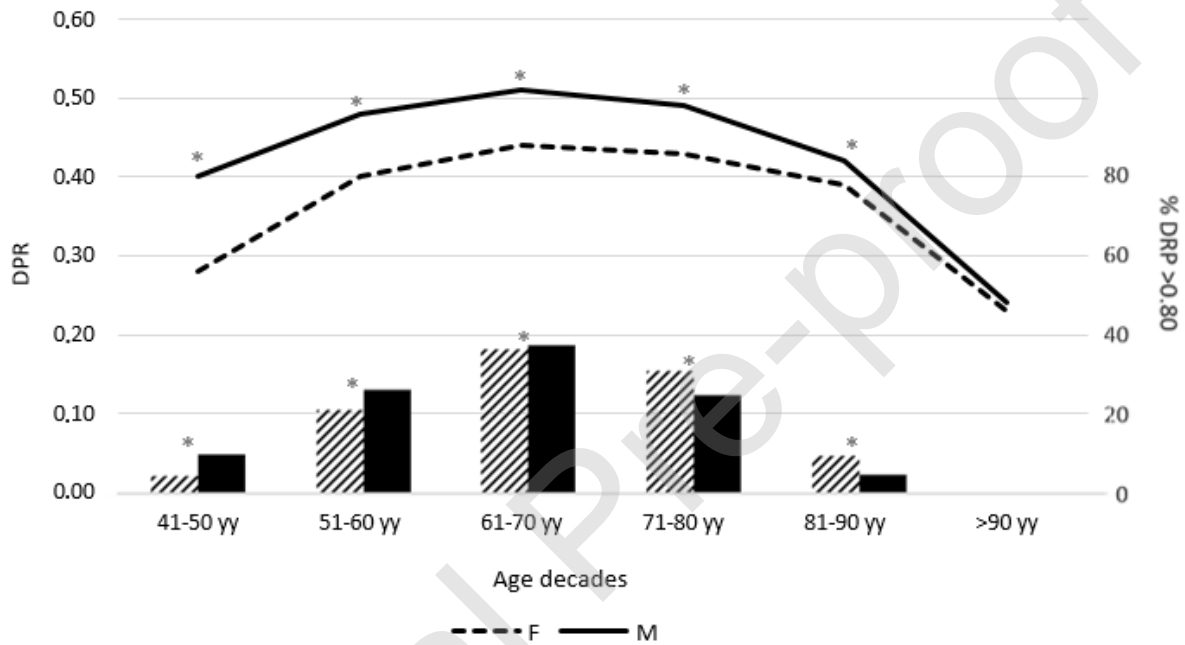

Figure 2. Proportion of adherent patients with statin medications in the year after the beginning of the therapy according to sex.
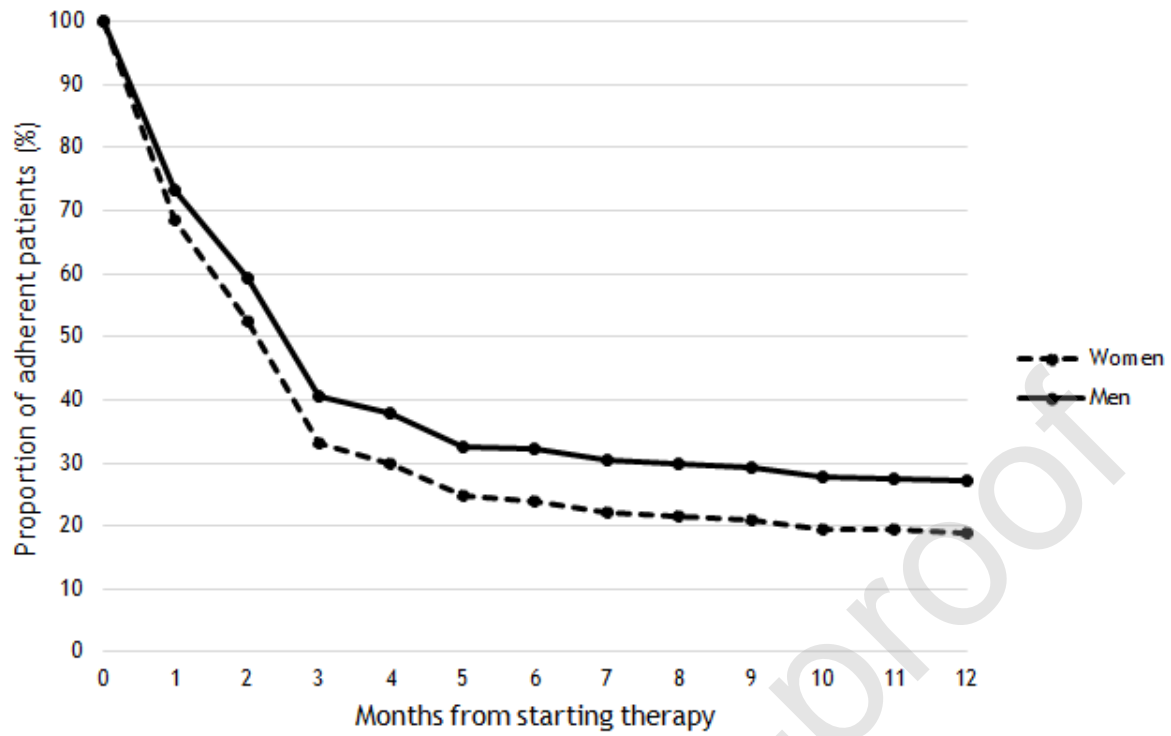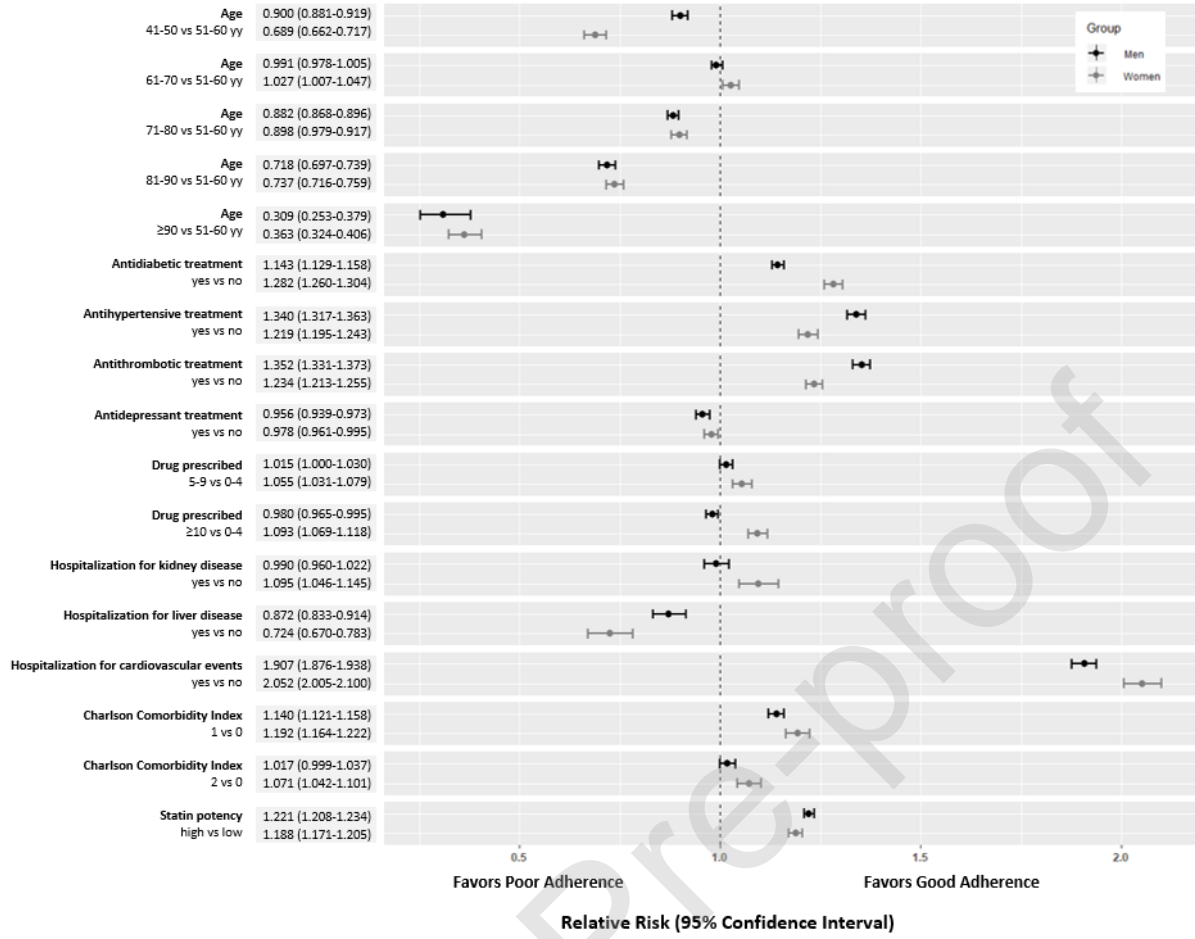
Figure 3. Relative risk (RR) of optimal adherence levels (PDC >0.80) by sex.

	Men	Women
Age 41-50 vs 51-60 yy	0.900 (0.881-0.919)	0.689 (0.662-0.717)
Age 61-70 vs 51-60 yy	0.991 (0.978-1.005)	1.027 (1.007-1.047)
Age 71-80 vs 51-60 yy	0.882 (0.868-0.896)	0.898 (0.979-0.917)
Age 81-90 vs 51-60 yy	0.718 (0.697-0.739)	0.737 (0.716-0.759)
Age ≥90 vs 51-60 yy	0.309 (0.253-0.379)	0.363 (0.324-0.406)
Antidiabetic treatment yes vs no	1.143 (1.129-1.158)	1.282 (1.260-1.304)
Antihypertensive treatment yes vs no	1.340 (1.317-1.363)	1.219 (1.195-1.243)
Antithrombotic treatment yes vs no	1.352 (1.331-1.373)	1.234 (1.213-1.255)
Antidepressant treatment yes vs no	0.956 (0.939-0.973)	0.978 (0.961-0.995)
Drug prescribed 5-9 vs 0-4	1.015 (1.000-1.030)	1.055 (1.031-1.079)
Drug prescribed ≥10 vs 0-4	0.980 (0.965-0.995)	1.093 (1.069-1.118)
Hospitalization for kidney disease yes vs no	0.990 (0.960-1.022)	1.095 (1.046-1.145)
Hospitalization for liver disease yes vs no	0.872 (0.833-0.914)	0.724 (0.670-0.783)
Hospitalization for cardiovascular events yes vs no	1.907 (1.876-1.938)	2.052 (2.005-2.100)
Charlson Comorbidity Index 1 vs 0	1.140 (1.121-1.158)	1.192 (1.164-1.222)
Charlson Comorbidity Index 2 vs 0	1.017 (0.999-1.037)	1.071 (1.042-1.101)
Statin potency high vs low	1.221 (1.208-1.234)	1.188 (1.171-1.205)

Favors Poor Adherence — Favors Good Adherence

Relative Risk (95% Confidence Interval)

References

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Table 1. Characteristics of the patients who were newly treated with statin drugs during 2002-2007 in the Lombardy Region (Italy)

		Men N=303,383	Women N=310,271	Standardized differences
Age (yy), mean±SD		62.9±10.6	65.7±10.8	0.263
Age (yy), %	41-50	14.34	8.80	0.227
	51-60	26.69	23.39	
	61-70	33.59	33.31	
	71-80	21.05	26.02	
	81-90	4.13	7.78	
	>90	0.21	0.70	
Hospitalization for CV events, %		24.25	10.64	0.365
Hospitalization for liver disease, %		1.40	0.83	0.054
Hospitalization for kidney disease, %		2.28	1.22	0.081
Prescribed drugs (N), %	0-4	31.88	23.43	0.292
	5-9	32.36	30.79	
	≥10	35.76	45.78	
Antidiabetic treatment, %		18.58	15.86	0.072
Antihypertensive treatment, %		68.88	68.18	0.015
Antithrombotic treatment, %		49.66	37.55	0.246
Antidepressant treatment, %		10.57	19.79	0.259
CCI, %	0	71.78	83.80	0.292
	1	15.09	8.65	
	≥2	13.13	7.55	
Statin, %	Simvastatin	34.60	34.20	0.133
	Lovastatin	1.55	1.79	
	Pravastatin	12.47	13.16	
	Fluvastatin	6.94	8.55	
	Atorvastatin	32.76	30.50	
	Rosuvastatin	11.79	11.80	
High potency statin, %		35.23	30.81	0.094

*CV-Cardiovascular; CCI-Charlson Comorbidity Index; SD-standard deviation; yy-year

Table 2. Adherence and persistence to statin therapy during follow-up

	Men N=303,383	Women N=310,271	Standardized differences
Filled Prescriptions, N	1,568,612	1,406,560	
Number of prescriptions, mean±SD	5.2±4.24	4.5±4.0	0.244
Patients with only one prescription, %	28.80	33.93	0.086
Adherence			
PDC, mean±SD	0.48±0.35	0.41±0.32	0.209
PDC >80%, %	27.08	18.77	0.199
Persistence without gaps ≥30 days			
Persistent patients, %	23.08	15.76	0.186
Days of continuous therapy, mean±SD	136.4±136.4	121.3±124.2	0.196
Persistence without gaps ≥60 days			
Persistent patients, %	35.53	27.14	0.182
Days of continuous therapy, mean±SD	181.9±148.1	155.5±141.7	0.182

* PDC - proportion of days covered; SD-standard deviation

Table 3. Association between cumulative adherence to statin therapy and risk of hospitalization for ischemic heart disease and/or non-haemorrhagic cerebrovascular disease. Stratified analysis by sex.

Sex		aHR*	95%CI
Men (N=175,069)	PDC ≤0.40	1	Ref
	0.41≤ PDC ≤0.80	0.891	0.868-0.915
	PDC >0.80	0.785	0.751-0.820
Women (N=175,069)	PDC ≤0.40	1	Ref
	0.41≤ PDC ≤0.80	0.857	0.826-0.890
	PDC >0.80	0.812	0.761-0.866

*adjusted for statin potency, co-medications at baseline, previous hospitalization for liver or kidney disease, and CCI

**PDC-proportion of days covered; aHR-adjusted hazard ratio; CI-confidence interval; Ref-reference