



HAL
open science

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

Elisabetta Poluzzi, Carlo Piccinni, Paolo Carta, Aurora Puccini, Monica Lanzoni, Domenico Motola, Alberto Vaccheri, Fabrizio Ponti, Nicola Montanaro

► To cite this version:

Elisabetta Poluzzi, Carlo Piccinni, Paolo Carta, Aurora Puccini, Monica Lanzoni, et al.. Cardiovascular events in statin recipients: impact of adherence to treatment in a 3-year record linkage study. *European Journal of Clinical Pharmacology*, 2010, 67 (4), pp.407-414. 10.1007/s00228-010-0958-3 . hal-00649879

HAL Id: hal-00649879

<https://hal.science/hal-00649879>

Submitted on 9 Dec 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



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



| | |
|-------------------------------|--|
| Journal: | <i>European Journal of Clinical Pharmacology</i> |
| Manuscript ID: | EJCP-2010-0221.R2 |
| Type of submission: | Original |
| Date Submitted by the Author: | 05-Nov-2010 |
| Complete List of Authors: | <p>Poluzzi, Elisabetta; University of Bologna, Department of Pharmacology Piccinni, Carlo; University of Bologna, Department of Pharmacology Carta, Paolo; University of Bologna, Department of Pharmacology Puccini, Aurora; Emilia Romagna Regional Health Authority, Drug Policy Service Lanzoni, Monica; Emilia Romagna Regional Health Authority, Drug Policy Service Motola, Domenico; University of Bologna, Department of Pharmacology Vaccheri, Alberto; University of Bologna, Department of Pharmacology De Ponti, Fabrizio; University of Bologna, Department of Pharmacology Montanaro, Nicola; University of Bologna, Department of Pharmacology</p> |
| | |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Elisabetta Poluzzi¹, Carlo Piccinni¹, Paolo Carta¹, Aurora Puccini², Monica Lanzoni², Domenico Motola¹, Alberto Vaccheri¹, Fabrizio De Ponti¹, and Nicola Montanaro¹

¹*Department of Pharmacology, University of Bologna, Via Irnerio 48, I-40126 Bologna, Italy*

²*Drug Policy Service, Emilia Romagna Regional Health Authority, Viale Aldo Moro 21, I-40127 Bologna, Italy*

Corresponding author

Nicola Montanaro
Department of Pharmacology, University of Bologna
Via Irnerio 48
40126 Bologna, Italy
e-mail: nicola.montanaro@unibo.it

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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
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
5
6 the occurrence of events and the degree of adherence to therapy.
7
8
9

10 11 12 **Methods**

13 *Sources of data*

14
15 Drug prescription data were retrieved from the Emilia Romagna Regional Health Authority
16
17 Database, which provides the following information for each reimbursed prescription: identification
18
19 code of the drug, ATC (Anatomical Therapeutic Chemical) code, number of packages dispensed,
20
21 patient code, date of prescription. The patient code allows retrieval of his/her drug history without
22
23 individual identification.
24
25
26
27

28
29 We collected data of statins and other drugs used for cerebro- or cardiovascular risk prevention (i.e.,
30
31 antiplatelet agents, nitrates, antihypertensives, antidiabetics), prescribed by general practitioners
32
33 (GPs) and reimbursed between January 2003 and February 2008 by the Health Authority of Emilia
34
35 Romagna (with both urban and rural area, 4,027,275 inhabitants). The following ATC codes were
36
37 considered: A10 – drugs used in diabetes; B01A – antithrombotic agents; C01DA – antianginal
38
39 drugs (nitrates); C02, C03, C07, C08, C09 – drugs used in the treatment of hypertension; C10 –
40
41 lipid modifying agents.
42
43
44
45

46
47 All statins are reimbursed by Italian Health Service for (i) familial hypercholesterolaemia, (ii)
48
49 patients with previous cardiovascular or cerebrovascular events, or (iii) patients with a 10-year
50
51 cardiovascular risk higher than 20%.
52

53
54 Data of hospital admissions for cardiovascular or cerebrovascular events, occurred from January
55
56 2003 to February 2008, were retrieved from the hospital discharge registry which provides the
57
58 following information: ICD-9 code (410-414: ischemic heart disease; 430-438: cerebrovascular
59
60

1
2
3 diseases; 440: atherosclerosis; 443: other peripheral vascular disease; 444: arterial embolism and
4 thrombosis;), type of the hospital and ward, duration of the hospital stay and patient code.
5
6
7

8 Data regarding age, sex and deaths were anonymously retrieved from vital statistics.
9

10 All the databases are managed by the Drug Policy Service of the Health Department of the Emilia-
11 Romagna Region, which provides anonymous data by attributing an anonymous code to each
12 patient. This code allows the record linkage of individual patient data among different databases
13 according to the provisions of privacy rules. The protocol was approved by the institutional ethics
14 committee.
15
16
17
18
19
20
21
22

23 *Study design*

24
25 Our cohort consisted of all patients who received at least one statin prescription between January
26 and February 2005 (recruitment period) and at least another prescription of statins during the first
27 year of follow-up. Patient drug prescriptions and cardiovascular hospital admissions were analysed
28 for 36 months following recruitment (March 2005 - February 2008, follow-up). Co-prescriptions of
29 cardiovascular drugs other than statins (recorded in the first year of follow-up) were used as a
30 component of patient risk profile, as well as hospital discharge records for cardiovascular events
31 occurred before recruitment (January 2003-December 2004).
32
33
34
35
36
37
38
39
40
41

42 Adherence was evaluated by analysing the amount of statins received during the 3 year-period:

- 43
44 • for each year, patients were considered “covered” if they received at least 300 tablets
45 (allowing a tolerance of ~20% over the 365 day period) [11] and
46
47
- 48 • patients who met the above criterion throughout the 3-year follow-up were considered as
49
50
51
52
53 “adherent”.

54 The amount of statins was evaluated as number of tablets purchased. In fact, the availability of
55 different dosage strengths for each active substance allow patients to take their daily medication as
56 one tablet.
57
58
59
60

Statistical analyses

1
2
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
8
9 (see table 2 for definitions). Age, sex, comorbidity (diabetes, hypertension-angina-heart failure and
10
11 thrombosis in the first year of the follow-up) were included as covariates in the models.
12
13

14
15 Only patients surviving the 3-year follow-up period were included in the logistic analysis.
16

17 To better describe the role of the adherence in cardiovascular prevention, two different stratified
18
19 models for primary and secondary prevention cohort were estimated. Patients in secondary
20
21 prevention were those who experienced a cardiovascular event before the recruitment. The effect of
22
23 adherence was assessed by a generalization of Mantel-Haenszel method in different subgroups
24
25 samples. The differences in subgroups were tested with Pearson χ^2 test. A p-value <0.05 was
26
27 considered significant.
28
29

30
31 All analyses were performed using STATA version 10 (StataCorp. 2001. College Station, TX: Stata
32
33 Corporation) and SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).
34
35
36
37

38 **Results**

39 *Adherence to statin regimen*

40
41 The cohort of statin recipients consisted of 137,217 subjects, with a mean age of 67 \pm 10 years and
42
43 1:1 female/male ratio (Table 1). During the three years of follow up, 6,491 subjects (5%) died.
44
45

46
47 Seventy-seven percent of subjects (106,167) received prescriptions of the same statin and
48
49 simvastatin was the most prescribed (32% of patients), followed by atorvastatin (24%). The
50
51 remaining 23% of patients were switched to another statin, especially rosuvastatin (23.6%) or
52
53 atorvastatin (12.6%). Moreover, 72% received only highly active statin regimens (i.e., at dosages
54
55 expected to reduce LDL-cholesterol by more than 30% [11]).
56
57

58
59 Eighty-five percent of patients received additional cardiovascular treatments on the first year of
60
follow-up: in particular, 77% (105,341) of subjects concomitantly received drugs for hypertension

1
2
3 or angina or heart failure, 54% (73,963) used antithrombotics and 16% (21,530) used antidiabetics
4
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.
10

11
12 In our cohort, 35% did not receive statin prescriptions in the 2 previous years (new users).
13

14
15 The proportions of patients receiving more than 300 tablets/year of statins and that of patients
16
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
20
21 that of patients taking less than 101 tablets showed an appreciable increase, from 6% in the first
22
23 year to 13% in the third one.
24
25

26
27 Sixty-two percent (81,666) of patients were covered for at least 1 year, 44% (60,894) for at least 2
28
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

33
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
37
38 variable” (Table 2).
39

40 41 *Cardiovascular events*

42
43 Within the whole cohort of 137,217 patients, 29% (39,708) experienced cerebro- or cardiovascular
44
45 events during the 3 year-follow-up (annual rate: 13%): 54% of events were represented by coronary
46
47 heart disease, followed by cerebrovascular accidents (18%).
48

49
50 Cerebro- and cardiovascular events occurred more frequently in non-adherent patients rather than
51
52 adherent group (reference), with the following ranking: strongly non-adherent (adjOR=1.19; 95%
53
54 CI 1.15-1.23), slightly non-adherent (1.25; 1.21-1.30), highly variable (1.69;1.62-1.77). These
55
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
59
60 secondary prevention (2.54; 2.46-2.62), those co-medicated for hypertension, angina or heart failure

1
2
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
4
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
10
11 treatment: strongly non adherent or highly variable regimens, previous CV events and concomitant
12
13 anti-thrombotic drugs.
14
15

16
17 Subgroup analysis showed a higher risk of events among non-adherent patients irrespective of risk
18
19 factors: adjOR 1.40 (95% CI 1.35-1.45) in patients using statins for primary prevention and
20
21 adjOR=1.59 (95% CI 1.51-1.68) in those using statins for secondary prevention (Figure 2). The
22
23 only exception was represented by the younger age group (<50 years), for whom the confidence
24
25 interval includes 1. Moreover, for subjects older than 80 years both in primary and secondary
26
27 prevention, and in patients with diabetes in primary prevention, the association between lack of
28
29 adherence and CV events was statistically stronger than in unstratified analysis.
30
31
32

33
34 Considering patients' prescriptions twelve months before and after the occurrence of an event, 53%
35
36 of patients increased their number of tablets after the event; so that a fraction (15%) of the non-
37
38 covered patients became covered in the year after the event. On the other hand, 26% of patients did
39
40 not change their number of tablets and the remaining 21% even decreased it.
41
42
43
44

45 46 **Discussion**

47
48 In our cohort of 137,217 patients, more than three quarters of statin recipients did not adhere to drug
49
50 therapy throughout the 3-year follow-up and, these patients showed more than 40% increase of
51
52 cardiovascular events when compared with adherent statin recipients.
53
54

55
56 Although the issue of lack of adherence to statin treatment has been already reported [11,18], in our
57
58 opinion, a population-based cohort study is important because it attempts to translate adherence to
59
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

1
2
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].

14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
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).

33
34
35
36
37
38
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
50
51
52
53
54
55
56
57
58
59
60

1
2
3 non-adherent patients by 6 and 8%, respectively in case of primary and secondary prevention. A
4
5 further limitation was the lack of information on lipidemia, which was an obstacle in the correct
6
7 association between adherence and cardiovascular outcomes. However information on lipidemia
8
9 would be very difficult to collect even by using physician's records. In addition, since our
10
11 prescription data were obtained only from reimbursement database, we probably excluded patients
12
13 not meeting the Italian reimbursement criteria, because at a lower CV risk. This lack of data could
14
15 have caused a slight overestimation of the role of adherence in the prevention of CV events.
16
17

18
19 Moreover, a positive attitude of patients towards their own health could be a confounding factor,
20
21 influencing independently both statin adherence and event occurrence, but also this information is
22
23 not available in administrative databases, which are the source of our study. Only studies based on
24
25 questionnaire or primary care database could collect this data and could quantify the magnitude of
26
27 the healthy adherer effect.
28
29

30
31 This phenomenon is usually indicated as "healthy adherer effect", as already acknowledged by
32
33 Dragomir [13], Rasmussen [21] and Anderson [22], who stated the difficulties in its quantification.
34
35 Nonetheless a generic "healthy adherer behaviour" could have generated a tolerable overestimation
36
37 of the protective effect of adherence.
38
39

40
41 Finally, because of the low frequency and the delayed onset of cardiovascular events in low-risk
42
43 patients, a longer follow up could provide further evidence on this population.
44
45

46
47 When addressing the health policy implications of our results showing the close relationship
48
49 between adherence to statins and their effectiveness, the fact that 3 out of 4 of statin recipients were
50
51 not adherent suggests that statin use in our community setting produces both scarce gain in terms of
52
53 health and waste of economic resources.
54

55
56 For efficient resource allocation, quantification of the non-adherent population to optimise overall
57
58 health gain in the community is a priority [17]. Each Health Authority faces two different scenarios:

59
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

1
2
3 events; (b) envisaging a strategy more stringently identifying the population with a likely benefit
4
5 (which implies less effort to ensure adherence, decreased overall burden of side effects, lower drug
6
7 cost, but incomplete population protection from cardiovascular risk) [17].
8
9

10 In the light of these potential benefit and limitations, there is debate on which strategy is better, but
11
12 certainly the specific risk profile of the resident population and the availability of economic
13
14 resources should guide decision makers.
15
16

17 In our community setting, we interpret the paradoxically lower odds of cardiovascular events in
18
19 strongly non-adherent patients as an indication that this group was at lower risk than the other non-
20
21 adherent patients. Indeed, the strongly non-adherent group probably included a number of subjects
22
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
26
27 should focus on the 28% that was not strictly adherent, but received a yearly amount of drug able to
28
29 cover at least 6 months (slightly non adherent patients), and on the 13% that alternated covered
30
31 years with years at very low intensity of treatment (highly variable patients). Notably, the last group
32
33 showed the highest odds of cardiovascular events (about 70% higher than adherent patients).
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

The study was supported by funds from the Emilia Romagna Region and the University of Bologna. The opinions expressed herein by A.P. and M.L. do not necessarily reflect those of the Emilia Romagna Health Authority.

References List

1. Zhang ZJ, Cheng Q, Jiang GX, Marroquin OC (2010) Statins in prevention of repeat revascularization after percutaneous coronary intervention--a meta-analysis of randomized clinical trials. *Pharmacol Res* 61:316-320
2. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ (2008) Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol* 51:37-45
3. Abramson JWright JM (2007) Are lipid-lowering guidelines evidence-based? *Lancet* 20;369:168-169
4. Yusuf S, Lonn E, Bosch J (2009) Lipid lowering for primary prevention. *Lancet* 373:1152-1155
5. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D (2008) Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol* 52:1769-1781
6. Muldoon MF (2009) Trial evidence for statin-based primary prevention remains dubious. *J Am Coll Cardiol* 53:2312-2313
7. Poluzzi E, Strahinja P, Lanzoni M, Vargiu A, Silvani MC, Motola D, Gaddi A, Vaccheri A, Montanaro N (2008) Adherence to statin therapy and patients' cardiovascular risk: a pharmacoepidemiological study in Italy. *Eur J Clin Pharmacol* 64:425-432

- 1
2
3 8. Connor A Tomson C (2009) Should statins be prescribed for primary prevention of
4
5 cardiovascular disease in patients with chronic kidney disease? *BMJ* 339:b2949. doi:
6
7 10.1136/bmj.b2949.:b2949-
8
9
- 10
11
12 9. Hlatky MA (2008) Expanding the orbit of primary prevention--moving beyond JUPITER. *N*
13
14 *Engl J Med* 20;359:2280-2282
15
16
17
- 18
19 10. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, de Craen AJ, Knopp
20
21 RH, Nakamura H, Ridker P, van Domburg R, Deckers JW (2009) The benefits of statins in
22
23 people without established cardiovascular disease but with cardiovascular risk factors: meta-
24
25 analysis of randomised controlled trials. *BMJ* 338:b2376. doi: 10.1136/bmj.b2376.:b2376-
26
27
28
29
- 30
31 11. Poluzzi E, Strahinja P, Lanzoni M, Vargiu A, Silvani MC, Motola D, Gaddi A, Vaccheri A,
32
33 Montanaro N (2008) Adherence to statin therapy and patients' cardiovascular risk: a
34
35 pharmacoepidemiological study in Italy. *Eur J Clin Pharmacol* 64:425-432
36
37
38
39
- 40
41 12. Perreault S, Ellia L, Dragomir A, Cote R, Blais L, Berard A, Lalonde L (2009) Effect of statin
42
43 adherence on cerebrovascular disease in primary prevention. *Am J Med* 122:647-655
44
45
46
47
- 48
49 13. Dragomir A, Cote R, White M, Lalonde L, Blais L, Berard A, Perreault S (2009) Relationship
50
51 between Adherence Level to Statins, Clinical Issues and Health-Care Costs in Real-Life
52
53 Clinical Setting. *Value Health* 13:87-94
54
55
- 56
57 14. Perreault S, Dragomir A, Blais L, Berard A, Lalonde L, White M, Pilon D (2009) Impact of
58
59 better adherence to statin agents in the primary prevention of coronary artery disease. *Eur J*
60
Clin Pharmacol 65:1013-1024

- 1
2
3 15. Deambrosis P, Terrazzani G, Walley T, Bader G, Giusti P, Debetto P, Chinellato A (2009)
4
5 Benefit of statins in daily practice? A six-year retrospective observational study. *Pharmacol*
6
7 *Res* 60:397-401
8
9
- 10
11
12 16. Corrao G, Conti V, Merlino L, Catapano AL, Mancina G (2010) Results of a retrospective
13
14 database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in
15
16 daily clinical practice in Italy. *Clin Ther* 32:300-310
17
18
- 19
20
21 17. Psaty BM (2010) Drug therapies for the primary prevention of cardiovascular events: trials
22
23 and errors: 2009 Ancel Keys memorial lecture. *Circulation* 121:940-945
24
25
26
27
- 28 18. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD (1999) Effect of initial drug choice on
29
30 persistence with antihypertensive therapy: the importance of actual practice data. *CMAJ*
31
32 160:41-46
33
34
35
36
- 37 19. Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD (2009) Continuation of statin
38
39 treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med* 169:260-
40
41 268
42
43
44
45
46
- 47 20. Suissa S (2008) Immeasurable time bias in observational studies of drug effects on mortality.
48
49 *Am J Epidemiol* 168:329-335
50
51
52
- 53 21. Rasmussen JN, Chong A, Alter DA (2007) Relationship between adherence to evidence-based
54
55 pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 297:177-
56
57 186
58
59
60
22. Andersohn FWillich SN (2009) The healthy adherer effect. *Arch Intern Med* 169:1635-1636

Table 1. Descriptive analysis of patients' characteristics and events

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

^a indication of gender was missing in 121 patients;

^b previous CV events were observed for the period 2003-2004;

^c 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;

^d 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

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

^a at least 300 tablets per year, ^b at least 200 tablets in each year, but not adherent through the whole 3-year period; ^c never covered and at least 1 year with less than 200 tablets; ^d 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> | |
| Lack of Adherence^a | 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) |
| Male gender^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) |
| Age class^c | 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) |
| Previous CV events^d | | <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) |
| Diabetes^e | | <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) |
| Angina, hypertension, heart failure^f | | <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) |
| Thrombosis^g | | <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) |

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

1
2
3
4 **Figure captions**
5
6
7

8 **Fig.1 Year-by-year coverage of patients with statin therapy.**
9

10 The size of each circle is proportional to the corresponding percentages of patients (value inside);
11 and the density of grey of the circle to the cumulative level of coverage, from black (always
12 covered) to white (never covered). The analysis includes only patients alive at the end of the
13 relevant year: the total alive patients were 136,013, 133,513, 130,727 in 2005, 2006 and 2007,
14 respectively
15
16
17
18
19
20
21
22
23
24

25 **Fig. 2 Influence of lack of adherence to statins on cardiovascular events, stratified by sex, age,**
26 **diabetes and other cardiovascular risk factors;** Points in the middle of lines indicate odds ratios;
27 horizontal lines, 95% confidence intervals. (A) primary prevention: patients without hospital
28 admission for CV event in two years before the recruitment (B) secondary prevention: patients with
29 at last one hospital admission for CV event in two years before recruitment .
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

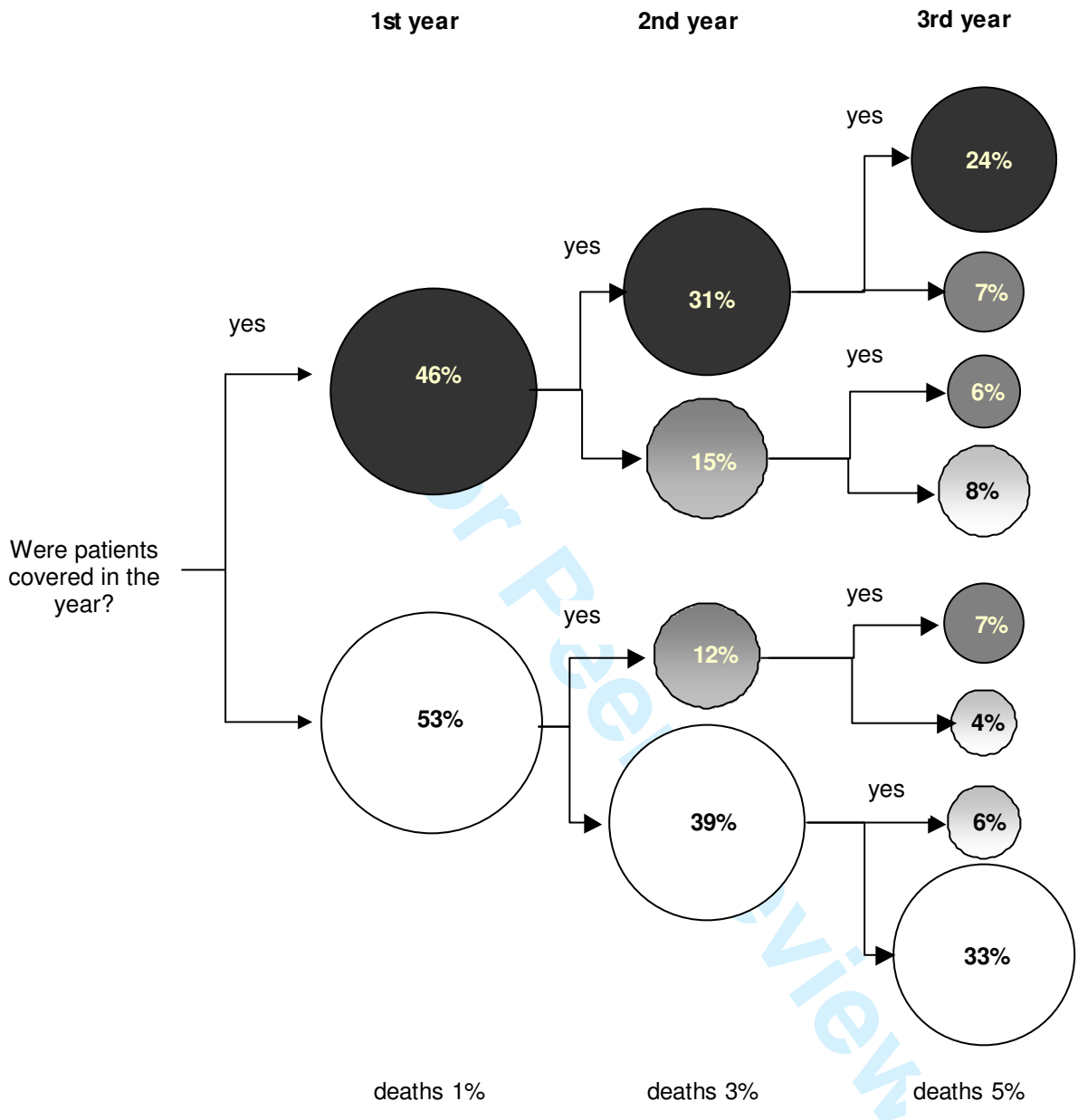


Fig. 1

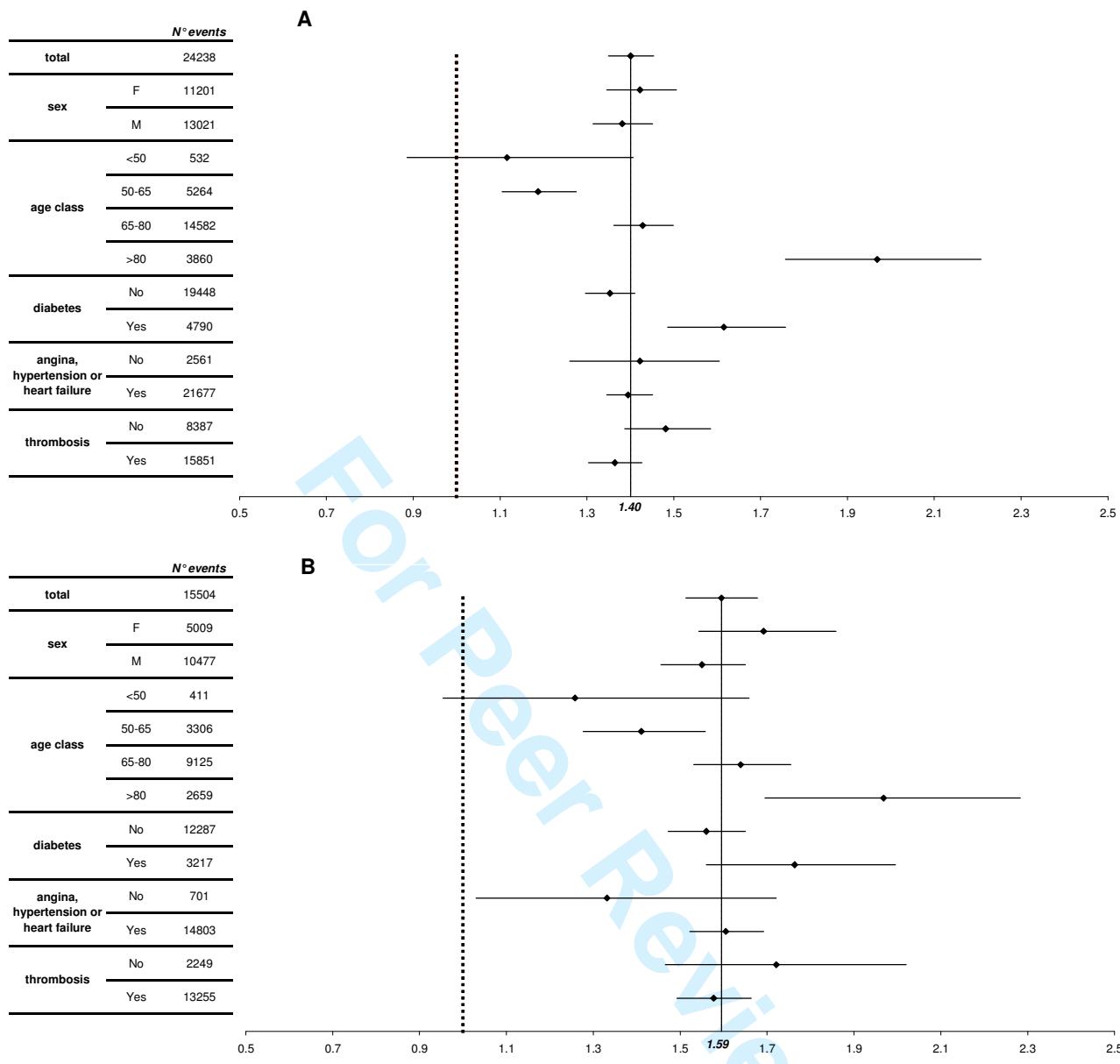


Fig.2

1
2 **Cardiovascular events in statin recipients: impact of adherence to treatment in a**
3
4 **3-year record-linkage study**
5

6 Elisabetta Poluzzi¹, Carlo Piccinni¹, Paolo Carta¹, Aurora Puccini², Monica Lanzoni², Domenico
7
8 Motola¹, Alberto Vaccheri¹, Fabrizio De Ponti¹, and Nicola Montanaro¹
9

10 ¹*Department of Pharmacology, University of Bologna, Via Irnerio 48, I-40126 Bologna, Italy*
11

12 ²*Drug Policy Service, Emilia Romagna Regional Health Authority, Viale Aldo Moro 21, I-40127*
13 *Bologna, Italy*
14

15
16
17
18 Corresponding author

19
20 Nicola Montanaro
21 Department of Pharmacology, University of Bologna
22 Via Irnerio 48
23 40126 Bologna, Italy
24 e-mail: nicola.montanaro@unibo.it
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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).

Deleted: 24

Deleted: lower

Deleted: about 30%

Deleted: non-

Deleted: in non-adherent patients

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.
5
6
7
8

9 10 **Methods**

11 *Sources of data*

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.
17
18

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
34
35
36

Deleted: 2005

1
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.

4
5
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.
13
14
15
16
17

18 *Study design*

19
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).
27
28
29
30
31
32
33

34 Adherence was evaluated by analysing the amount of statins received during the 3 year-period:

- 35
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
- 38
39 • patients who met the above criterion throughout the 3-year follow-up were considered as
40
41 “adherent”.
42

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.
47
48

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 χ^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 ± 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

1
2 or angina or heart failure, 54% (73,963) used antithrombotics and 16% (21,530) used antidiabetics
3
4 (Table 1). Along the remaining two years of follow-up, a further 2.5% of patients per year received
5
6 antihypertensive prescriptions, a further 5% received antithrombotics and a further 2.5% received
7
8 antidiabetics.

9
10 In our cohort, 35% did not receive statin prescriptions in the 2 previous years (new users).

11
12 The proportions of patients receiving more than 300 tablets/year of statins and that of patients
13
14 receiving 201-300 tablets/year were stable along the three years of follow-up (45% and 24%
15
16 respectively), whereas that of patients receiving 101-200 tablets decreased from 24% to 19% and
17
18 that of patients taking less than 101 tablets showed an appreciable increase, from 6% in the first
19
20 year to 13% in the third one.

21
22 Sixty-two percent (81,666) of patients were covered for at least 1 year, 44% (60,894) for at least 2
23
24 years and 24% (32,355) for the whole 3-year period and only this last figure represents the adherent
25
26 population according to our criteria. (Figure 1).

27
28 Among the 98,371 patients who did not meet the criteria to be considered “adherent”, 28% (38,328)
29
30 were “slightly non-adherent”, 30% (41,678) “strongly non-adherent”, and 13% (18,382) “highly
31
32 variable” (Table 2).

33 *Cardiovascular events*

34
35 Within the whole cohort of 137,217 patients, 29% (39,708) experienced cerebro- or cardiovascular
36
37 events during the 3 year-follow-up (annual rate: 13%); 54% of events were represented by coronary
38
39 heart disease, followed by cerebrovascular accidents (18%).

40
41 Cerebro- and cardiovascular events occurred more frequently in non-adherent patients rather than
42
43 adherent group (reference), with the following ranking: strongly non-adherent (adjOR=1.19; 95%
44
45 CI 1.15-1.23), slightly non-adherent (1.25; 1.21-1.30), highly variable (1.69;1.62-1.77). These
46
47 events increased with age (e.g., patients older than 80: adjOR=2.78; 95% CI 2.56-3.03) and were
48
49 statistically more frequent in men (adjOR=1.39; 95% CI 1.35-1.43), in patients using statins for
50
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

- Deleted: only one
- Formatted: Not Highlight
- Deleted: d
- Formatted: Not Highlight
- Formatted: Not Highlight
- Deleted: irrespective of their risk profile,
- Deleted: about
- Deleted: 30
- Formatted: Not Highlight
- Deleted: reduction
- Formatted: Not Highlight
- Deleted: non-
- Deleted: In other words, a statin adherent regimen may avoid about 1 out of 3 cardiovascular events.

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

Formatted: Font: (Default) Times
New Roman, 12 pt, Font color: Auto,
Complex Script Font: Times New
Roman, 12 pt

1
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,
17
18 influencing independently both statin adherence and event occurrence, but also this information is
19
20 not available in administrative databases, which are the source of our study. Only studies based on
21
22 questionnaire or primary care database could collect this data and could quantify the magnitude of
23
24 the healthy adherer effect.

Deleted: difficult to collect.

25
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.

37
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.

45
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
25
26 cover at least 6 months (slightly non adherent patients), and on the 13% that alternated covered
27
28 years with years at very low intensity of treatment (highly variable patients). Notably, the last group
29
30 showed the highest odds of cardiovascular events (about 70% higher than adherent patients).
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

The study was supported by funds from the Emilia Romagna Region and the University of Bologna.

The opinions expressed herein by A.P. and M.L. do not necessarily reflect those of the Emilia Romagna Health Authority.

For Peer Review

References List

1. Zhang ZJ, Cheng Q, Jiang GX, Marroquin OC (2010) Statins in prevention of repeat revascularization after percutaneous coronary intervention--a meta-analysis of randomized clinical trials. *Pharmacol Res* 61:316-320
2. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ (2008) Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol* 51:37-45
3. Abramson JWright JM (2007) Are lipid-lowering guidelines evidence-based? *Lancet* 20;369:168-169
4. Yusuf S, Lonn E, Bosch J (2009) Lipid lowering for primary prevention. *Lancet* 373:1152-1155
5. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D (2008) Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol* 52:1769-1781
6. Muldoon MF (2009) Trial evidence for statin-based primary prevention remains dubious. *J Am Coll Cardiol* 53:2312-2313
7. Poluzzi E, Strahinja P, Lanzoni M, Vargiu A, Silvani MC, Motola D, Gaddi A, Vaccheri A, Montanaro N (2008) Adherence to statin therapy and patients' cardiovascular risk: a pharmacoepidemiological study in Italy. *Eur J Clin Pharmacol* 64:425-432

- 1
2 8. Connor ATomson C (2009) Should statins be prescribed for primary prevention of
3
4 cardiovascular disease in patients with chronic kidney disease? *BMJ* 339:b2949. doi:
5
6 10.1136/bmj.b2949.:b2949-
7
- 8
9
10 9. Hlatky MA (2008) Expanding the orbit of primary prevention--moving beyond JUPITER. *N*
11
12 *Engl J Med* 20;359:2280-2282
13
- 14
15 10. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, de Craen AJ, Knopp
16
17 RH, Nakamura H, Ridker P, van Domburg R, Deckers JW (2009) The benefits of statins in
18
19 people without established cardiovascular disease but with cardiovascular risk factors: meta-
20
21 analysis of randomised controlled trials. *BMJ* 338:b2376. doi: 10.1136/bmj.b2376.:b2376-
22
23
- 24
25 11. Poluzzi E, Strahinja P, Lanzoni M, Vargiu A, Silvani MC, Motola D, Gaddi A, Vaccheri A,
26
27 Montanaro N (2008) Adherence to statin therapy and patients' cardiovascular risk: a
28
29 pharmacoepidemiological study in Italy. *Eur J Clin Pharmacol* 64:425-432
30
31
- 32
33 12. Perreault S, Ellia L, Dragomir A, Cote R, Blais L, Berard A, Lalonde L (2009) Effect of statin
34
35 adherence on cerebrovascular disease in primary prevention. *Am J Med* 122:647-655
36
37
- 38
39 13. Dragomir A, Cote R, White M, Lalonde L, Blais L, Berard A, Perreault S (2009) Relationship
40
41 between Adherence Level to Statins, Clinical Issues and Health-Care Costs in Real-Life
42
43 Clinical Setting. *Value Health* 13:87-94
44
- 45
46 14. Perreault S, Dragomir A, Blais L, Berard A, Lalonde L, White M, Pilon D (2009) Impact of
47
48 better adherence to statin agents in the primary prevention of coronary artery disease. *Eur J*
49
50 *Clin Pharmacol* 65:1013-1024
51

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
15. Deambrosis P, Terrazzani G, Walley T, Bader G, Giusti P, Debetto P, Chinellato A (2009) Benefit of statins in daily practice? A six-year retrospective observational study. *Pharmacol Res* 60:397-401
 16. Corrao G, Conti V, Merlino L, Catapano AL, Mancina G (2010) Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. *Clin Ther* 32:300-310
 17. Psaty BM (2010) Drug therapies for the primary prevention of cardiovascular events: trials and errors: 2009 Ancel Keys memorial lecture. *Circulation* 121:940-945
 18. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD (1999) Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. *CMAJ* 160:41-46
 19. Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD (2009) Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med* 169:260-268
 20. [Suissa S \(2008\) Immeasurable time bias in observational studies of drug effects on mortality. *Am J Epidemiol* 168:329-335](#)
 21. Rasmussen JN, Chong A, Alter DA (2007) Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 297:177-186
 22. Andersohn FWillich SN (2009) The healthy adherer effect. *Arch Intern Med* 169:1635-1636

Formatted: Font color: Blue

Table 1. Descriptive analysis of patients' characteristics and events

| | | Number of patients | % | Events | % in the class |
|--|------------|--------------------|------------|---------------|----------------|
| Gender^a | F | 67,238 | 49% | 16,210 | 24% |
| | M | 69,858 | 51% | 23,498 | 34% |
| Age class | <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% |
| Previous CV events^b | Yes | 29,144 | 21% | 15,504 | 53% |
| | No | 108,073 | 79% | 24,238 | 22% |
| Diabetes^c | Yes | 21,530 | 16% | 8,007 | 37% |
| | No | 115,687 | 84% | 31,735 | 27% |
| Angina, hypertension, heart failure^c | Yes | 105,341 | 77% | 36,480 | 35% |
| | No | 31,876 | 23% | 3,262 | 10% |
| Thrombosis^c | Yes | 73,963 | 54% | 29,106 | 39% |
| | No | 63,254 | 46% | 10,636 | 17% |
| Three year adherence^d | Yes | 32,355 | 24% | 8,803 | 27% |
| | No | 104,862 | 76% | 30,939 | 30% |
| <u>New users</u> | <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> |

Formatted: Centered

^a indication of gender was missing in 121 patients;^b previous CV events were observed for the period 2003-2004;^c 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;^d 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

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

^a at least 300 tablets per year, ^b at least 200 tablets in each year, but not adherent through the whole 3-year period; ^c never covered and at least 1 year with less than 200 tablets; ^d 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> |
| Lack of Adherence^a | 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) |
| Male gender^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) |
| Age class^c | 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) |
| Previous CV events^d | | <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) |
| Diabetes^e | | <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) |
| Angina, hypertension, heart failure^f | | <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) |
| Thrombosis^g | | <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) |

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

1
2 **Figure captions**
3
4
5

6 **Fig.1 Year-by-year coverage of patients with statin therapy.**
7

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
13
14
15
16
17

18
19
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

23 horizontal lines, 95% confidence intervals. (A) primary prevention: patients without hospital
24 admission for CV event in two years before the recruitment (B) secondary prevention: patients with
25 at last one hospital admission for CV event in two years before recruitment .
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

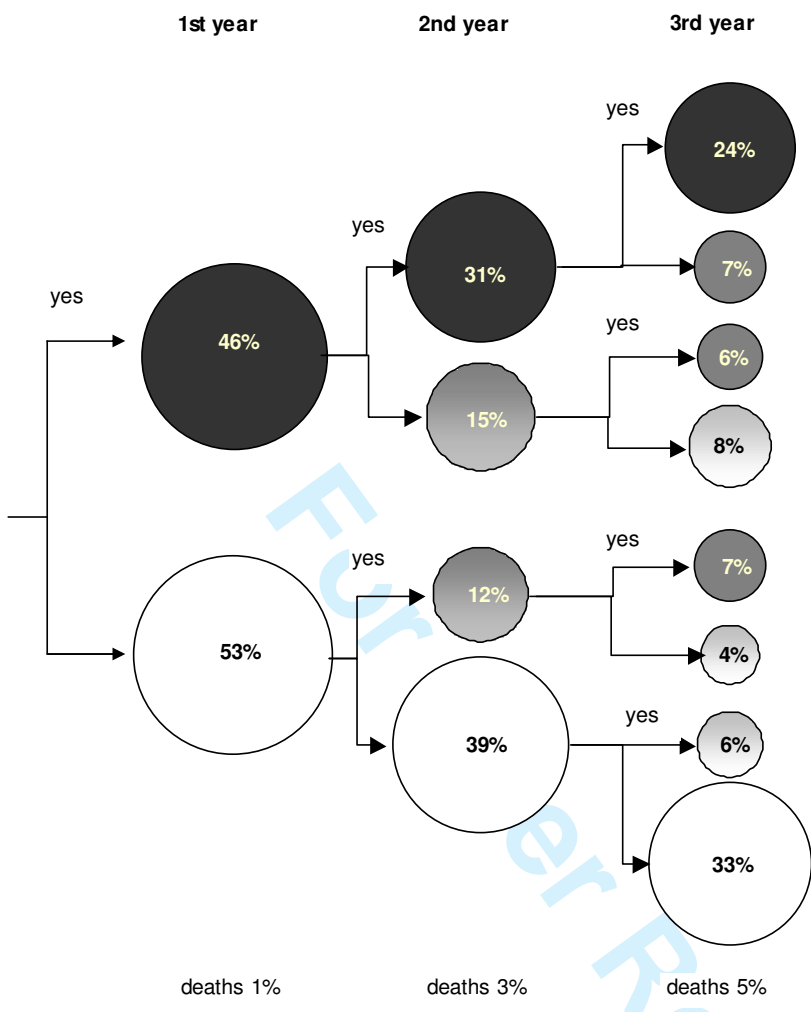


Fig. 1

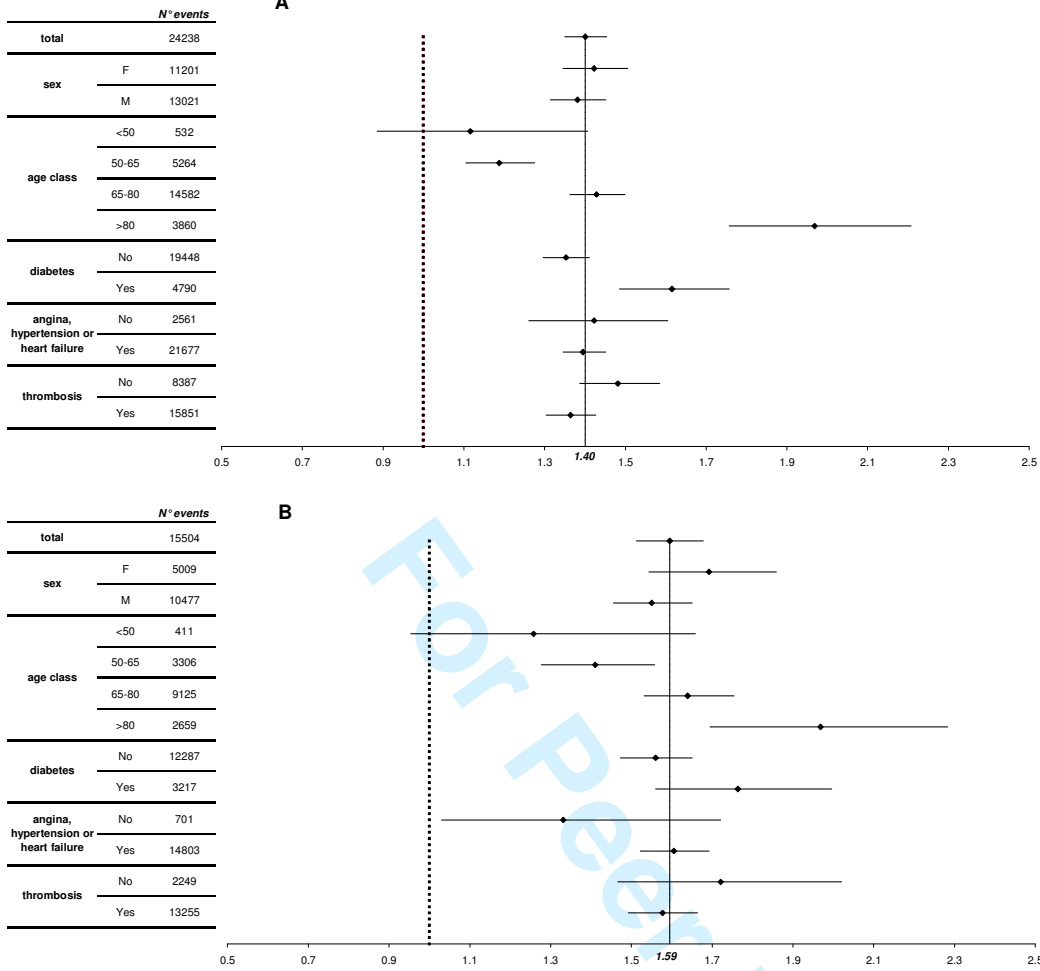


Fig.2