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**Cardiovascular events in statin recipients: impact of adherence to treatment in a 3-year record-linkage study**



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# **Cardiovascular events in statin recipients: impact of adherence to treatment in a 3-year record-linkage study**

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## Abstract

### Purpose

In the general population, lack of adherence to statin therapy remains a widespread phenomenon and an important matter of concern both in terms of cost-effectiveness and risk-benefit profile. This study aimed to evaluate the occurrence of cardiovascular events in Italian statin recipients, focusing on the relationship between degree of adherence to therapy and occurrence of events in a 3-year follow-up.

### Methods

Our cohort consisted of all patients from Emilia Romagna (4,027,275 inhabitants) who received statin prescriptions in January–February 2005 and was followed up to 36 months for cardiovascular hospital admission (ie. coronary disease, cerebrovascular accidents, peripheral artheropathy), adherence to statin treatment (proportion of days covered:  $\geq 80\%$ ) and use of other cardiovascular drugs. The relationship between adherence and cardiovascular events was analysed by multivariate logistic regression; age, sex, other cardiovascular drugs and previous events were covariates of the model.

### Results

Patients non-adherent to statin regimen over the 3-year period (76% of the cohort) had higher odds of events, irrespective of risk factors, by more than 40% when compared with adherent patients. Odds of events were in particular: strongly non-adherent adjOR=1.19 (CI95% 1.15-1.23), slightly non-adherent adjOR=1.25 (1.21-1.30), highly variable in the amount of statins received adjOR=1.69 (1.62-1.77).

### Conclusions

This study shows the key role of adherence to statins in the cardiovascular prevention at any level of risk. Appropriateness of statin use needs not only careful selection of patients to be treated, but also cooperation between patient and physician to ensure continued drug use whenever treatment is appropriate.

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**Keywords:** statins, medication adherence, general practice, cardiovascular disease, medical record-linkage

For Peer Review

## Introduction

Randomised controlled trials have clearly shown the benefits of lipid-lowering drug treatment for cardiovascular prevention, but how much these translate into actual benefit in the general population is not as well established. Whereas there is consensus on the benefits in secondary prevention [1,2] recommendations to use statins in primary prevention are currently a matter of debate [3-6] and in fact statins are used mostly in the latter setting (75% of statin recipients [7]). Some authors cast doubt on the benefit of statins in patients with low cardiovascular risk [8] whereas others suggested the use of statins (alone or even in the so-called polypill) even in normolipidemic subjects [4,9,10].

Lack of adherence is probably the most relevant factor differencing randomised controlled trials from clinical practice.

In the general population, lack of adherence to statin therapy remains a widespread phenomenon and, consequently, an important matter of concern both in terms of cost-effectiveness and risk-benefit profile. We have previously shown that, among statin recipients, less than 50% were prescribed an amount of drug consistent with daily treatment and this coverage was only slightly higher in patients in secondary prevention, in those aged 50–69 years and among males. Moreover, adherence significantly increased with the complexity of other cardiovascular treatments [11]. On the contrary, prescription of a highly active statin regimen (which can be used as a proxy of the severity of hypercholesterolemia) did not correlate with coverage.

The role of adherence to statins in preventing cardiovascular events in general practice is currently under investigation by different points of view (i.e., risk-benefit and cost-benefit profile) and some investigators have already published useful experiences in different countries [12-16]. However, the scenario is far from complete and the evidence is still partial and insufficient to support Health Policy strategies [17].

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3 The aim of this study was to evaluate the occurrence of cardiovascular events in all patients treated  
4 with statins in Emilia Romagna (about 4,000,000 inhabitants), focusing on the relationship between  
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6 the occurrence of events and the degree of adherence to therapy.  
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## 10 11 12 **Methods**

### 13 *Sources of data*

14  
15 Drug prescription data were retrieved from the Emilia Romagna Regional Health Authority  
16 Database, which provides the following information for each reimbursed prescription: identification  
17 code of the drug, ATC (Anatomical Therapeutic Chemical) code, number of packages dispensed,  
18 patient code, date of prescription. The patient code allows retrieval of his/her drug history without  
19 individual identification.  
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29 We collected data of statins and other drugs used for cerebro- or cardiovascular risk prevention (i.e.,  
30 antiplatelet agents, nitrates, antihypertensives, antidiabetics), prescribed by general practitioners  
31 (GPs) and reimbursed between January 2003 and February 2008 by the Health Authority of Emilia  
32 Romagna (with both urban and rural area, 4,027,275 inhabitants). The following ATC codes were  
33 considered: A10 – drugs used in diabetes; B01A – antithrombotic agents; C01DA – antianginal  
34 drugs (nitrates); C02, C03, C07, C08, C09 – drugs used in the treatment of hypertension; C10 –  
35 lipid modifying agents.  
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46 All statins are reimbursed by Italian Health Service for (i) familial hypercholesterolaemia, (ii)  
47 patients with previous cardiovascular or cerebrovascular events, or (iii) patients with a 10-year  
48 cardiovascular risk higher than 20%.  
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53 Data of hospital admissions for cardiovascular or cerebrovascular events, occurred from January  
54 2003 to February 2008, were retrieved from the hospital discharge registry which provides the  
55 following information: ICD-9 code (410-414: ischemic heart disease; 430-438: cerebrovascular  
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3 diseases; 440: atherosclerosis; 443: other peripheral vascular disease; 444: arterial embolism and  
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5 thrombosis;), type of the hospital and ward, duration of the hospital stay and patient code.  
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9 Data regarding age, sex and deaths were anonymously retrieved from vital statistics.

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11 All the databases are managed by the Drug Policy Service of the Health Department of the Emilia-  
12  
13 Romagna Region, which provides anonymous data by attributing an anonymous code to each  
14  
15 patient. This code allows the record linkage of individual patient data among different databases  
16  
17 according to the provisions of privacy rules. The protocol was approved by the institutional ethics  
18  
19 committee.  
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### 22 23 *Study design*

24  
25 Our cohort consisted of all patients who received at least one statin prescription between January  
26  
27 and February 2005 (recruitment period) and at least another prescription of statins during the first  
28  
29 year of follow-up. Patient drug prescriptions and cardiovascular hospital admissions were analysed  
30  
31 for 36 months following recruitment (March 2005 - February 2008, follow-up). Co-prescriptions of  
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33 cardiovascular drugs other than statins (recorded in the first year of follow-up) were used as a  
34  
35 component of patient risk profile, as well as hospital discharge records for cardiovascular events  
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37 occurred before recruitment (January 2003-December 2004).  
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42 Adherence was evaluated by analysing the amount of statins received during the 3 year-period:

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- 45 • for each year, patients were considered “covered” if they received at least 300 tablets  
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47 (allowing a tolerance of ~20% over the 365 day period) [11] and  
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  - 49 • patients who met the above criterion throughout the 3-year follow-up were considered as  
50  
51 “adherent”.  
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54 The amount of statins was evaluated as number of tablets purchased. In fact, the availability of  
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56 different dosage strengths for each active substance allow patients to take their daily medication as  
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58 one tablet.  
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### *Statistical analyses*

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3 To evaluate the association between cardiovascular events and adherence to statin treatment, a  
4  
5 logistic multivariate regression analysis was performed, by grouping non-adherent patients into 3  
6  
7 different categories: “strongly non adherent”, “slightly non adherent” and “highly variable” patients  
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9 (see table 2 for definitions). Age, sex, comorbidity (diabetes, hypertension-angina-heart failure and  
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11 thrombosis in the first year of the follow-up) were included as covariates in the models.  
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15 Only patients surviving the 3-year follow-up period were included in the logistic analysis.  
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17  
18 To better describe the role of the adherence in cardiovascular prevention, two different stratified  
19  
20 models for primary and secondary prevention cohort were estimated. Patients in secondary  
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22 prevention were those who experienced a cardiovascular event before the recruitment. The effect of  
23  
24 adherence was assessed by a generalization of Mantel-Haenszel method in different subgroups  
25  
26 samples. The differences in subgroups were tested with Pearson  $\chi^2$  test. A p-value <0.05 was  
27  
28 considered significant.  
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32 All analyses were performed using STATA version 10 (StataCorp. 2001. College Station, TX: Stata  
33  
34 Corporation) and SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).  
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## 39 **Results**

### 40 *Adherence to statin regimen*

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42 The cohort of statin recipients consisted of 137,217 subjects, with a mean age of  $67 \pm 10$  years and  
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44 1:1 female/male ratio (Table 1). During the three years of follow up, 6,491 subjects (5%) died.  
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47  
48 Seventy-seven percent of subjects (106,167) received prescriptions of the same statin and  
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50 simvastatin was the most prescribed (32% of patients), followed by atorvastatin (24%). The  
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52 remaining 23% of patients were switched to another statin, especially rosuvastatin (23.6%) or  
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54 atorvastatin (12.6%). Moreover, 72% received only highly active statin regimens (i.e., at dosages  
55  
56 expected to reduce LDL-cholesterol by more than 30% [11]).  
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60 Eighty-five percent of patients received additional cardiovascular treatments on the first year of  
follow-up: in particular, 77% (105,341) of subjects concomitantly received drugs for hypertension

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3 or angina or heart failure, 54% (73,963) used antithrombotics and 16% (21,530) used antidiabetics  
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5 (Table 1). Along the remaining two years of follow-up, a further 2.5% of patients per year received  
6  
7 antihypertensive prescriptions, a further 5% received antithrombotics and a further 2.5% received  
8  
9 antidiabetics.  
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11  
12 In our cohort, 35% did not receive statin prescriptions in the 2 previous years (new users).  
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15 The proportions of patients receiving more than 300 tablets/year of statins and that of patients  
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17 receiving 201-300 tablets/year were stable along the three years of follow-up (45% and 24%  
18  
19 respectively), whereas that of patients receiving 101-200 tablets decreased from 24% to 19% and  
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21 that of patients taking less than 101 tablets showed an appreciable increase, from 6% in the first  
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23 year to 13% in the third one.  
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27 Sixty-two percent (81,666) of patients were covered for at least 1 year, 44% (60,894) for at least 2  
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29 years and 24% (32,355) for the whole 3-year period and only this last figure represents the adherent  
30  
31 population according to our criteria. (Figure 1).  
32

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34 Among the 98,371 patients who did not meet the criteria to be considered “adherent”, 28% (38,328)  
35  
36 were “slightly non-adherent”, 30% (41,678) “strongly non-adherent”, and 13% (18,382) “highly  
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38 variable” (Table 2).  
39

#### 40 41 *Cardiovascular events*

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43 Within the whole cohort of 137,217 patients, 29% (39,708) experienced cerebro- or cardiovascular  
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45 events during the 3 year-follow-up (annual rate: 13%): 54% of events were represented by coronary  
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47 heart disease, followed by cerebrovascular accidents (18%).  
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50 Cerebro- and cardiovascular events occurred more frequently in non-adherent patients rather than  
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52 adherent group (reference), with the following ranking: strongly non-adherent (adjOR=1.19; 95%  
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54 CI 1.15-1.23), slightly non-adherent (1.25; 1.21-1.30), highly variable (1.69;1.62-1.77). These  
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56 events increased with age (e.g., patients older than 80: adjOR=2.78; 95% CI 2.56-3.03) and were  
57  
58 statistically more frequent in men (adjOR=1.39; 95% CI 1.35-1.43), in patients using statins for  
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60 secondary prevention (2.54; 2.46-2.62), those co-medicated for hypertension, angina or heart failure

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3 (2.77; 2.65-2.89), using antithrombotics (1.87; 1.81-1.93), and with diabetes (1.36; 1.31-1.40; see  
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5 table 3). By considering separately new users and already in treatment patients, the analysis  
6  
7 confirmed the significant variables, with minor differences between the two groups. The following  
8  
9 variables weighed on the occurrence of CV events more in new users rather than in those already in  
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11 treatment: strongly non adherent or highly variable regimens, previous CV events and concomitant  
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13 anti-thrombotic drugs.  
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17 Subgroup analysis showed a higher risk of events among non-adherent patients irrespective of risk  
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19 factors: adjOR 1.40 (95% CI 1.35-1.45) in patients using statins for primary prevention and  
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21 adjOR=1.59 (95% CI 1.51-1.68) in those using statins for secondary prevention (Figure 2). The  
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23 only exception was represented by the younger age group (<50 years), for whom the confidence  
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25 interval includes 1. Moreover, for subjects older than 80 years both in primary and secondary  
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27 prevention, and in patients with diabetes in primary prevention, the association between lack of  
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29 adherence and CV events was statistically stronger than in unstratified analysis.  
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34 Considering patients' prescriptions twelve months before and after the occurrence of an event, 53%  
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36 of patients increased their number of tablets after the event; so that a fraction (15%) of the non-  
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38 covered patients became covered in the year after the event. On the other hand, 26% of patients did  
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40 not change their number of tablets and the remaining 21% even decreased it.  
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## 45 46 **Discussion**

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48 In our cohort of 137,217 patients, more than three quarters of statin recipients did not adhere to drug  
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50 therapy throughout the 3-year follow-up and, these patients showed more than 40% increase of  
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52 cardiovascular events when compared with adherent statin recipients.  
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56 Although the issue of lack of adherence to statin treatment has been already reported [11,18], in our  
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58 opinion, a population-based cohort study is important because it attempts to translate adherence to  
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60 statin regimen into actual cardiovascular benefit in unselected patients in a community setting.  
Some previous studies provided useful findings to clarify this topic. A study on a large Israeli

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3 cohort [19] found a strong association between intensity of statin therapy (in terms of number of  
4 tablets/year) and improved survival both in primary and secondary prevention, even higher than that  
5 found in clinical trials (up to 45% of risk reduction). Also a Canadian study showed the important  
6 role of adherence to statins in the prevention of both cerebrovascular events (reduction of risk:  
7 26%) and coronary disease (18%) [12-14]. Two recent Italian studies focused on incident statin  
8 recipients for primary prevention. On one hand, Deambrosis et al. found a better cholesterol  
9 outcome in adherent patients, but a paradoxical association between adherence and hospitalisation  
10 for coronary events [15]. This finding was probably affected by a confounding factor, represented  
11 by the basal cardiovascular risk, which conditioned independently both adherence and hospital  
12 admissions. On the other hand, Corrao et al. found a protective role of adherence on nonfatal  
13 ischemic heart disease (reduction of risk: 15-20%) [16].

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29 Our results (although not directly comparable to those of the above studies because of different  
30 parameters in outcomes and in observed population) substantially agree on the clinical importance  
31 of continued statin use and provide a wider picture on cardiovascular outcomes in all users (both  
32 incident users and already in treatment at recruitment).

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39 The approach used in this study has strengths and limitations. In our opinion, one strength was  
40 represented by performing our analysis in a large community setting, including all statin recipients,  
41 no matter what the length of therapy before the recruitment was, and including all meaningful  
42 cardiovascular outcomes. On the one hand, the findings provided by this approach refer to prevalent  
43 statin users, whereas other studies frequently selected only incident users, which represent only a  
44 minority of overall statin recipients. On the other hand, our method intrinsically lacks in  
45 completeness on prior morbidity and drug history, and could be affected by the immeasurable time  
46 bias [20] because of the lack of information on statin exposure during hospitalisations. In the worst  
47 case scenario, this bias could have generated a misclassification of 586 non-adherent subjects (0.4%  
48 of the cohort), who would pass to adherent status by considering all hospitalisation days as covered  
49 days. On the basis of these data, we found a possible overestimation of the risk of events among  
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3 non-adherent patients by 6 and 8%, respectively in case of primary and secondary prevention. A  
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5 further limitation was the lack of information on lipidemia, which was an obstacle in the correct  
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7 association between adherence and cardiovascular outcomes. However information on lipidemia  
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9 would be very difficult to collect even by using physician's records. In addition, since our  
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11 prescription data were obtained only from reimbursement database, we probably excluded patients  
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13 not meeting the Italian reimbursement criteria, because at a lower CV risk. This lack of data could  
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15 have caused a slight overestimation of the role of adherence in the prevention of CV events.  
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19 Moreover, a positive attitude of patients towards their own health could be a confounding factor,  
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21 influencing independently both statin adherence and event occurrence, but also this information is  
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23 not available in administrative databases, which are the source of our study. Only studies based on  
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25 questionnaire or primary care database could collect this data and could quantify the magnitude of  
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27 the healthy adherer effect.  
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31 This phenomenon is usually indicated as "healthy adherer effect", as already acknowledged by  
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33 Dragomir [13], Rasmussen [21] and Anderson [22], who stated the difficulties in its quantification.  
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35 Nonetheless a generic "healthy adherer behaviour" could have generated a tolerable overestimation  
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37 of the protective effect of adherence.  
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41 Finally, because of the low frequency and the delayed onset of cardiovascular events in low-risk  
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43 patients, a longer follow up could provide further evidence on this population.  
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47 When addressing the health policy implications of our results showing the close relationship  
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49 between adherence to statins and their effectiveness, the fact that 3 out of 4 of statin recipients were  
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51 not adherent suggests that statin use in our community setting produces both scarce gain in terms of  
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53 health and waste of economic resources.  
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56 For efficient resource allocation, quantification of the non-adherent population to optimise overall  
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58 health gain in the community is a priority [17]. Each Health Authority faces two different scenarios:

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60 (a) encouraging efforts to cover a large population entails inherent problems in ensuring adherence,  
increased overall burden of side effects, in an attempt to reduce as many as possible cardiovascular

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3 events; (b) envisaging a strategy more stringently identifying the population with a likely benefit  
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5 (which implies less effort to ensure adherence, decreased overall burden of side effects, lower drug  
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7 cost, but incomplete population protection from cardiovascular risk) [17].  
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10 In the light of these potential benefit and limitations, there is debate on which strategy is better, but  
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12 certainly the specific risk profile of the resident population and the availability of economic  
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14 resources should guide decision makers.  
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17 In our community setting, we interpret the paradoxically lower odds of cardiovascular events in  
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19 strongly non-adherent patients as an indication that this group was at lower risk than the other non-  
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21 adherent patients. Indeed, the strongly non-adherent group probably included a number of subjects  
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23 who actually did not require pharmacological lipid-lowering treatment. Therefore, we would not  
24  
25 recommend measures to improve adherence in this group. Probably, efforts to improve adherence  
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27 should focus on the 28% that was not strictly adherent, but received a yearly amount of drug able to  
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29 cover at least 6 months (slightly non adherent patients), and on the 13% that alternated covered  
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31 years with years at very low intensity of treatment (highly variable patients). Notably, the last group  
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33 showed the highest odds of cardiovascular events (about 70% higher than adherent patients).  
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## Conclusions

This study shows the key role of adherence to statins in the prevention of cardiovascular events at any level of risk in a community setting. Appropriate use of statins needs both strict selection of patients before starting drug treatment and patient-physician cooperation for continued drug use whenever the treatment was appropriately started.

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Table 1. Descriptive analysis of patients' characteristics and events

		Number of patients	%	Events	% in the class
<b>Gender<sup>a</sup></b>	F	67,238	49%	16,210	24%
	M	69,858	51%	23,498	34%
<b>Age class</b>	<50	6,750	5%	943	14%
	50-65	41,914	31%	8,573	20%
	65-80	73,763	54%	23,707	32%
	>80	14,790	11%	6,519	44%
<b>Previous CV events<sup>b</sup></b>	Yes	29,144	21%	15,504	53%
	No	108,073	79%	24,238	22%
<b>Diabetes<sup>c</sup></b>	Yes	21,530	16%	8,007	37%
	No	115,687	84%	31,735	27%
<b>Angina, hypertension, heart failure<sup>c</sup></b>	Yes	105,341	77%	36,480	35%
	No	31,876	23%	3,262	10%
<b>Thrombosis<sup>c</sup></b>	Yes	73,963	54%	29,106	39%
	No	63,254	46%	10,636	17%
<b>Three year adherence<sup>d</sup></b>	Yes	32,355	24%	8,803	27%
	No	104,862	76%	30,939	30%
<b>New users</b>	Yes	48,386	35%	13,681	28%
	No	88,831	65%	26,061	29%

<sup>a</sup> indication of gender was missing in 121 patients;

<sup>b</sup> previous CV events were observed for the period 2003-2004;

<sup>c</sup> concomitant CV disorders were evaluated by the prescription of the relevant drugs in the first year of follow-up. The following ATC codes were considered: A10 – drugs used in diabetes; C01DA – antianginal drugs (nitrates); C02, C03, C07, C08, C09 – drugs used in the treatment of hypertension and B01A – antithrombotic agents;

<sup>d</sup> patients were considered adherent when they were prescribed at least 300 doses of statins for each of the 3-year follow-up; patients who died during follow-up were included in the non-adherent group.

**Table 2. Distribution of patients according to adherence to statins**

	<b>N.</b>	<b>%</b>
<b>Adherent patients<sup>a</sup></b>	32,339	24%
<b>Slightly non adherent patients<sup>b</sup></b>	38,328	28%
<b>Strongly non adherent patients<sup>c</sup></b>	41,678	30%
<b>Highly variable patients<sup>d</sup></b>	18,382	13%
<b>Deaths during the 3-year period</b>	6,490	5%

<sup>a</sup> at least 300 tablets per year, <sup>b</sup> at least 200 tablets in each year, but not adherent through the whole 3-year period; <sup>c</sup> never covered and at least 1 year with less than 200 tablets; <sup>d</sup> large differences among the number of tablets per year (ie. Patients with differences of at least 200 pills year by year).

Table 3. Variables influencing occurrence of cardiovascular events

	<u>New users</u> <u>N = 48,386</u>		<u>Already in treatment patients</u> <u>N = 88,831</u>		<u>Total</u> <u>N = 137,217</u>	
	<u>OR (CI95%)</u>	<u>adjOR (CI95%)</u>	<u>OR (CI95%)</u>	<u>adjOR (CI95%)</u>	<u>OR (CI95%)</u>	<u>adjOR (CI95%)</u>
<b>Lack of Adherence<sup>a</sup></b>						
strongly non adherent	<u>0.73 (0.68-0.77)</u>	<u>1.16 (1.09-1.25)</u>	<u>0.75 (0.72-0.79)</u>	<u>1.07 (1.03-1.12)</u>	0.75 (0.72-0.77)	1.19 (1.15-1.23)
slightly non adherent	<u>0.98 (0.93-1.04)</u>	<u>1.22 (1.15-1.30)</u>	<u>1.04 (0.99-1.08)</u>	<u>1.27 (1.21-1.32)</u>	1.01 (0.98-1.05)	1.25 (1.21-1.30)
highly variable	<u>1.31 (1.23-1.40)</u>	<u>1.83 (1.70-1.96)</u>	<u>1.26 (1.21-1.32)</u>	<u>1.65 (1.58-1.74)</u>	1.28 (1.23-1.33)	1.69 (1.62-1.77)
<b>Male gender<sup>b</sup></b>	<u>1.55 (1.49-1.61)</u>	<u>1.39 (1.33-1.46)</u>	<u>1.62 (1.57-1.67)</u>	<u>1.40 (1.35-1.44)</u>	1.59 (1.56-1.63)	1.39 (1.35-1.43)
<b>Age class<sup>c</sup></b>						
50-65	<u>1.56(1.40-1.74)</u>	<u>1.24 (1.10-1.39)</u>	<u>1.61 (1.46-1.78)</u>	<u>1.39 (1.25-1.54)</u>	1.58 (1.47-1.70)	1.30 (1.20-1.41)
65-80	<u>2.80 (2.52-3.11)</u>	<u>1.86 (1.65-2.09)</u>	<u>3.01 (2.74-3.31)</u>	<u>2.23 (2.01-2.48)</u>	2.92 (2.72-3.13)	2.04 (1.88-2.20)
>80	<u>4.87 (4.33-5.47)</u>	<u>2.54 (2.22-2.91)</u>	<u>4.92 (4.44-5.44)</u>	<u>3.05 (2.73-3.41)</u>	4.85 (4.50-5.24)	2.78 (2.56-3.03)
<b>Previous CV events<sup>d</sup></b>	<u>4.61 (4.40-4.84)</u>	<u>2.86 (2.72-3.02)</u>	<u>3.62 (3.51-3.75)</u>	<u>2.38 (2.29-2.47)</u>	3.93 (3.83-4.04)	2.54 (2.46-2.62)
<b>Diabetes<sup>e</sup></b>	<u>1.48 (1.41-1.56)</u>	<u>1.29 (1.22-1.36)</u>	<u>1.64 (1.57-1.70)</u>	<u>1.39 (1.33-1.45)</u>	1.56 (1.52-1.61)	1.36 (1.31-1.40)
<b>Angina, hypertension, heart failure<sup>f</sup></b>	<u>4.72 (4.43-5.02)</u>	<u>2.79 (2.60-2.99)</u>	<u>4.60 (4.38-4.83)</u>	<u>2.76 (2.61-2.92)</u>	4.65 (4.47-4.83)	2.77 (2.65-2.89)
<b>Thrombosis<sup>g</sup></b>	<u>3.54 (3.39-3.69)</u>	<u>1.96 (1.86-2.06)</u>	<u>3.04 (2.95-3.14)</u>	<u>1.83 (1.76-1.90)</u>	3.21 (3.13-3.29)	1.87 (1.81-1.93)

<sup>a</sup> reference: adherent subjects; <sup>b</sup> reference: female gender; <sup>c</sup> reference: <50 years;; <sup>d</sup> reference: subjects without previous cardiovascular events; <sup>e</sup> subjects without antidiabetic drugs; <sup>f</sup> reference: subjects without prescription of drugs for angina, hypertension or heart failure; <sup>g</sup> reference: subjects without prescriptions of antithrombotic agen

## Figure captions

### **Fig.1 Year-by-year coverage of patients with statin therapy.**

The size of each circle is proportional to the corresponding percentages of patients (value inside); and the density of grey of the circle to the cumulative level of coverage, from black (always covered) to white (never covered). The analysis includes only patients alive at the end of the relevant year: the total alive patients were 136,013, 133,513, 130,727 in 2005, 2006 and 2007, respectively

**Fig. 2 Influence of lack of adherence to statins on cardiovascular events, stratified by sex, age, diabetes and other cardiovascular risk factors;** Points in the middle of lines indicate odds ratios; horizontal lines, 95% confidence intervals. (A) primary prevention: patients without hospital admission for CV event in two years before the recruitment (B) secondary prevention: patients with at last one hospital admission for CV event in two years before recruitment .

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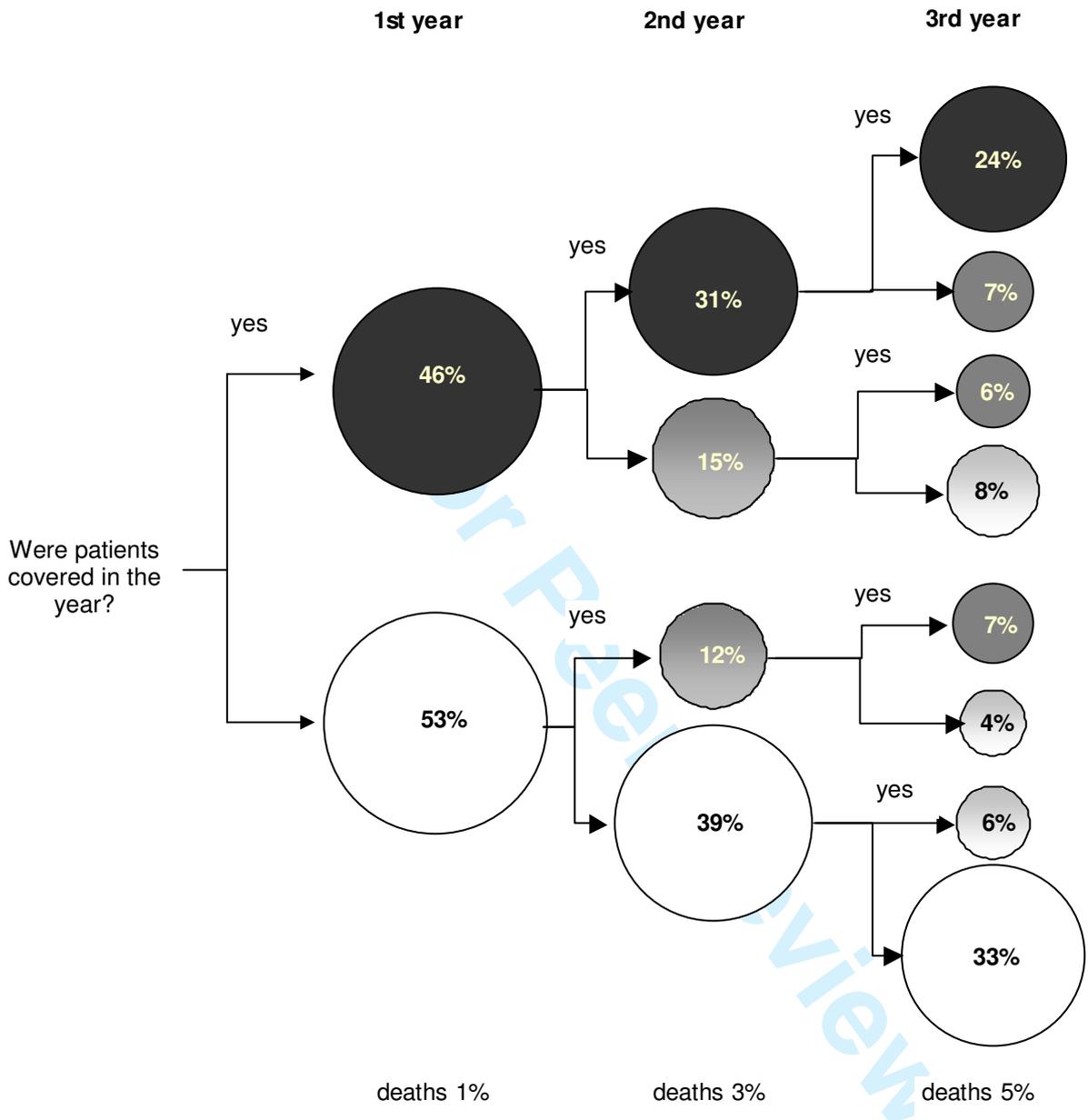


Fig. 1

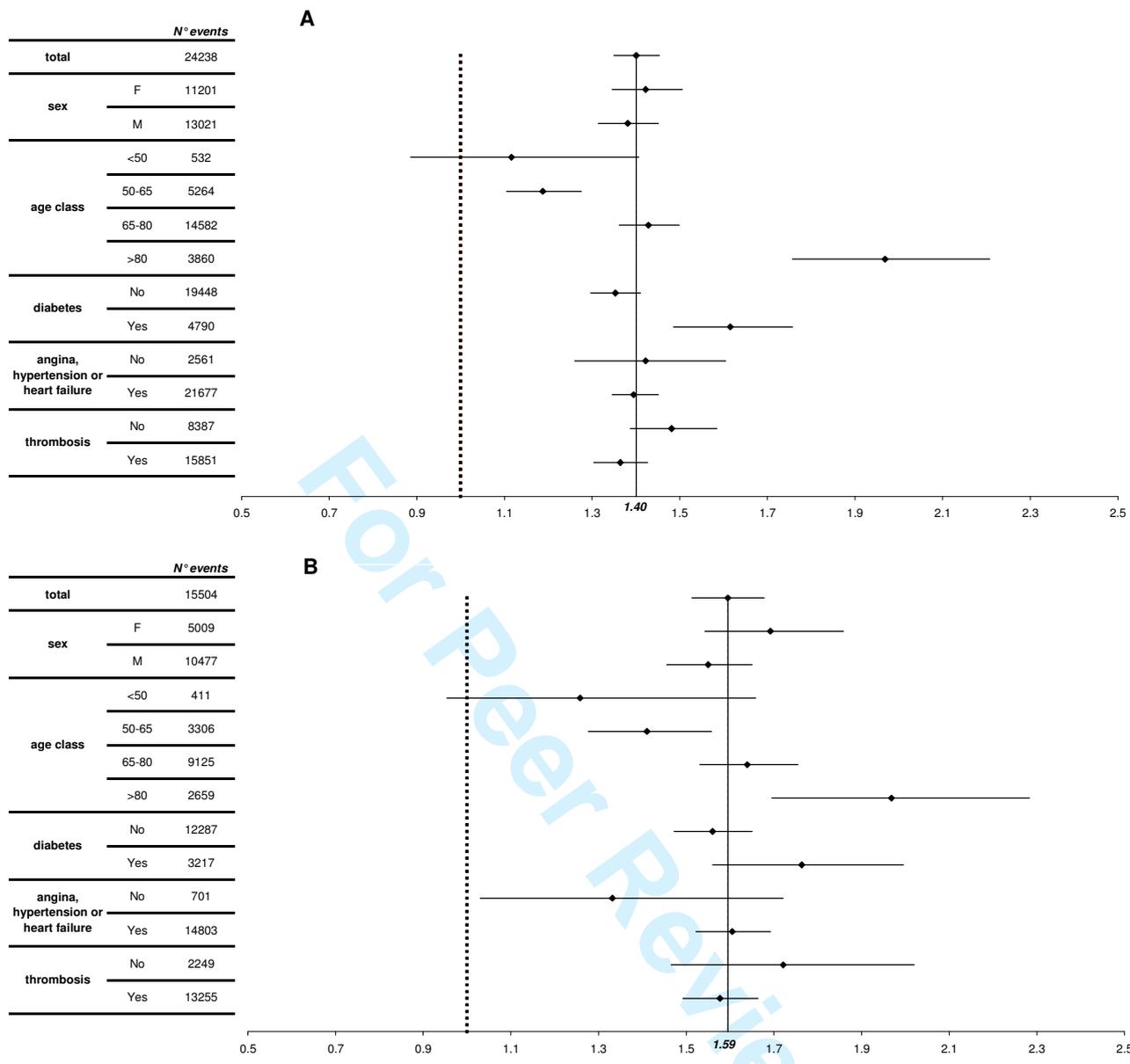


Fig.2

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2 **Cardiovascular events in statin recipients: impact of adherence to treatment in a**  
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4 **3-year record-linkage study**  
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8 Motola<sup>1</sup>, Alberto Vaccheri<sup>1</sup>, Fabrizio De Ponti<sup>1</sup>, and Nicola Montanaro<sup>1</sup>  
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## Abstract

### Purpose

In the general population, lack of adherence to statin therapy remains a widespread phenomenon and an important matter of concern both in terms of cost-effectiveness and risk-benefit profile. This study aimed to evaluate the occurrence of cardiovascular events in Italian statin recipients, focusing on the relationship between degree of adherence to therapy and occurrence of events in a 3-year follow-up.

### Methods

Our cohort consisted of all patients from Emilia Romagna (4,027,275 inhabitants) who received statin prescriptions in January–February 2005 and was followed up to 36 months for cardiovascular hospital admission (ie. coronary disease, cerebrovascular accidents, peripheral artheropathy), adherence to statin treatment (proportion of days covered:  $\geq 80\%$ ) and use of other cardiovascular drugs. The relationship between adherence and cardiovascular events was analysed by multivariate logistic regression; age, sex, other cardiovascular drugs and previous events were covariates of the model.

### Results

Patients non-adherent to statin regimen over the 3-year period (76% of the cohort) had higher odds of events, irrespective of risk factors, by more than 40% when compared with adherent patients. Odds of events were in particular: strongly non-adherent adjOR=1.19 (CI95% 1.15-1.23), slightly non-adherent adjOR=1.25 (1.21-1.30), highly variable in the amount of statins received adjOR=1.69 (1.62-1.77).

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### Conclusions

This study shows the key role of adherence to statins in the cardiovascular prevention at any level of risk. Appropriateness of statin use needs not only careful selection of patients to be treated, but also cooperation between patient and physician to ensure continued drug use whenever treatment is appropriate.

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**Keywords:** statins, medication adherence, general practice, cardiovascular disease, medical record-linkage

For Peer Review

## Introduction

Randomised controlled trials have clearly shown the benefits of lipid-lowering drug treatment for cardiovascular prevention, but how much these translate into actual benefit in the general population is not as well established. Whereas there is consensus on the benefits in secondary prevention [1,2] recommendations to use statins in primary prevention are currently a matter of debate [3-6] and in fact statins are used mostly in the latter setting (75% of statin recipients [7]). Some authors cast doubt on the benefit of statins in patients with low cardiovascular risk [8] whereas others suggested the use of statins (alone or even in the so-called polypill) even in normolipidemic subjects [4,9,10].

Lack of adherence is probably the most relevant factor differencing randomised controlled trials from clinical practice.

In the general population, lack of adherence to statin therapy remains a widespread phenomenon and, consequently, an important matter of concern both in terms of cost-effectiveness and risk-benefit profile. We have previously shown that, among statin recipients, less than 50% were prescribed an amount of drug consistent with daily treatment and this coverage was only slightly higher in patients in secondary prevention, in those aged 50–69 years and among males. Moreover, adherence significantly increased with the complexity of other cardiovascular treatments [11]. On the contrary, prescription of a highly active statin regimen (which can be used as a proxy of the severity of hypercholesterolemia) did not correlate with coverage.

The role of adherence to statins in preventing cardiovascular events in general practice is currently under investigation by different points of view (i.e., risk-benefit and cost-benefit profile) and some investigators have already published useful experiences in different countries [12-16]. However, the scenario is far from complete and the evidence is still partial and insufficient to support Health Policy strategies [17].

1  
2 The aim of this study was to evaluate the occurrence of cardiovascular events in all patients treated  
3 with statins in Emilia Romagna (about 4,000,000 inhabitants), focusing on the relationship between  
4 the occurrence of events and the degree of adherence to therapy.  
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## 9 **Methods**

### 10 *Sources of data*

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12 Drug prescription data were retrieved from the Emilia Romagna Regional Health Authority  
13 Database, which provides the following information for each reimbursed prescription: identification  
14 code of the drug, ATC (Anatomical Therapeutic Chemical) code, number of packages dispensed,  
15 patient code, date of prescription. The patient code allows retrieval of his/her drug history without  
16 individual identification.  
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19 We collected data of statins and other drugs used for cerebro- or cardiovascular risk prevention (i.e.,  
20 antiplatelet agents, nitrates, antihypertensives, antidiabetics), prescribed by general practitioners  
21 (GPs) and reimbursed between January 2003 and February 2008 by the Health Authority of Emilia  
22 Romagna (with both urban and rural area, 4,027,275 inhabitants). The following ATC codes were  
23 considered: A10 – drugs used in diabetes; B01A – antithrombotic agents; C01DA – antianginal  
24 drugs (nitrates); C02, C03, C07, C08, C09 – drugs used in the treatment of hypertension; C10 –  
25 lipid modifying agents.  
26

27 All statins are reimbursed by Italian Health Service for (i) familial hypercholesterolaemia, (ii)  
28 patients with previous cardiovascular or cerebrovascular events, or (iii) patients with a 10-year  
29 cardiovascular risk higher than 20%.  
30

31 Data of hospital admissions for cardiovascular or cerebrovascular events, occurred from January  
32 2003 to February 2008, were retrieved from the hospital discharge registry which provides the  
33 following information: ICD-9 code (410-414: ischemic heart disease; 430-438: cerebrovascular  
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2 diseases; 440: atherosclerosis; 443: other peripheral vascular disease; 444: arterial embolism and  
3 thrombosis;), type of the hospital and ward, duration of the hospital stay and patient code.

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6 Data regarding age, sex and deaths were anonymously retrieved from vital statistics.

7  
8 All the databases are managed by the Drug Policy Service of the Health Department of the Emilia-  
9 Romagna Region, which provides anonymous data by attributing an anonymous code to each  
10 patient. This code allows the record linkage of individual patient data among different databases  
11 according to the provisions of privacy rules. The protocol was approved by the institutional ethics  
12 committee.  
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### 18 *Study design*

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20 Our cohort consisted of all patients who received at least one statin prescription between January  
21 and February 2005 (recruitment period) and at least another prescription of statins during the first  
22 year of follow-up. Patient drug prescriptions and cardiovascular hospital admissions were analysed  
23 for 36 months following recruitment (March 2005 - February 2008, follow-up). Co-prescriptions of  
24 cardiovascular drugs other than statins (recorded in the first year of follow-up) were used as a  
25 component of patient risk profile, as well as hospital discharge records for cardiovascular events  
26 occurred before recruitment (January 2003-December 2004).  
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34 Adherence was evaluated by analysing the amount of statins received during the 3 year-period:

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36 • for each year, patients were considered “covered” if they received at least 300 tablets  
37 (allowing a tolerance of ~20% over the 365 day period) [11] and
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39 • patients who met the above criterion throughout the 3-year follow-up were considered as  
40  
41 “adherent”.  
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43  
44 The amount of statins was evaluated as number of tablets purchased. In fact, the availability of  
45 different dosage strengths for each active substance allow patients to take their daily medication as  
46 one tablet.  
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### 49 *Statistical analyses*

To evaluate the association between cardiovascular events and adherence to statin treatment, a logistic multivariate regression analysis was performed, by grouping non-adherent patients into 3 different categories: “strongly non adherent”, “slightly non adherent” and “highly variable” patients (see table 2 for definitions). Age, sex, comorbidity (diabetes, hypertension-angina-heart failure and thrombosis in the first year of the follow-up) were included as covariates in the models.

Only patients surviving the 3-year follow-up period were included in the logistic analysis.

To better describe the role of the adherence in cardiovascular prevention, two different stratified models for primary and secondary prevention cohort were estimated. Patients in secondary prevention were those who experienced a cardiovascular event before the recruitment. The effect of adherence was assessed by a generalization of Mantel-Haenszel method in different subgroups samples. The differences in subgroups were tested with Pearson  $\chi^2$  test. A p-value  $<0.05$  was considered significant.

All analyses were performed using STATA version 10 (StataCorp. 2001. College Station, TX: Stata Corporation) and SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

## Results

### *Adherence to statin regimen*

The cohort of statin recipients consisted of 137,217 subjects, with a mean age of  $67 \pm 10$  years and 1:1 female/male ratio (Table 1). During the three years of follow up, 6,491 subjects (5%) died.

Seventy-seven percent of subjects (106,167) received prescriptions of the same statin and simvastatin was the most prescribed (32% of patients), followed by atorvastatin (24%). The remaining 23% of patients were switched to another statin, especially rosuvastatin (23.6%) or atorvastatin (12.6%). Moreover, 72% received only highly active statin regimens (i.e., at dosages expected to reduce LDL-cholesterol by more than 30% [11]).

Eighty-five percent of patients received additional cardiovascular treatments on the first year of follow-up: in particular, 77% (105,341) of subjects concomitantly received drugs for hypertension

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2 or angina or heart failure, 54% (73,963) used antithrombotics and 16% (21,530) used antidiabetics  
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4 (Table 1). Along the remaining two years of follow-up, a further 2.5% of patients per year received  
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6 antihypertensive prescriptions, a further 5% received antithrombotics and a further 2.5% received  
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8 antidiabetics.

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10 In our cohort, 35% did not receive statin prescriptions in the 2 previous years (new users).

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12 The proportions of patients receiving more than 300 tablets/year of statins and that of patients  
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14 receiving 201-300 tablets/year were stable along the three years of follow-up (45% and 24%  
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16 respectively), whereas that of patients receiving 101-200 tablets decreased from 24% to 19% and  
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18 that of patients taking less than 101 tablets showed an appreciable increase, from 6% in the first  
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20 year to 13% in the third one.

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22 Sixty-two percent (81,666) of patients were covered for at least 1 year, 44% (60,894) for at least 2  
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24 years and 24% (32,355) for the whole 3-year period and only this last figure represents the adherent  
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26 population according to our criteria. (Figure 1).

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28 Among the 98,371 patients who did not meet the criteria to be considered “adherent”, 28% (38,328)  
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30 were “slightly non-adherent”, 30% (41,678) “strongly non-adherent”, and 13% (18,382) “highly  
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32 variable” (Table 2).

### 33 *Cardiovascular events*

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35 Within the whole cohort of 137,217 patients, 29% (39,708) experienced cerebro- or cardiovascular  
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37 events during the 3 year-follow-up (annual rate: 13%): 54% of events were represented by coronary  
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39 heart disease, followed by cerebrovascular accidents (18%).

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41 Cerebro- and cardiovascular events occurred more frequently in non-adherent patients rather than  
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43 adherent group (reference), with the following ranking: strongly non-adherent (adjOR=1.19; 95%  
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45 CI 1.15-1.23), slightly non-adherent (1.25; 1.21-1.30), highly variable (1.69;1.62-1.77). These  
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47 events increased with age (e.g., patients older than 80: adjOR=2.78; 95% CI 2.56-3.03) and were  
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49 statistically more frequent in men (adjOR=1.39; 95% CI 1.35-1.43), in patients using statins for  
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51 secondary prevention (2.54; 2.46-2.62), those co-medicated for hypertension, angina or heart failure

(2.77; 2.65-2.89), using antithrombotics (1.87; 1.81-1.93), and with diabetes (1.36; 1.31-1.40; see table 3). By considering separately new users and already in treatment patients, the analysis confirmed the significant variables, with minor differences between the two groups. The following variables weighed on the occurrence of CV events more in new users rather than in those already in treatment: strongly non adherent or highly variable regimens, previous CV events and concomitant anti-thrombotic drugs.

Subgroup analysis showed a higher risk of events among non-adherent patients irrespective of risk factors: adjOR 1.40 (95% CI 1.35-1.45) in patients using statins for primary prevention and adjOR=1.59 (95% CI 1.51-1.68) in those using statins for secondary prevention (Figure 2). The only exception was represented by the younger age group (<50 years), for whom the confidence interval includes 1. Moreover, for subjects older than 80 years both in primary and secondary prevention, and in patients with diabetes in primary prevention, the association between lack of adherence and CV events was statistically stronger than in unstratified analysis.

Considering patients' prescriptions twelve months before and after the occurrence of an event, 53% of patients increased their number of tablets after the event; so that a fraction (15%) of the non-covered patients became covered in the year after the event. On the other hand, 26% of patients did not change their number of tablets and the remaining 21% even decreased it.

## Discussion

In our cohort of 137,217 patients, more than three quarters of statin recipients did not adhere to drug therapy throughout the 3-year follow-up and, these patients showed more than 40% increase of cardiovascular events when compared with adherent statin recipients.

Although the issue of lack of adherence to statin treatment has been already reported [11,18], in our opinion, a population-based cohort study is important because it attempts to translate adherence to statin regimen into actual cardiovascular benefit in unselected patients in a community setting. Some previous studies provided useful findings to clarify this topic. A study on a large Israeli

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1 cohort [19] found a strong association between intensity of statin therapy (in terms of number of  
2 tablets/year) and improved survival both in primary and secondary prevention, even higher than that  
3 found in clinical trials (up to 45% of risk reduction). Also a Canadian study showed the important  
4 role of adherence to statins in the prevention of both cerebrovascular events (reduction of risk:  
5 26%) and coronary disease (18%) [12-14]. Two recent Italian studies focused on incident statin  
6 recipients for primary prevention. On one hand, Deambrosis et al. found a better cholesterol  
7 outcome in adherent patients, but a paradoxical association between adherence and hospitalisation  
8 for coronary events [15]. This finding was probably affected by a confounding factor, represented  
9 by the basal cardiovascular risk, which conditioned independently both adherence and hospital  
10 admissions. On the other hand, Corrao et al. found a protective role of adherence on nonfatal  
11 ischemic heart disease (reduction of risk: 15-20%) [16].

12 Our results (although not directly comparable to those of the above studies because of different  
13 parameters in outcomes and in observed population) substantially agree on the clinical importance  
14 of continued statin use and provide a wider picture on cardiovascular outcomes in all users (both  
15 incident users and already in treatment at recruitment).

16 The approach used in this study has strengths and limitations. In our opinion, one strength was  
17 represented by performing our analysis in a large community setting, including all statin recipients,  
18 no matter what the length of therapy before the recruitment was, and including all meaningful  
19 cardiovascular outcomes. On the one hand, the findings provided by this approach refer to prevalent  
20 statin users, whereas other studies frequently selected only incident users, which represent only a  
21 minority of overall statin recipients. On the other hand, our method intrinsically lacks in  
22 completeness on prior morbidity and drug history, and could be affected by the immeasurable time  
23 bias [20] because of the lack of information on statin exposure during hospitalisations. In the worst  
24 case scenario, this bias could have generated a misclassification of 586 non-adherent subjects (0.4%  
25 of the cohort), who would pass to adherent status by considering all hospitalisation days as covered  
26 days. On the basis of these data, we found a possible overestimation of the risk of events among

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2 non-adherent patients by 6 and 8%, respectively in case of primary and secondary prevention. A  
3  
4 further limitation was the lack of information on lipidemia, which was an obstacle in the correct  
5  
6 association between adherence and cardiovascular outcomes. However information on lipidemia  
7  
8 would be very difficult to collect even by using physician's records. In addition, since our  
9  
10 prescription data were obtained only from reimbursement database, we probably excluded patients  
11  
12 not meeting the Italian reimbursement criteria, because at a lower CV risk. This lack of data could  
13  
14 have caused a slight overestimation of the role of adherence in the prevention of CV events.

15  
16 Moreover, a positive attitude of patients towards their own health could be a confounding factor,  
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18 influencing independently both statin adherence and event occurrence, but also this information is  
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20 not available in administrative databases, which are the source of our study. Only studies based on  
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22 questionnaire or primary care database could collect this data and could quantify the magnitude of  
23  
24 the healthy adherer effect.

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26 This phenomenon is usually indicated as "healthy adherer effect", as already acknowledged by  
27  
28 Dragomir [13], Rasmussen [21] and Anderson [22], who stated the difficulties in its quantification.  
29  
30 Nonetheless a generic "healthy adherer behaviour" could have generated a tolerable overestimation  
31  
32 of the protective effect of adherence.

33  
34 Finally, because of the low frequency and the delayed onset of cardiovascular events in low-risk  
35  
36 patients, a longer follow up could provide further evidence on this population.

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38 When addressing the health policy implications of our results showing the close relationship  
39  
40 between adherence to statins and their effectiveness, the fact that 3 out of 4 of statin recipients were  
41  
42 not adherent suggests that statin use in our community setting produces both scarce gain in terms of  
43  
44 health and waste of economic resources.

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46 For efficient resource allocation, quantification of the non-adherent population to optimise overall  
47  
48 health gain in the community is a priority [17]. Each Health Authority faces two different scenarios:  
49  
50 (a) encouraging efforts to cover a large population entails inherent problems in ensuring adherence,  
51  
52 increased overall burden of side effects, in an attempt to reduce as many as possible cardiovascular

1  
2 events; (b) envisaging a strategy more stringently identifying the population with a likely benefit  
3  
4 (which implies less effort to ensure adherence, decreased overall burden of side effects, lower drug  
5  
6 cost, but incomplete population protection from cardiovascular risk) [17].

7  
8 In the light of these potential benefit and limitations, there is debate on which strategy is better, but  
9  
10 certainly the specific risk profile of the resident population and the availability of economic  
11  
12 resources should guide decision makers.

13  
14 In our community setting, we interpret the paradoxically lower odds of cardiovascular events in  
15  
16 strongly non-adherent patients as an indication that this group was at lower risk than the other non-  
17  
18 adherent patients. Indeed, the strongly non-adherent group probably included a number of subjects  
19  
20 who actually did not require pharmacological lipid-lowering treatment. Therefore, we would not  
21  
22 recommend measures to improve adherence in this group. Probably, efforts to improve adherence  
23  
24 should focus on the 28% that was not strictly adherent, but received a yearly amount of drug able to  
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26 cover at least 6 months (slightly non adherent patients), and on the 13% that alternated covered  
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28 years with years at very low intensity of treatment (highly variable patients). Notably, the last group  
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30 showed the highest odds of cardiovascular events (about 70% higher than adherent patients).  
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**Conclusions**

This study shows the key role of adherence to statins in the prevention of cardiovascular events at any level of risk in a community setting. Appropriate use of statins needs both strict selection of patients before starting drug treatment and patient-physician cooperation for continued drug use whenever the treatment was appropriately started.

**Acknowledgments**

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For Peer Review

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Table 1. Descriptive analysis of patients' characteristics and events

		Number of patients	%	Events	% in the class
<b>Gender<sup>a</sup></b>	F	67,238	49%	16,210	24%
	M	69,858	51%	23,498	34%
<b>Age class</b>	<50	6,750	5%	943	14%
	50-65	41,914	31%	8,573	20%
	65-80	73,763	54%	23,707	32%
	>80	14,790	11%	6,519	44%
<b>Previous CV events<sup>b</sup></b>	Yes	29,144	21%	15,504	53%
	No	108,073	79%	24,238	22%
<b>Diabetes<sup>c</sup></b>	Yes	21,530	16%	8,007	37%
	No	115,687	84%	31,735	27%
<b>Angina, hypertension, heart failure<sup>c</sup></b>	Yes	105,341	77%	36,480	35%
	No	31,876	23%	3,262	10%
<b>Thrombosis<sup>c</sup></b>	Yes	73,963	54%	29,106	39%
	No	63,254	46%	10,636	17%
<b>Three year adherence<sup>d</sup></b>	Yes	32,355	24%	8,803	27%
	No	104,862	76%	30,939	30%
<b><u>New users</u></b>	<u>Yes</u>	<u>48,386</u>	<u>35%</u>	<u>13,681</u>	<u>28%</u>
	<u>No</u>	<u>88,831</u>	<u>65%</u>	<u>26,061</u>	<u>29%</u>

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<sup>a</sup> indication of gender was missing in 121 patients;<sup>b</sup> previous CV events were observed for the period 2003-2004;<sup>c</sup> concomitant CV disorders were evaluated by the prescription of the relevant drugs in the first year of follow-up. The following ATC codes were considered: A10 – drugs used in diabetes; C01DA – antianginal drugs (nitrates); C02, C03, C07, C08, C09 – drugs used in the treatment of hypertension and B01A – antithrombotic agents;<sup>d</sup> patients were considered adherent when they were prescribed at least 300 doses of statins for each of the 3-year follow-up; patients who died during follow-up were included in the non-adherent group.

**Table 2. Distribution of patients according to adherence to statins**

	<b>N.</b>	<b>%</b>
<b>Adherent patients<sup>a</sup></b>	32,339	24%
<b>Slightly non adherent patients<sup>b</sup></b>	38,328	28%
<b>Strongly non adherent patients<sup>c</sup></b>	41,678	30%
<b>Highly variable patients<sup>d</sup></b>	18,382	13%
<b>Deaths during the 3-year period</b>	6,490	5%

<sup>a</sup> at least 300 tablets per year, <sup>b</sup> at least 200 tablets in each year, but not adherent through the whole 3-year period; <sup>c</sup> never covered and at least 1 year with less than 200 tablets; <sup>d</sup> large differences among the number of tablets per year (ie. Patients with differences of at least 200 pills year by year).

Table 3. Variables influencing occurrence of cardiovascular events

		<u>New users</u> N = 48,386		<u>Already in treatment patients</u> N = 88,831		<u>Total</u> N = 137,217	
		<u>OR (CI95%)</u>	<u>adjOR (CI95%)</u>	<u>OR (CI95%)</u>	<u>adjOR (CI95%)</u>	<u>OR (CI95%)</u>	<u>adjOR (CI95%)</u>
<b>Lack of Adherence<sup>a</sup></b>	strongly non adherent	<u>0.73 (0.68-0.77)</u>	<u>1.16 (1.09-1.25)</u>	<u>0.75 (0.72-0.79)</u>	<u>1.07 (1.03-1.12)</u>	0.75 (0.72-0.77)	1.19 (1.15-1.23)
	slightly non adherent	<u>0.98 (0.93-1.04)</u>	<u>1.22 (1.15-1.30)</u>	<u>1.04 (0.99-1.08)</u>	<u>1.27 (1.21-1.32)</u>	1.01 (0.98-1.05)	1.25 (1.21-1.30)
	highly variable	<u>1.31 (1.23-1.40)</u>	<u>1.83 (1.70-1.96)</u>	<u>1.26 (1.21-1.32)</u>	<u>1.65 (1.58-1.74)</u>	1.28 (1.23-1.33)	1.69 (1.62-1.77)
<b>Male gender<sup>b</sup></b>		<u>1.55 (1.49-1.61)</u>	<u>1.39 (1.33-1.46)</u>	<u>1.62 (1.57-1.67)</u>	<u>1.40 (1.35-1.44)</u>	1.59 (1.56-1.63)	1.39 (1.35-1.43)
<b>Age class<sup>c</sup></b>	50-65	<u>1.56(1.40-1.74)</u>	<u>1.24 (1.10-1.39)</u>	<u>1.61 (1.46-1.78)</u>	<u>1.39 (1.25-1.54)</u>	1.58 (1.47-1.70)	1.30 (1.20-1.41)
	65-80	<u>2.80 (2.52-3.11)</u>	<u>1.86 (1.65-2.09)</u>	<u>3.01 (2.74-3.31)</u>	<u>2.23 (2.01-2.48)</u>	2.92 (2.72-3.13)	2.04 (1.88-2.20)
	>80	<u>4.87 (4.33-5.47)</u>	<u>2.54 (2.22-2.91)</u>	<u>4.92 (4.44-5.44)</u>	<u>3.05 (2.73-3.41)</u>	4.85 (4.50-5.24)	2.78 (2.56-3.03)
<b>Previous CV events<sup>d</sup></b>		<u>4.61 (4.40-4.84)</u>	<u>2.86 (2.72-3.02)</u>	<u>3.62 (3.51-3.75)</u>	<u>2.38 (2.29-2.47)</u>	3.93 (3.83-4.04)	2.54 (2.46-2.62)
<b>Diabetes<sup>e</sup></b>		<u>1.48 (1.41-1.56)</u>	<u>1.29 (1.22-1.36)</u>	<u>1.64 (1.57-1.70)</u>	<u>1.39 (1.33-1.45)</u>	1.56 (1.52-1.61)	1.36 (1.31-1.40)
<b>Angina, hypertension, heart failure<sup>f</sup></b>		<u>4.72 (4.43-5.02)</u>	<u>2.79 (2.60-2.99)</u>	<u>4.60 (4.38-4.83)</u>	<u>2.76 (2.61-2.92)</u>	4.65 (4.47-4.83)	2.77 (2.65-2.89)
<b>Thrombosis<sup>g</sup></b>		<u>3.54 (3.39-3.69)</u>	<u>1.96 (1.86-2.06)</u>	<u>3.04 (2.95-3.14)</u>	<u>1.83 (1.76-1.90)</u>	3.21 (3.13-3.29)	1.87 (1.81-1.93)

<sup>a</sup> reference: adherent subjects; <sup>b</sup> reference: female gender; <sup>c</sup> reference: <50 years;; <sup>d</sup> reference: subjects without previous cardiovascular events; <sup>e</sup> subjects without antidiabetic drugs; <sup>f</sup> reference: subjects without prescription of drugs for angina, hypertension or heart failure; <sup>g</sup> reference: subjects without prescriptions of antithrombotic agen

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6 **Fig.1 Year-by-year coverage of patients with statin therapy.**  
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8 The size of each circle is proportional to the corresponding percentages of patients (value inside);  
9 and the density of grey of the circle to the cumulative level of coverage, from black (always  
10 covered) to white (never covered). The analysis includes only patients alive at the end of the  
11 relevant year: the total alive patients were 136,013, 133,513, 130,727 in 2005, 2006 and 2007,  
12 respectively  
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20 **Fig. 2 Influence of lack of adherence to statins on cardiovascular events, stratified by sex, age,**

21 **diabetes and other cardiovascular risk factors;** Points in the middle of lines indicate odds ratios;  
22 horizontal lines, 95% confidence intervals. (A) primary prevention: patients without hospital  
23 admission for CV event in two years before the recruitment (B) secondary prevention: patients with  
24 at last one hospital admission for CV event in two years before recruitment .  
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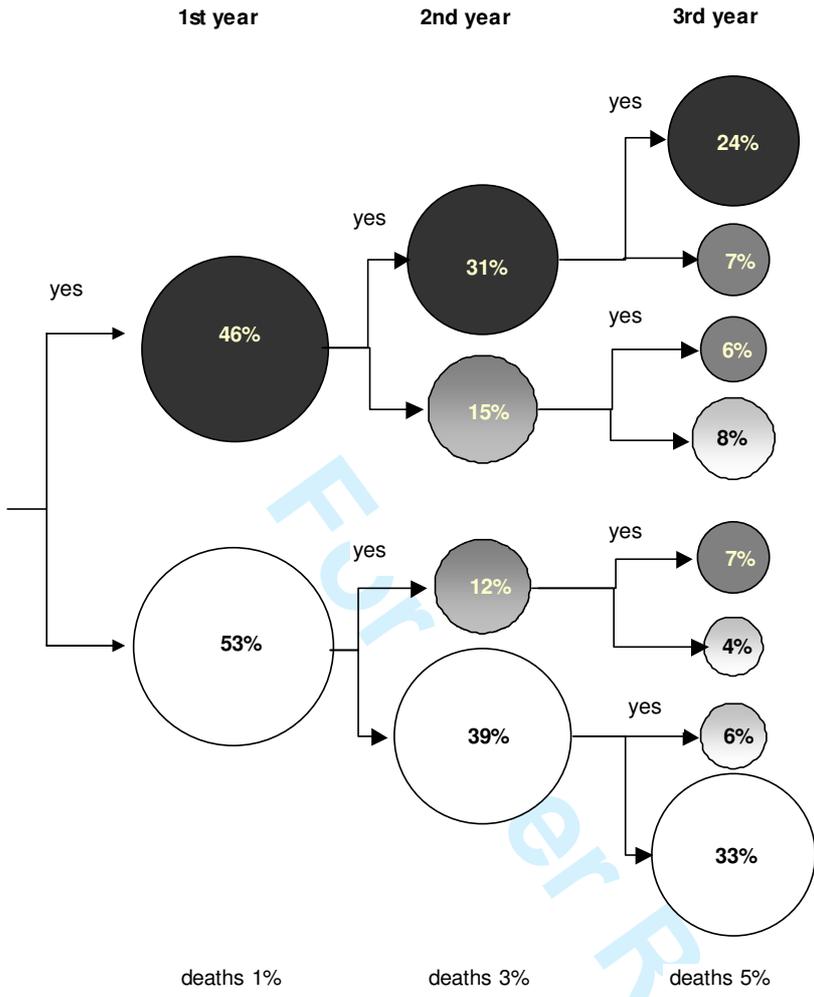


Fig. 1

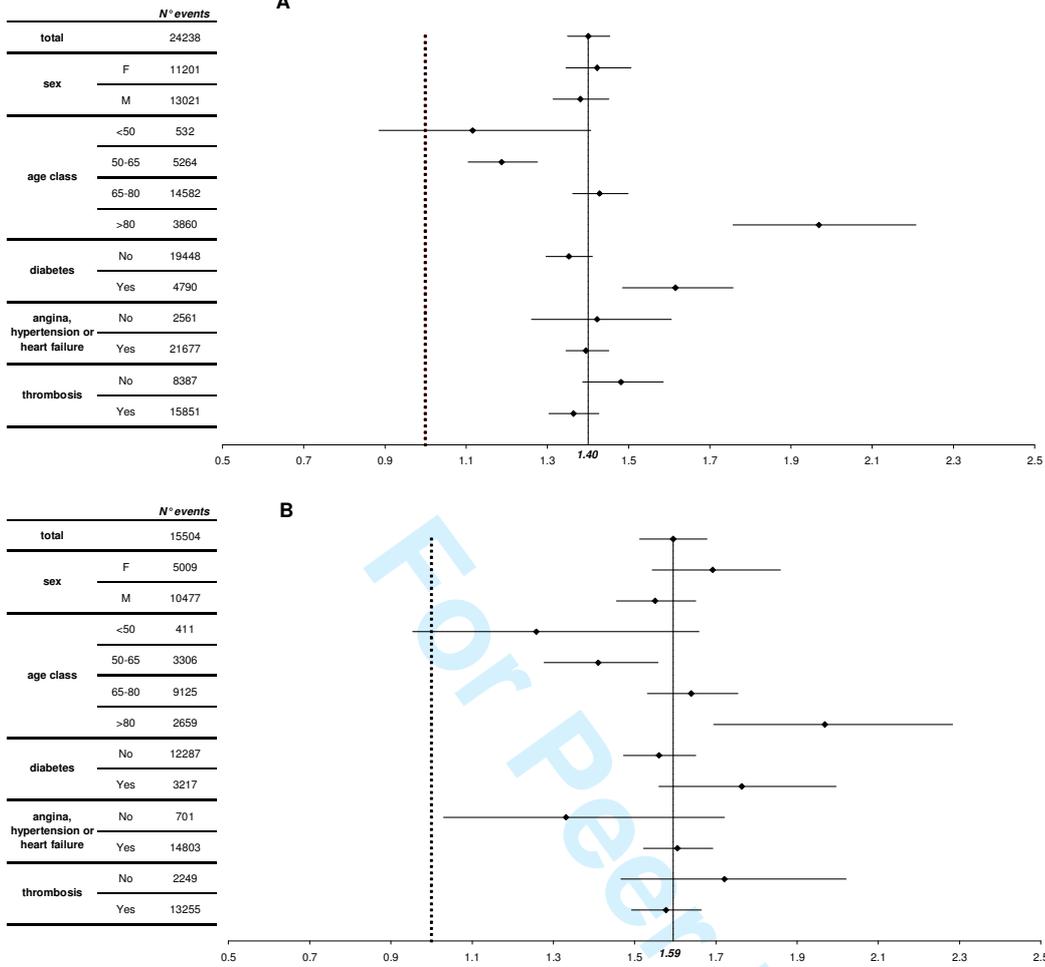


Fig.2