Adherence to Lipid-Lowering Treatment by Single-Pill Combination of Statin and Ezetimibe

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ABSTRACT

Introduction: Although several studies have shown that a simplified cardiovascular drug treatment leads to better treatment adherence,

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limited and conflicting findings have been reported on the separate or single-pill combination of the now recommended association between a statin and ezetimibe. We addressed this issue in a large cohort of patients newly treated with statins to whom ezetimibe was additionally administered, either separately or as a single-pill combination.

Methods: A total of 256,012 patients (age 40–80 years) from the Lombardy Region (Italy) newly treated with statins during 2011–2013 were followed until 2018 to identify those to whom ezetimibe was added. The 2881 and 5351 patients who started a two-pill or a single-pill combination, respectively, of statin and ezetimibe were identified and matched for propensity score. Adherence to drug therapy at 1 year was measured as the ratio between the number of days in which the drug was available and the days of follow-up (the proportion of days covered; PDC). Patients who had a PDC > 75% or < 25% were, respectively, defined as highly and poorly adherent to drug therapy. Analysis was extended to the association between adherence and the risk of fatal/non-fatal cardiovascular events.

Results: Compared to those prescribed a two-pill combination, those prescribed a single-pill combination had an 87% (75–99%) greater odds of being highly adherent and a 79% (72–84%) lower odds of being poorly adherent to treatment. These advantages were manifest in all strata of age, sex, and clinical profile. The risk of

cardiovascular outcomes decreased by 55% in patients with high adherence compared to those with low adherence.

Conclusion: Patients who were prescribed a single-pill combination of statin/ezetimibe more frequently exhibit a good adherence and less frequently bad adherence to treatment than those prescribed a two-pill combination of these drugs.

Keywords: Statins; Ezetimibe; Adherence; Persistence; Population-based study

Key Summary Points

Why carry out this study?

Medication adherence is low in clinical practice and is associated with greater risk for adverse outcomes. The use of a single-pill combination of two drugs has been shown to improve medication adherence for antihypertensive drug treatment.

We sought to investigate the adherence to lipid-lowering therapy in a large cohort of patients newly treated with statins comparing those who added ezetimibe separately and those who switched to the single-pill combination of the two drugs.

What was learned from the study?

Compared to those prescribed a two-pill combination of statin and ezetimibe, those prescribed a single-pill combination had an 87% (confidence interval 75–99%) greater odds of being highly adherent and a 79% (72–84%) lower odds of being poorly adherent to treatment.

The present study suggests that the single-pill formulation of statin and ezetimibe improves adherence and persistence to lipid-lowering drug therapy at all ages and at different levels of cardiovascular risk. This offers robust support to use this combination in patients who are not at lipid-lowering drugs–cholesterol target with statin alone.

INTRODUCTION

Poor adherence to lipid-lowering drugs is a major challenge for the treatment of dyslipidemia because the number of patients who fail to take the prescribed drugs is high, and this leads to an insufficient control of the lipid profile [1], as well as to an increased risk of hospitalization and death [2–5].

There is general agreement that an effective way to improve adherence to treatment is treatment simplification, i.e., reduction of the number of tablets to be taken daily [6]. This has been consistently found for antihypertensive drug treatment, for which adherence has been reported to be better when two blood pressure-lowering drugs are given in a single pill rather than separately [7]. Such evidence, however, is not equally clear for single-pill combination of two lipid-lowering drugs such as a statin and ezetimibe. A higher adherence to treatment among patients receiving a single-pill combination of two lipid-lowering drugs has been reported in one study [8], whereas no difference in adherence between single-pill and two-pill combinations has been reported in another study [9].

The European guidelines on dyslipidemia issued in 2016 [10] recommended reducing an abnormal lipid profile to the desired target first by using statin monotherapy up to a maximal dose within the therapeutic range and then to add ezetimibe to a previous ineffective or only partially effective statin treatment. Public European healthcare systems have strengthened this recommendation in more recent lipid guidelines [11], which has given further support to the use of dual drug treatment to achieve lipid control, and has made the statin/ezetimibe combination reimbursable.

The aim of our study was to assess adherence and persistence to lipid-lowering treatment with a statin and ezetimibe prescribed separately or in a single-pill formulation. Data were collected in a large cohort of patients from the Lombardy region who were newly treated with a statin and in whom ezetimibe was added to their initial treatment, either separately or in a single-pill combination. The analysis was

extended to the incidence of cardiovascular mortality and hospitalization for cardiovascular events in the two groups to see whether different levels of adherence resulted into differences in the risk of clinical outcomes.

METHODS

Data Source

Data were retrieved from the healthcare utilization databases of Lombardy, a region of Italy that accounts for about 16% (more than 10 million) of its population. The Italian population is covered by the National Health Service (NHS), and in Lombardy this has been associated for about 20 years with an automated system of databases to collect a variety of information, including: (1) an archive of residents who receive NHS assistance (the whole resident population) reporting demographic and administrative data, other than the dates in which the individual started (birth or immigration into the region) or stopped (death or emigration) to be a NHS beneficiary; (2) hospitalization (primary diagnosis, coexisting conditions, and procedures); and (3) outpatient prescriptions of all the drugs reimbursed by the NHS, including statins and ezetimibe.

Because a unique identification code was used for all the databases, their linkage allowed the identification of the complete care pathway of NHS beneficiaries. To preserve privacy, each identification code was automatically anonymized, the inverse process being only allowed by the Regional Authority upon request of judicial Authorities. Details on healthcare utilization databases of the Lombardy region in the field of pharmaco-epidemiology have been reported in previous studies [12–14].

The authors of the present manuscript were allowed access to these databases through an agreement with Lombardy Region for the current study ('Ricerca Finalizzata 2016', NET-2016-02363853. According to the rules from the Italian Medicines Agency (available at: http://www.agenziafarmaco.gov.it/sites/default/files/det_20marzo2008.pdf), retrospective studies using administrative databases do not require

Ethics Committee protocol approval. No identifiable information was made available to the authors.

Cohort Selection and Follow-Up

The target population included Lombardy residents, aged 40–80 years, who were beneficiaries of the NHS. Of these, those who were prescribed a statin during 2011–2013 were identified, and the date of the first dispensation was defined as the *index statin prescription date*. To ensure the inclusion of new users of a statin [15], patients who had received a statin prescription within 5 years before the index prescription were excluded. The included patients were followed until the earliest date among death, emigration, or December 31, 2018 to identify those adding ezetimibe to statin either separately or in a single-pill combination. The date of the first dispensation of the two lipid-lowering drugs was defined as the *index combination prescription date*. Among these patients, we excluded those (1) with less than 1 year of follow-up (patients who died and those who moved to other regions), and (2) who received only one statin/ezetimibe prescription during the first year after the index combination prescription date. The remaining patients were included into the *final cohort*, and the cohort members were followed from the index combination prescription date for 365 days. This follow-up duration was selected because previous studies have shown that the largest fraction of treatment discontinuation occurs during the first year of treatment [16, 17]. A detailed description of the cohort selection is shown in Supplementary Figure S1.

Adherence To and Discontinuation of Lipid-Lowering Treatment

All lipid-lowering drugs dispensed to each cohort member during the 1-year follow-up were identified. The period covered by any single prescription was calculated from the number of tablets in the dispensed canisters, assuming a treatment schedule of one tablet per day [17]. For overlapping prescriptions, a

patient was assumed to have completed the former prescription before starting the second one.

Adherence to therapy was assessed as the cumulative number of days covered by the lipid-lowering drug therapy divided by the number of days of follow-up, a quantity referred to as "proportion of days covered" by prescriptions (PDC) [18]. Three categories of adherence were considered: low ($< 25\%$), intermediate (25–75%), and high ($> 75\%$) PDC values. These cut-off values were chosen because, in previous studies on the Lombardy database, these adherence levels to statin drug treatment showed a clear association with a reduction (PDC $> 75\%$) and an increase (PDC $< 25\%$) of cardiovascular outcomes and mortality [13, 14]. The primary goal of the study was to compare the patients' odds of being highly adherent to treatment, i.e., to have a PDC $> 75\%$, in the single-pill versus the two-pill combination group. Secondary aims were to compare the two groups for the odds of being poorly adherent (i.e., to have a PDC $< 25\%$) as well as to assess treatment discontinuation. The latter measure extended information on adherence to persistence on treatment. Starting from the index combination prescription date, consecutively refilled prescriptions were considered uninterrupted, i.e., treatment to be persistent, if the time-span between the end of one prescription and the beginning of the following one was less than 90 days; if the between-prescription timespan was longer, treatment discontinuation was assumed [19].

Covariates

Additional data included: (1) age and gender, (2) duration of and adherence to statin therapy, (3) potency of statin at the index statin prescription date, (4) previous use of cardiovascular and non-cardiovascular drugs, and (5) previous hospitalization(s) for cardiovascular events, diabetes, kidney diseases, respiratory diseases, and cancer. In addition, the number of co-medications dispensed in the year prior to the index statin prescription date was assessed and categorized as 0–4, 5–9, and ≥ 10. Furthermore,

the clinical profile was assessed by the Multi-source Comorbidity Score, a prognostic score that has been shown to predict all-cause death and hospitalization of Italian people more precisely than other widely used scores [20]. Three categories of clinical profile were considered: good ($0 \leq$ score ≤ 4), intermediate ($5 \leq$ score ≤ 14), and poor (score ≥ 15).

Clinical Outcomes

Details on the assessment of mortality and hospitalization for cardiovascular outcomes in the health utilization database of Lombardy are provided in previous studies [13, 14]. In the present study, the outcome of interest was the composite cardiovascular mortality (i.e., death from ischemic heart disease, cerebrovascular disease, and heart failure) and hospitalizations in which stroke, myocardial infarction, or heart failure were listed by their appropriate codes as the primary diagnosis. The clinical outcomes data were collected after the assessment of drug adherence, i.e., from 1 year after the index combination prescription date until censoring (the earliest among emigration or data availability, i.e., December 31, 2019). The median follow-up during which clinical outcomes were assessed was 2.2 years.

Data Analysis

Members of the final cohort were classified by the treatment strategy, i.e., whether a two-pill or single-pill combination statin/ezetimibe was dispensed at the index combination prescription date, according to the intention-to-treat-approach.

To mitigate the potential confounding effect of a different clinical profile between groups, a 1:1 propensity-score matching design was adopted [21]. The propensity to be prescribed a single-pill combination was derived through a logistic regression model, which includes the above-mentioned covariates. For each patient treated with a single-pill combination, one patient who received a two-pill combination was randomly selected from the cohort to be matched for propensity score using a nearest-

neighbor matching algorithm without replacement [22]. Comparisons between groups for continuous variables were performed with the t test and ANOVA, whereas the chi-square test was calculated for categorical variables. In addition, to compare clinical characteristics and adherence to treatment between groups, standardized mean differences were also used. Equipoise was considered to be reached when the between-group comparison of covariates had a mean standardized difference of < 0.1 [23]. Finally, log-binomial regression models were fitted to estimate the risk ratio, and its 95% confidence interval (CI), of treatment adherence and persistence in relation to drug strategy, using the two-pill combination as reference.

To assess the association between drug adherence and the composite outcome (mortality and hospitalization for cardiovascular events), a Cox model was fitted to estimate the hazard ratio and its 95% CI. To account for its possible change over time, adherence was inserted in the model as a time-dependent variable. Adjustments were made for sex, age, number of co-treatments, hospitalization for cardiovascular disease, and the clinical status as assessed by the Multisource Comorbidity Score. Analysis was extended to the association between the drug treatment strategy (single pill or separately administered drug statin and ezetimibe combination) to determine the effect of the drug treatment strategy per se on the outcome onset.

Sensitivity Analyses

To verify the robustness of our findings, three sensitivity analyses were performed. First, to estimate the association between treatment strategy and drug adherence over a longer time-window, the adherence-related analysis was repeated by selecting patients who had at least 2 years of follow-up. Second, because the prescribed drug doses are not recorded in our database, the hypothesis was made that patients separately adding ezetimibe to statin might reduce the daily drug dosage, making the duration of the prescription greater and thus

adherence to treatment higher than the one estimated by our method. To verify the possibility that between-group differences in treatment adherence between patients on single-pill and two-pill combinations might be explained by differences in drug doses, we increased the coverage of each prescription up to 3 times in patients who received two-pill combinations.

Third, because administrative databases suffer from lack of important clinical information, the potential bias associated with unmeasured confounders was investigated by the rule-out approach [24] to estimate the extension of the overall confounding required to fully account for the exposure–outcome association. We set the possible unmeasured confounder: (1) to have a 30% prevalence in the study population, (2) to increase the propensity of high adherence up to ten-fold, and (3) to reduce the risk of low adherence up to 50-fold more in patients exposed than in those unexposed to the confounder.

RESULTS

Patients

The distribution of the exclusion criteria is shown in Fig. 1. Of the 848,103 patients aged 40–80 years who had statin prescriptions during 2011–2013, 256,012 were incident users. Among these: (1) 4116 and 8713 patients, respectively, made use of two-pill and single-pill combinations of statin and ezetimibe; (2) 2881 and 5351 met the inclusion criteria; and (3) 2129 matched couples were included in the final cohort.

The baseline characteristics of the included patients are shown in Table 1. Compared with patients on two-pill combinations, those treated with a single-pill combination were more frequently female, less adherent to statin monotherapy, less often treated with high-potency statin, antihypertensive and antithrombotic agents, and with an overall lower number of prescribed drugs. Cardiovascular disease was less common in the single-pill combination group, which showed a slightly better clinical profile in the Multisource Comorbidity Score.
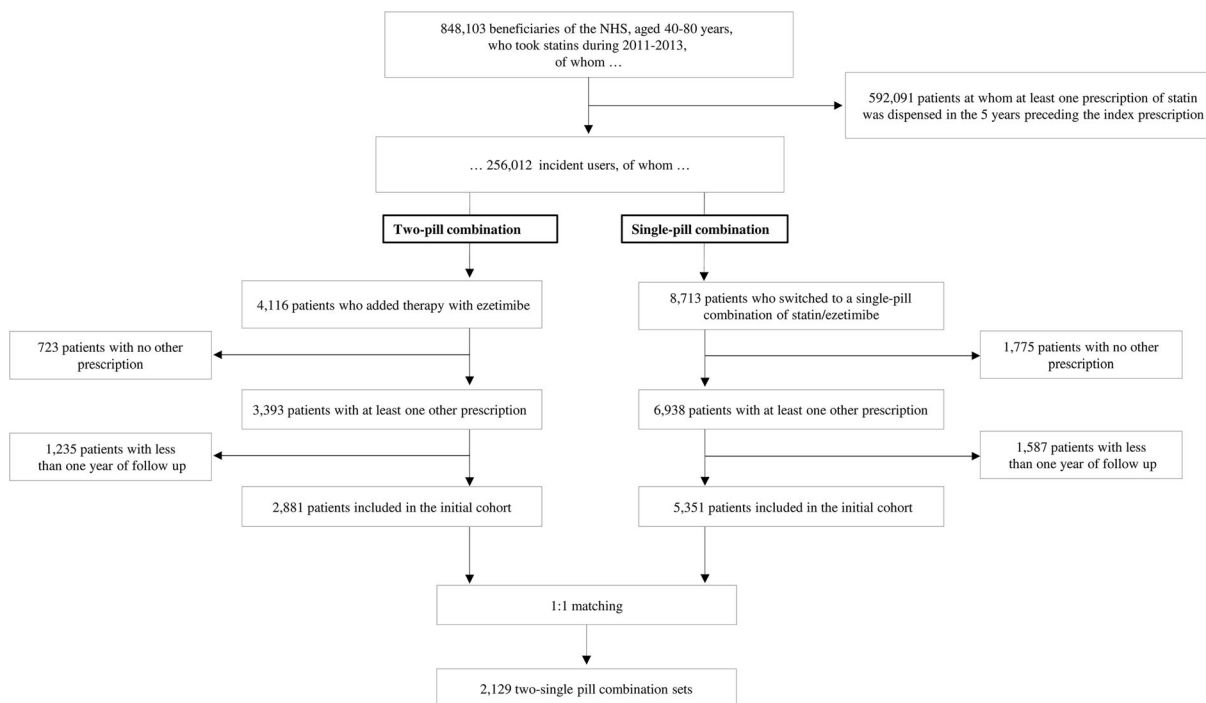
Fig. 1 Flow-chart of inclusion and exclusion criteria

After propensity-score matching, there was no evidence that demographic, clinical, or therapeutic baseline features differed between the two groups.

Among patients on a two-pill combination, 57% made use of atorvastatin, 32% of rosuvastatin, and 5% of simvastatin (Supplementary Table S1). 94% of patients in the single-pill combination group used the simvastatin/ezetimibe combination, and only 6% used the rosuvastatin/ezetimibe combination.

Adherence To and Discontinuation of Lipid-Lowering Treatment

Among patients on a two-pill combination, 756 (35.5%), 1,102 (51.8%), and 271 (12.7%) exhibited high, intermediate, and low adherence, respectively. The corresponding figures for patients under a single-pill combination were 1,451 (68.2%), 621 (29.2%), and 57 (2.7%), the between-group differences being always statistically significant (standardized difference: 0.727). Adherence to lipid-lowering drug

therapy was higher among patients on single-pill combination irrespectively of age, gender, and clinical profile (Fig. 2).

Figure 3 shows that, compared to those prescribed a two-pill combination of statin and ezetimibe, patients on a single-pill combination had a greater chance of being highly adherent to treatment (1.87, 95% CI: 1.75–1.99). This was the case in all strata of age, both sexes, and in patients with different clinical statuses. It was also the case for both single-pill combinations available in Italy, i.e., compared to patients prescribed a two-pill combination, the odds of being highly adherent to treatment increased with the single-pill combination of simvastatin/ezetimibe (1.84, 1.72–1.96) as well as of rosuvastatin/ezetimibe (2.47, 2.31–2.65).

As shown in Fig. 4, the effect of single-pill vs. two-pill combination for the odds of being poorly adherent to treatment were specular to those obtained for the odds of being highly adherent to treatment i.e., compared to the two-pill combination, the single-pill combination reduced the propensity of being low

Table 1 Baseline characteristics of original and matched cohort members according to the drug treatment strategy, i.e, two-pill or single-pill combinations of statin and ezetimibe

	Original cohort				Matched cohort			
	Two-pill combination (n = 2881)	Single-pill combination (n = 5351)	Standardized difference	p value	Two-pill combination (n = 2129)	Single-pill combination (n = 2129)	Standardized difference	p value
Male gender	1885 (65.4%)	2988 (55.8%)	0.197	< 0.001	1311 (61.6%)	1334 (62.7%)	0.022	0.468
Age (years)								
40–54	869 (30.2%)	1495 (27.9%)	0.084	< 0.001	608 (28.6%)	578 (27.2%)	0.065	0.205
55–64	1,076 (37.4%)	1858 (34.7%)			795 (37.3%)	770 (36.2%)		
65–80	936 (32.5%)	1998 (37.3%)			726 (34.1%)	781 (36.7%)		
Therapy based on statin								
Duration of therapy (years): mean (SD)	4.2 (1.5)	4.1 (1.5)	0.067	0.711	4.3 (1.5)	4.2 (1.5)	0.067	0.655
Adherence with therapy (PDC): mean (SD)	0.72 (0.3)	0.50 (0.3)	0.733	< 0.001	0.66 (0.3)	0.66 (0.3)	0.000	1.000
High potency of statins at baseline	1967 (68.3%)	2804 (52.4%)	0.258	< 0.001	1326 (62.3%)	1326 (62.3%)	0.000	1.000
Co-treatments								
Antihypertensive drugs	2570 (89.2%)	4362 (81.5%)	0.219	< 0.001	1852 (87.0%)	1856 (87.2%)	0.006	0.855
Antithrombotic drugs	2259 (78.4%)	3235 (60.5%)	0.397	< 0.001	1555 (73.0%)	1581 (74.3%)	0.030	0.366
Antiarrhythmic drugs	167 (5.8%)	322 (6.0%)	0.009	0.686	132 (6.2%)	130 (6.1%)	0.004	0.899
NSAIDs	1333 (46.3%)	2681 (50.1%)	0.077	< 0.001	1028 (48.3%)	1019 (47.9%)	0.008	0.783
Antigout drugs	328 (11.4%)	716 (13.4%)	0.061	0.010	253 (11.9%)	251 (11.8%)	0.003	0.924
Antidiabetics drugs	892 (31.0%)	1762 (32.9%)	0.042	0.069	686 (32.2%)	665 (31.2%)	0.022	0.489
Respiratory medicine	613 (21.3%)	1329 (24.8%)	0.085	< 0.001	493 (23.2%)	478 (22.5%)	0.017	0.584
Antidepressant drugs	460 (16.0%)	987 (18.5%)	0.066	0.005	367 (17.2%)	348 (16.4%)	0.021	0.436

Table 1 continued

	Original cohort				Matched cohort			
	Two-pill combination (n = 2881)	Single-pill combination (n = 5351)	Standardized difference	p value	Two-pill combination (n = 2129)	Single-pill combination (n = 2129)	Standardized difference	p value
Number of co-treatments								
0–4	906 (31.4%)	2034 (38.0%)	0.151	< 0.001	688 (32.2%)	699 (32.8%)	0.023	0.843
5–9	1403 (48.7%)	2301 (43.0%)			1006 (47.3%)	987 (46.4%)		
≥ 10	572 (19.9%)	1016 (19.0%)			435 (20.4%)	443 (20.8%)		
Comorbidities								
Cardiovascular disease	1765 (61.3%)	2220 (41.5%)	0.404	< 0.001	1166 (54.8%)	1134 (53.3%)	0.030	0.325
Ischemic heart disease	1493 (51.8%)	1609 (30.1%)	0.452	< 0.001	943 (44.3%)	892 (41.9%)	0.048	0.115
Diabetes	631 (21.9%)	1345 (25.1%)	0.076	< 0.001	500 (23.5%)	486 (22.8%)	0.017	0.661
Kidney disease	75 (2.6%)	180 (3.4%)	0.045	0.058	61 (2.9%)	63 (3.0%)	0.006	0.855
Respiratory disease	976 (33.9%)	1917 (35.8%)	0.041	0.077	751 (35.3%)	739 (34.7%)	0.013	0.700
Cancer	177 (6.1%)	354 (6.6%)	0.019	0.406	141 (6.6%)	126 (5.9%)	0.029	0.343
Clinical profile[a]								
Good	1429 (49.5%)	3060 (57.2%)	0.190	< 0.001	1106 (52.0%)	1123 (52.8%)	0.021	0.854
Intermediate	1288 (44.7%)	1933 (36.1%)			898 (42.2%)	880 (41.3%)		
Poor	164 (5.7%)	358 (6.7%)			125 (5.9%)	126 (5.9%)		

PDC proportion of days covered, *SD* standard deviation

[a] The clinical profile was assessed by the Multisource Comorbidity Score according to the hospital admission and the drugs prescribed in the 5-year period before the index date. Three categories of clinical profile were considered: good (0 ≤ score ≤ 4), intermediate (5 ≤ score ≤ 14), and poor (score ≥ 15)
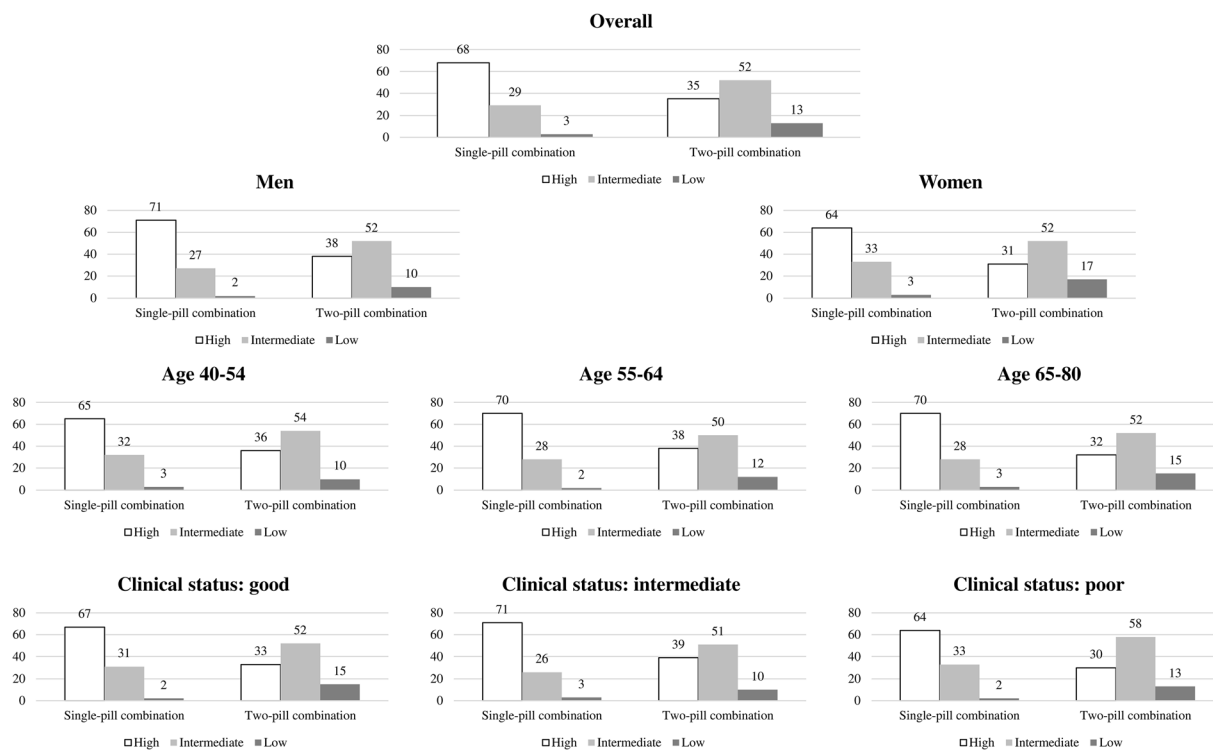
Fig. 2 Adherence to drug therapy according to the drug treatment strategy, i.e., single-pill versus two-pill combination of a statin and ezetimibe. Adherence was classified into three categories according to the proportion of days of the follow-up covered by prescriptions (PDC): low (< 25%), intermediate (25–75%), and high (> 75%) PDC values. Data are shown for the entire cohort and for different demographic and clinical subgroups

adherent by 83% (0.21, 0.16–0.28), this being the case in all age strata, both sexes and all clinical profiles. No analysis of the effect of the two single-pill combinations (simvastatin/ezetimibe and rosuvastatin/ezetimibe) was performed because of the low statistical potency of the sample size.

Figure 5 shows the results obtained on treatment discontinuation. Compared to patients on two-pill combinations, treatment discontinuation was lower among patients under single-pill combination (25.2% vs. 46.7%, standardized difference: 0.460). From the risk ratio estimation, patients under single-pill combination had a lower risk of treatment discontinuation than those on two-pill combination (0.72, 0.69–0.76), irrespectively from gender, age, clinical profile, and different single-pill combination type (simvastatin/ezetimibe: 0.74, 0.70–0.77; rosuvastatin/ezetimibe: 0.63, 0.58–0.67).

Adherence to Lipid-Lowering Treatment and Clinical Outcomes

The characteristics of cohort members according to the categories of adherence and drug treatment strategy in relation to the risk of clinical outcomes are reported in Supplementary Table S1. Overall, adherent patients were more frequently male and younger (two-pill combination group). They also more often exhibited previous hospitalization for cardiovascular disease and were more often treated with a high-potency statin, antihypertensive agents, or antithrombotic agents.

The cohort members accumulated 9430 person-years of observation (on average, 2.2 years per patient) and generated 208 outcomes (52 deaths and 156 hospitalizations). There were 222 outcomes every 10,000 person-years among patients on two-pill combinations, and 219 outcomes every 10,000 person-years among
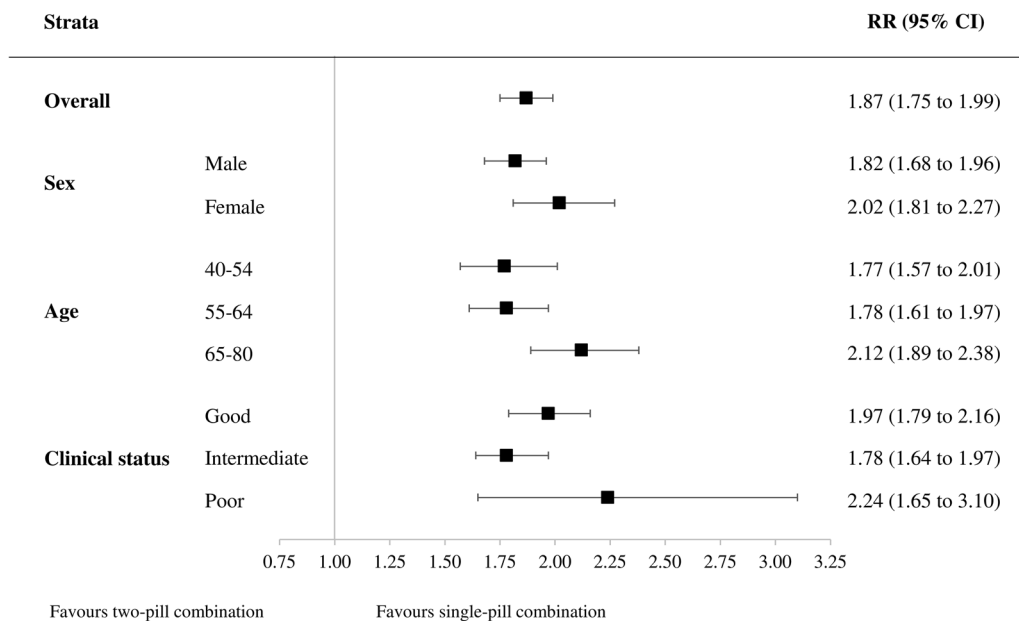
Fig. 3 Risk ratios (RR), and 95% confidence intervals (CI), estimating the association between high adherence to treatment (PDC > 75%) and single-pill combination between statin and ezetimibe vs two-pill or separate administration of the two drugs. Data are shown for the entire cohort and for different demographic and clinical subgroups
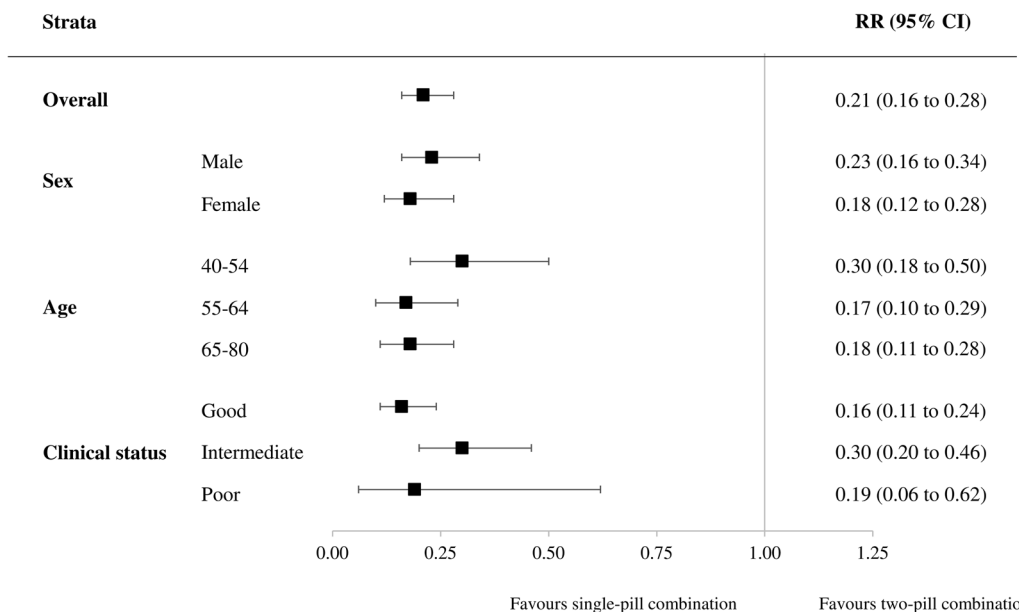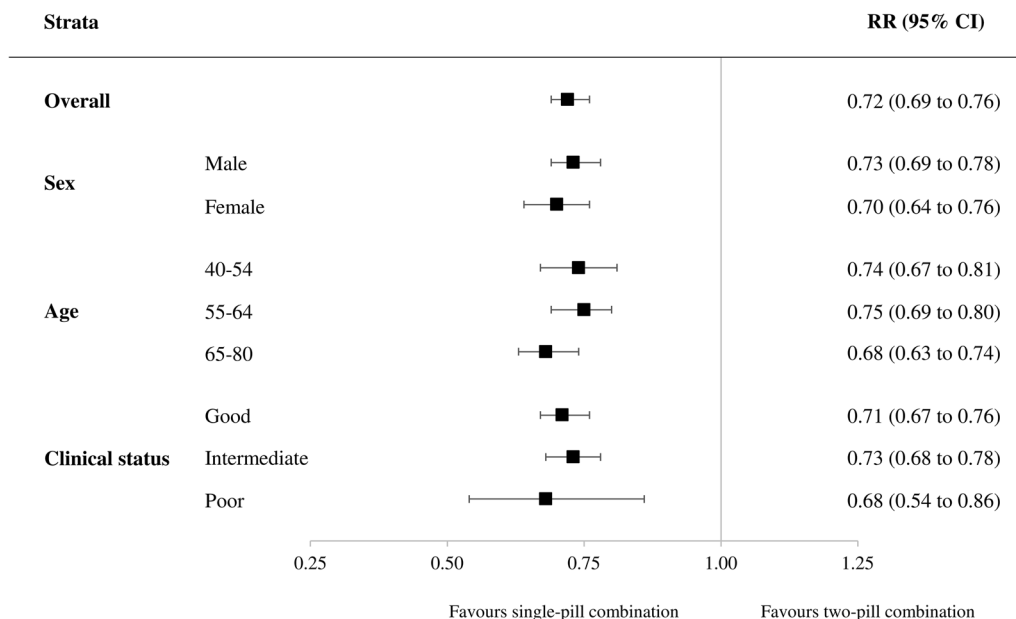

Fig. 4 Risk ratios (RR), and 95% confidence intervals (CI), estimating the association between low adherence to treatment (PDC < 25%) and single-pill combination between statin and ezetimibe versus two-pill or separate administration of the two drugs

Strata		RR (95% CI)
Overall		0.72 (0.69 to 0.76)
Sex	Male	0.73 (0.69 to 0.78)
	Female	0.70 (0.64 to 0.76)
Age	40-54	0.74 (0.67 to 0.81)
	55-64	0.75 (0.69 to 0.80)
	65-80	0.68 (0.63 to 0.74)
Clinical status	Good	0.71 (0.67 to 0.76)
	Intermediate	0.73 (0.68 to 0.78)
	Poor	0.68 (0.54 to 0.86)

Favours single-pill combination   Favours two-pill combination

Fig. 5 Risk ratios (RR), and 95% confidence intervals (CI), estimating the association between single-pill versus two-pill administration of a statin and ezetimibe and treatment discontinuation

those under a single-pill combination. The cumulative incidence of cardiovascular outcomes (cardiovascular mortality and hospitalization) was not significantly different in patients on two-drug combinations exhibiting low, intermediate, and high adherence to treatment, while, in patients under single-pill combinations, clinical outcomes showed a reduction when adherence was intermediate (− 17%) or high (− 42%) compared to its low level. As shown in Fig. 6, according to the Cox model, there was a clear trend toward a progressive reduction of the adjusted risk of composite outcome as adherence with drug therapy increased, i.e., compared with low adherence, patients with intermediate and high adherence showed an adjusted risk reduction of 41% (95% CI, − 6 to 67%) and 55% (20–75%), respectively. There was no evidence that drug treatment strategy affected the composite outcome (hazard ratio: 0.98, 0.73–1.32) after adjusting for drug adherence.

Sensitivity Analyses

Adherence to lipid-lowering drug therapy was still greater among patients prescribed a single-pill combination after 2 years of follow-up. Among patients on two-pill combinations, 35.8% and 22.1%, showed a high and low adherence, respectively, the corresponding figures among patients prescribed a single-pill combination being 65.9% and 9.3% (standardized difference: 0.640). The risk of treatment discontinuation was also lower in the single-pill than in the two-pill combination group (31.3% vs. 54.4%, standardized difference: 0.480).

Supplementary Figure S2 shows that patients on a two-pill combination should have reduced the daily dosage at least 2.5 times to nullify the observed between-group difference in treatment adherence with the single-pill combination.

Supplementary Figure S3, left panel, shows that an unmeasured confounder should (1) have increased at least four-fold the propensity of being highly adherent to treatment, and (2) been at least four-fold less prevalent in patients under two-pill combination, to account for the
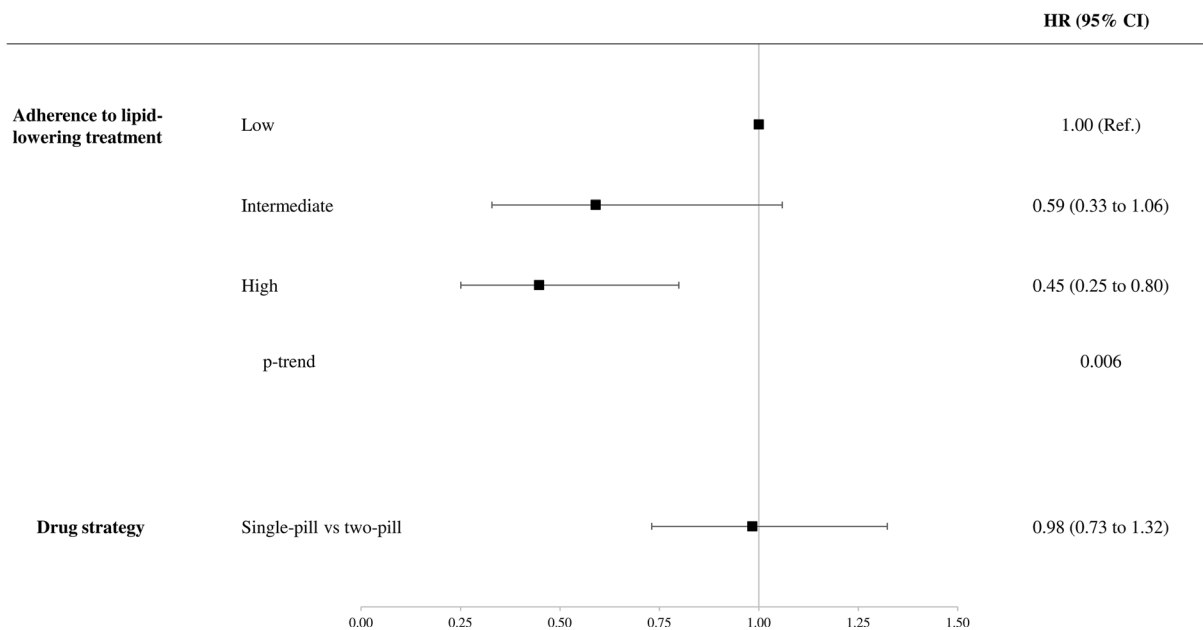
Fig. 6 Hazard ratios (HR), and 95% confidence intervals (CI), for the composite outcome (cardiovascular mortality or cardiovascular hospitalization) with low, intermediate, and high adherence to lipid-lowering drugs, and drug treatment strategy (i.e., single-pill vs. two-pill combination of a statin and ezetimibe), after adjustment for the covariates mentioned under Methods in the entire cohort of patients

effect of single-pill combination on high adherence to treatment. Stronger confounder–outcome and exposure–outcome associations are required for moving to the null the effect of single-pill combination on low adherence to treatment (Supplementary Figure S3, right panel), as well as to account for the single-pill-related benefits in different demographic and clinical conditions.

DISCUSSION

The present real-world investigation of a cohort of patients treated with statins and the addition of ezetimibe confirms previous observations that in the real-life setting adherence with and persistence of lipid-lowering drug treatment is low [14, 17, 25]. Our study, however, provides several new findings. First, the propensity of being highly adherent to lipid-lowering drug therapy was more common in patients prescribed a single-pill combination of statin and ezetimibe than in those in whom ezetimibe was added separately from the statin administration. Second, the single-pill combination treatment strategy reduced the risk of patients to be poorly adherent as well as to discontinue lipid-lowering treatment. Third, the above advantages were by no means quantitatively marginal and were seen regardless of the patients' sex, age, and clinical profile, the improvement in adherence being especially marked in some of these subgroups. For example, the single-pill combination conferred a 82% and 102% increase in the propensity to be highly adherent among men and women, respectively, the increase being 124% in patients with a poor clinical profile, and 112% among patients older than 65 years. In the entire cohort and in subgroups, the improvements were even more marked for the risk of being poorly adherent or experiencing treatment discontinuation, which means that single-pill combinations of two lipid-lowering agents can substantially help in making a two-drug lipid-lowering treatment much more regular and persistent. Finally, and most importantly, in the patients of the present

study, the risk of fatal and nonfatal cardiovascular events showed a reduction as adherence to lipid-lowering treatment increased from low to intermediate and high. This confirms previous observations on the protective effect of high adherence to lipid-lowering treatment by a number of studies, including those from our healthcare database [4, 14, 26–28], which have also demonstrated the protective effect of persistence on treatment, because stopping cardiovascular protective medicines is associated with a marked increase of adverse outcomes [29]. In this context, however, our present data provide two other observations. First, in patients with high adherence, the risk of outcomes was 55% less than in those with low adherence, which emphasizes the paramount importance of adherence to treatment for protection of dyslipidemic patients. Second, there was no difference in outcomes between the single- and separate-pill treatment strategies when data were adjusted for adherence, which suggests that the difference in adherence between the two groups played a major role. This offers robust support to use the single-pill combination of statin and ezetimibe in patients who are not at LDL-cholesterol target in people with different cardiovascular risk levels [11] as recently recommended [30].

Three other findings of our study deserve to be mentioned. First, an improvement of adherence to treatment associated with single-pill dual lipid-lowering combinations was observed also during a longer follow-up (2 years), which allows to conclude that the benefit of this therapeutic approach is long lasting. Second, 5351 out of the 8232 (65%) patients who added ezetimibe to the statin therapy adopted the single-pill strategy, which shows that in a real-life setting a single-pill combination is the favorite treatment strategy when two lipid-lowering drugs are required. Third, although both single-pill combinations available in the Italian market were associated with an improved adherence to treatment, the improvement was greater with the rosuvastatin/ezetimibe than with the simvastatin/ezetimibe single-pill combination. However, this comparison was based on a more limited number of patients and, because of the more recent availability of the rosuvastatin /ezetimibe combination, the size of the two groups was imbalanced, which makes further studies necessary before concluding that the rosuvastatin/ezetimibe combination is superior to the simvastatin/ezetimibe combination.

Our study has strengths and limitations. The strengths are that the study was based on a large and unselected population exposed to real-life medical practice, which was made possible because the Italian healthcare system is cost-free and involves virtually all citizens [13, 14, 16, 20]. For studies on adherence to treatment, this approach first represents an important advantage because the patients' behavioral modifications induced by the awareness of being under observation typical of trials and many observational studies are avoided [31]. Second, the drug prescription database provides highly accurate data because pharmacists are required to report prescriptions in detail to obtain reimbursement, and incorrect reports about the dispensed drugs have legal consequences [32]. Third, patients were "recruited" at the time of their initial lipid-lowering therapy, a "new-user" approach that reduced the potential for selection bias [15]. Finally, the robustness of our main findings was confirmed by the sensitivity analyses.

The weaknesses, on the other hand, are that over-the-counter medicines were not recorded in our database, and that we were able to measure drug prescription but not drug consumption [12]. First, because our database did not include the prescribed daily doses, we had to assume that patients were under a treatment schedule of one tablet per day. If patients under two-pill combinations used lower doses of the drugs, their adherence to treatment would be greater than the one estimated by our method. However, one of our sensitivity analyses shows that only a strong unrealistic between-group imbalance in the daily drug dosage would have nullified the favorable effect of single-pill combination on adherence to treatment. Second, because in more than half of the patients on a two-pill combination the statin prescribed was different from that of the single-pill combination (e.g., atorvastatin rather than simvastatin or rosuvastatin), our findings might be affected

by differences among individual statins [33]. Finally, like other administrative databases, the Lombardy administrative database does not include some important clinical data (e.g., lipid profile, blood pressure, blood glucose), which means that our study's findings cannot entirely exclude confounding. However, a sensitivity analysis showed that the association of the simplified lipid-lowering treatment with drug adherence could only be eliminated by an unmeasured residual confounder of large and unrealistic dimensions. In addition, our results offer evidence that the use of the single-pill statin/ezetimibe combination was associated with what represents the major goal of treatment, i.e. patient protection. Improved adherence was the major responsible factor because correction for adherence entirely eliminated the protective effect of the simplified lipid-lowering treatment.

CONCLUSIONS

In our real-life cohort of patients the single-pill combination of statin and ezetimibe substantially improved adherence to drug therapy compared to the corresponding two-pill combination of the two drugs. Confirming previous findings on the protective effect of adherence to lipid-lowering treatment, an improvement in adherence was associated with a reduction in the risk of fatal/non-fatal cardiovascular events. Thus, via an improvement of adherence, single-pill combination of statin and ezetimibe may improve cardiovascular protection in people in whom dyslipidaemia makes two-drug lipid-lowering treatment necessary.

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Data Availability. The data that support the findings of this study are available from Lombardy Region, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the Lombardy Region upon reasonable request.

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