On the hypothetical universal use of statins in primary prevention: an observational analysis on low-risk patients and economic consequences of a potential wide prescription rate

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Abstract

Purpose Recent guidelines expand indications for statins. However, research on practical economic feasibility and cost-effectiveness in low-risk people is lacking. We aimed to describe the incidence of cardiovascular events (CVE), their total direct costs and the hypothetical effects of wide provision of statins on those rates and expenditures.

Methods We conducted a population-based cohort study using administrative data among low risk individuals. Estimators of effects of statins were taken from Cholesterol Treatment trialist metaanalysis and from Heart Protection Study trial. Two statin prices were used for analyses: National Italian Health System (€ 0.36) and the International Drug Price Indicator (€ 0.021).

Results Overall, 920,067 persons at low risk were identified and 14,849 CVE were registered (incidence rate 27.3 per 10, 000 person-years). Direct costs for hospitalizations for CVE were 143 M €. Universal provision of statins would result in a significant decrease in CVE rates, from 27.3 to 17.5 per 10, 000 person-years (PY) (95 % confidence interval (CI): 15.8–19.4). Universal prescription of simvastatin 20 mg would cost 802 M €. Otherwise, provision of simvastatin at International Drug Price Indicator's prices would be both clinically effective and cost saving in men older than age 44 (observed expenditures 120 M €, expected 97.4 M €) but not in women (observed expenditures 22.7 M €, expected 36.5 M €).

Conclusions Among a low-risk population, hypothetical universal provision of low-cost simvastatin to men over 44 years could be both clinically effective and a cost-saving strategy.

Keywords Cardiovascular risk · Statins · Lipid lowering · Epidemiology · Pharmacoepidemiology · Cohort · Myocardial infarction

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Introduction

Much controversy has arisen around appropriate use of statins in the context of primary prevention of cardiovascular events (CVE) with respect to the level of cardiovascular risk and time to initiate treatment. These debates range from positions stating that universal provision of statins after age 50 years—independent of cholesterol measurements—is an important public health strategy aimed at reducing the burden of death and disability from CVE, to those discouraging wide use of these agents based mostly on concerns about the balance between efficacy and safety [1, 2].

Recently, the American College of Cardiology-American Heart Association (ACC-AHA) Task Force released new practice guidelines for the treatment of high blood cholesterol [3]. These also are controversial, because the new recommendations have major impact on clinical, philosophical, and economic aspects of medical practice [4]. While

recommendations based on thresholds for assessing risk may be practical and necessary in many circumstances, equally important is that every healthcare system considers their own resources, outcomes and medical/economic options in order to reflect their own priorities and opportunities. As has been noted elsewhere, public policy that only sets thresholds but fails to define process is destined to fail [5].

The burden of cardiovascular diseases constitutes a major health challenge around the world for both developing and developed countries [6]. Fighting this population-wide risk requires coordinated actions on multiple fronts, and societal-level approaches constitute a more strategic action than those based on the individual management of risk [7]. Population lifestyle approaches are generally considered fundamental strategies to reduce cardiovascular risk. Even so, only a small portion of the population adheres to ideal levels of these life-style strategies for cardiovascular health [8, 9]. On the other hand, access to safe and effective medicines, particularly statins, constitutes a milestone for the prevention of premature cardiovascular death and disability [10]. Statins have extensively demonstrated their clinical efficacy and safety in prevention settings, and recent evidence largely refutes major criticism about safety [11, 12]. Thus, a strategy based on wide prescription of statins using age as the sole eligibility criterion could theoretically impact the burden of cardiovascular disease. The current challenges to implementing such a strategy are financing this global recommendation and the reasonable philosophical viewpoint on life medicalization. While generic substitution has reduced the price of several strategic medicines, the challenges of generic substitutions still persist, and the availability of generic medicine at low price is not yet sufficiently guaranteed [13, 14]. In fact, research on the practical economic feasibility of extending statin prescriptions are lacking, particularly cost-effectiveness estimates of prescriptions in low-risk people [12]. In any case, these analyses must be part of the conceptual framework of this debate.

Using a large database of an Italian population with a low to very low cardiovascular risk, we described the incidence of major cardiovascular events (CVE), the total direct costs related to these events from the health system perspective, and the hypothetical effects of a wide provision of statins on the incidence rates and health system expenditures.

Materials and methods

We identified all persons living in one Italian region (Puglia) from 2002 to 2010 and qualified as having low to very low cardiovascular risk. For our purposes, we linked all databases that included detailed information on hospitalization, pharmacological treatments, and death/life status of a population of 4,040,990 people. Of these, people aged 40 to 65 years and considered at low to very low cardiovascular risk were

selected for the present analysis (see below for cohort definition). According to the Italian law, no ethical approval is required to perform this type of analysis, so no committee was involved in this study.

Data sources

Hospital discharge records included information on primary diagnoses and up to 5 coexisting conditions, procedures, date of admission, discharge, and in-hospital death. All diagnoses were coded according to the International Classification of Disease, Ninth Revision [15].

The prescription database provided the community prescriptions reimbursed by the National Health System with drugs coded according to the Anatomical Therapeutic Chemical (ATC) Classification and qualified with respect to dosages, date of first prescription, and duration of exposure [16].

This strategy to produce epidemiological information has been validated [17, 18].

Cohort definition

The study cohort was people aged 40 to 65 years who had not been hospitalized for cardiovascular reasons within the 2 years prior to index date of January 1, 2004. Cardiovascular hospitalizations were defined as stroke, peripheral vascular disease (PVD), embolic episode, myocardial infarction (MI), chronic angina, unstable angina, heart failure (HF), or atrial fibrillation (AF). Additionally, the 24-month period preceding the index date was analyzed for chronic exposures to certain pharmacological treatments in order to exclude individuals with certain cardiovascular and non-cardiovascular conditions associated with increased risk: hypertension (beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or diuretics), congestive HF (the aforementioned plus digitalis, amiodarone, anticoagulation), coronary artery disease (nitrates or antiplatelet agents), or diabetes (insulin, sulfonylureas, biguanides, thiazolidinediones) as reported elsewhere [18]. Individuals with other non-cardiovascular conditions including malignancy, depression, and chronic obstructive pulmonary disease were also excluded using both hospitalization and prescription criteria.

Using these restrictions, a population aged 40 to 65 without previous history of cardiovascular hospitalizations and with no previous exposure to any cardiovascular treatment or anti-diabetic agents was identified.

Outcomes definitions

All persons were followed up to 6 calendar years or until the occurrence of a major CVE. These events were defined as

follows: Major CVE—time to the first occurrence of a hospitalization for MI, stable or unstable angina, or stroke. These events were identified based on the validated discharge diagnosis used in first position in the hospital record card. Cardiovascular death—all deaths that occurred within 180 days following a hospitalization for MI, stable or unstable angina, revascularization procedures, HF, or stroke. All deaths that occurred outside that timeframe were not considered cardiovascular death, and patients were censored at that time.

Statistical analysis

For all analyses, the study population was divided into four age categories (<45, 45 to ≤50, 50 to ≤55, and >55 years). For each category, outcome incidence rates were computed per 10, 000 person-years (PY) of follow-up for both the overall cohort and the sex and age categories. Differences between genders were compared as rate differences, with their corresponding 95 % confidence intervals (95 % CI).

Observed expenditures (in €) were computed as the sum of hospital expenditures due to major CVE in the whole population and across each age-sex category.

To estimate the potential effects of statin therapy, we computed the expected risk reduction according to the expected reduction in LDL-cholesterol level. This was done by computing the expected risk ratios (RR) as the product of (log)RRs by the LDL-cholesterol (in mmol/L) reduction with simvastatin 20 mg/day, under the assumption that a log-linear relationship exists between LDL-cholesterol and risk without a lower boundary [19]. Observed incidence rates and expenditures were then multiplied by the expected RRs to obtain incidence rates and expenditures potentially to be observed under universal statin therapy. Computations of expected effects on outcomes and expenditures were conducted with the weighted estimator of LDL-cholesterol reduction as reported by Law et al., that is, for simvastatin 20 mg, the expected reduction in LDL-cholesterol is 1.54 mmol/l (95 % CI 1.46 to 1.63) [19]. Estimators of RRs were taken from reported effects by the Cholesterol Treatment Trialists for every mmol/L of reduction on major CVE in primary prevention, except for PVD whose estimator of expected effect was computed using RR for non-coronary revascularization as reported in Heart Protection Study trial [11, 20]. These RRs were as follows: 0.79 (95 % CI 0.77 to 0.81) for CVE, 0.76 (95 % CI 0.73 to 0.79) for MI, 0.85 (95 % CI 0.80 to 0.89) for stroke, 0.84 (95 % CI 0.74 to 0.95), 0.88 (95 % CI 0.84 to 0.91) for CV death, and 0.96 (95 % CI 0.92 to 1.01) for non-CV death.

Expected expenditures were computed as the product of observed expenditures among individuals experiencing an event by the expected RRs plus the cost of statin therapy (as daily cost of therapy until the event or last follow-up date whichever came first). Expected expenditures were estimated using two different simvastatin prices. The simvastatin 20-mg

prices used in our calculations were the National Italian Health System price (€ 0.35786, daily) for the drug and the median buyer's price taken from the International Drug Price Indicator (€ 0.021388, daily) [21].

Analyses on expenditures due to therapy assumed that all individuals would take the drug for the entire follow-up period. To further explore the relationship between observed and expected expenditures, we repeated the analyses using age deciles instead the four-age categories. We conducted sensitivity analyses to explore the effects of hypothetical changes in hospital and statin's costs on the health system expenditures.
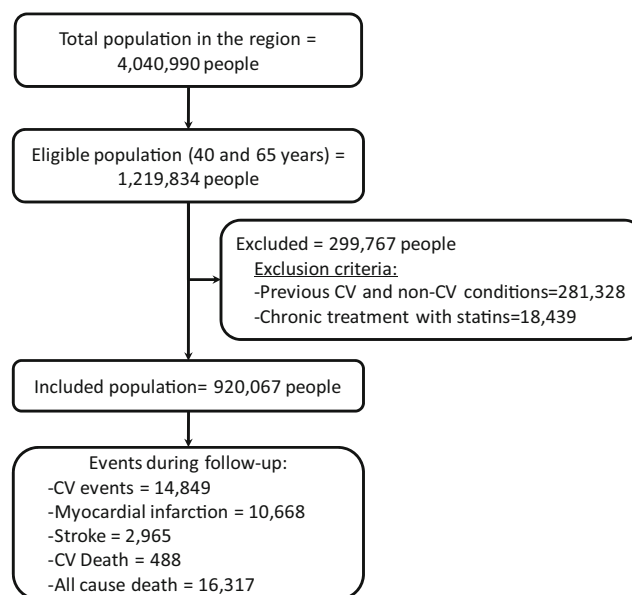
All analyses were conducted with SPSS 12.0 for Windows (SPSS Inc, Chicago, Ill, USA) and with R statistical package (R Foundation for Statistical Computing, Vienna, Austria).

Results

Low-risk population and outcomes

A total of 920,067 people considered at low cardiovascular risk were identified. The median age was 50.4 years (interquartile range, 44.8–56.7). Of these, 455,062 (49.4 %) were males and 465,005 (50.6 %) females (Fig. 1).

Overall, 14,849 CVE (1.6 %) occurred during a mean follow-up of 5.14 years, leading to an incidence rate 27.3 events/10,000 PY and an annual risk of 0.26 %. Events increased with age (from 0.7 % [incidence rate 12.4 events/10,000 PY, and an annual risk of 0.12 %] in those aged 40 to 45 years to 2.7 % [45.4 events/10,000 PY, with an annual risk of 0.45 %] in those aged >55 years) and were mostly concentrated in males (overall incidence rate difference (95 % CI) between males and females: 35.35 (34.45−36.24) for every

Fig. 1 Flow chart of study population

Total population in the region = 4,040,990 people

Eligible population (40 and 65 years) = 1,219,834 people

Excluded = 299,767 people
Exclusion criteria:
-Previous CV and non-CV conditions=281,328
-Chronic treatment with statins=18,439

Included population= 920,067 people

Events during follow-up:
-CV events = 14,849
-Myocardial infarction = 10,668
-Stroke = 2,965
-CV Death = 488
-All cause death = 16,317

10,000 PY). Among this population, the highest risk category was males aged 55 to 65, who had a 4.3 % risk at 6 years (72.11 events/10,000 PY); in contrast, the lowest risk category was women aged 40 to 45 where the 10-year risk was less than 1 % (4.68 events/10,000 PY) (Table 1).

The most common CVEs were MI followed by stroke and PVD (Table 1).

Cardiovascular deaths were rare; overall, 488 deaths occurred during follow-up (0.1 % events annually or an incidence rate of 0.91 events/10.000 PY) (Table 1).

Table 1 Outcomes by age groups and gender

	All subjects (n=920,067)	Men (n=455,062)	Women (n=465,005)	IR[a] All subjects	IR[b] Men	IR[c] Women	Rate difference[d] (95 % CI)
All CV events							
<45 years	1,896 (0.7%)	1,519 (1.2%)	377 (0.3%)	12.44	21.18	4.68	16.50 (15.34 to 17.67)
≥45 and <50 y	2,703 (1.2%)	2,178 (2.0%)	525 (0.5%)	20.87	35.70	7.67	28.03 (26.40 to 29.67)
≥50 and <55 y	3,274 (1.8%)	2,711 (3.0%)	563 (0.6%)	30.12	51.00	10.13	40.87 (38.77 to 42.96)
>55 y	6,976 (2.7%)	5,577 (4.3%)	1,399 (1.1%)	45.38	72.11	18.32	53.80 (51.68 to 55.92)
All ages	14,849 (1.6%)	11,985 (2.6%)	2,864 (0.6%)	27.28	45.53	10.19	35.35 (34.45 to 36.24)
MI							
<45 years	1,330 (0.5%)	1,154 (0.9%)	176 (0.1%)	8.78	16.24	2.19	14.05 (13.05 to 15.04)
≥45 and <50 y	2,045 (0.9%)	1,742 (1.6%)	303 (0.3%)	15.97	28.94	4.47	24.47 (23.02 to 25.92)
≥50 and <55 y	2,476 (1.4%)	2,123 (2.4%)	353 (0.4%)	23.23	40.60	6.50	34.10 (32.24 to 35.96)
>55 y	4,837 (1.9%)	3,986 (3.1%)	851 (0.7%)	32.55	52.44	11.72	40.72 (38.91 to 42.53)
All ages	10,668 (1.2%)	9,005 (2.0%)	1,683 (0.4%)	19.99	34.69	6.12	28.57 (27.80 to 29.35)
Stroke							
<45 years	447 (0.2%)	278 (0.2%)	169 (0.1%)	2.95	3.90	2.10	1.79 (1.24 to 2.35)
≥45 and <50 y	504 (0.2%)	321 (0.3%)	183 (0.2%)	3.92	5.30	2.70	2.60 (1.90 to 3.30)
≥50 and <55 y	527 (0.3%)	371 (0.4%)	156 (0.2%)	4.92	7.02	2.87	4.15 (3.31 to 4.00)
>55 y	1,487 (0.6%)	1,047 (0.8%)	440 (0.4%)	9.94	13.61	6.05	7.56 (6.56 to 8.55)
All ages	2,965 (0.3%)	2,017 (0.4%)	948 (0.2%)	5.52	7.71	3.44	4.26 (3.86 to 4.66)
PVD							
<45 years	125 (0.0%)	91 (0.1%)	34 (0.0%)	0.82	1.26	0.42	0.84 (0.55 to 1.14)
≥45 and <50 y	183 (0.1%)	134 (0.1%)	49 (0.0%)	1.40	2.17	0.71	1.46 (1.04 to 1.88)
≥50 and <55 y	310 (0.2%)	252 (0.3%)	58 (0.1%)	2.82	4.66	1.04	3.62 (2.98 to 4.25)
>55 y	824 (0.3%)	707 (0.5%)	117 (0.1%)	5.28	8.92	1.52	7.40 (6.68 to 8.11)
All ages	1,442 (0.2%)	1,184 (0.3%)	258 (0.1%)	2.63	4.43	0.92	3.52 (3.24 to 3.79)
CV death							
<45 years	43 (0.02%)	31 (0.02%)	12 (0.01%)	0.28	0.43	0.15	0.29 (0.11 to 0.46)
≥45 and <50 y	53 (0.02%)	39 (0.03%)	14 (0.01%)	0.41	0.64	0.21	0.44 (0.21 to 0.67)
≥50 and <55 y	81 (0.05%)	57 (0.1%)	24 (0.03%)	0.76	1.08	0.44	0.64 (0.31 to 0.97)
>55 y	311 (0.1%)	226 (0.2%)	85 (0.1%)	2.07	2.93	1.17	1.76 (1.30 to 2.21)
All ages	488 (0.1%)	353 (0.1%)	135 (0.03%)	0.91	1.35	0.49	0.86 (0.69 to 1.02)
Non-CV death							
<45 years	1,952 (0.7%)	1,181 (0.9%)	771 (0.6%)	12.86	16.54	9.59	6.95 (5.79 to 8.11)
≥45 and <50 y	2,340 (1.1%)	1,428 (1.3%)	912 (0.8%)	18.19	23.53	13.42	10.10 (8.60 to 11.60)
≥50 and <55 y	3,160 (1.7%)	2,048 (2.3%)	1,112 (1.2%)	29.44	38.69	20.44	18.25 (16.19 to 20.31)
>55 y	8,377 (3.4%)	5,696 (4.5%)	2,681 (2.2%)	55.82	73.75	36.81	36.94 (34.57 to 39.30)
All ages	15,829 (1.7%)	10,353 (2.3%)	5,476 (1.2%)	29.43	39.47	19.87	19.60 (18.68 to 20.53)

[a] Incidence rate (number of events for 10,000 subjects/year of follow-up). Total follow-up=5,339,154 person-years (PY)

[b] Incidence rate in males (number of events for 10,000 subjects/year of follow-up). Total follow-up=2,590,560 PY

[c] Incidence rate in females (number of events for 10,000 subjects/year of follow-up). Total follow-up=2,748,594 PY

[d] All p values for rate differences <0.001

Cost of CVE

Direct costs for all CVE hospitalizations were nearly 143 M €. The majority of these costs, nearly 120 M €, were for the treatment of CVEs in males and the remaining nearly 23 M € was for females. Most of these expenditures were related to hospitalizations for MI (110 M €) followed by stroke (nearly 24 M €) and PVD (13 M €) (Table 2).

Analyses of potential effects of statins on CVE and mortality

We estimated that universal provision of simvastatin 20 mg/daily would have reduced LDL-cholesterol by 1.54 (1.46−1.63) mmol/L and that such effect would have resulted in a reduction of CVE leading to a HR of 0.64 (95 % CI 0.58−0.71), MI 0.59 (95 % CI 0.52−0.67), stroke 0.78 (95 % CI 0.71−0.84), PVD 0.77 (95 % CI 0.63−0.92), cardiovascular death 0.78 (95 % CI 0.67−0.92) and all cause death 0.87 (95 % CI 0.78−0.95).

These reductions would result in a significant difference in the observed rate of CVE from 27.28 events/10,000 PY to a predicted rate of 17.46 events (95 % CI 15.82−19.37), meaning an incidence rate reduction of 9.82 events/10,000 PY, mostly by reducing the occurrence of non-fatal MI among men (Table 3).

Observed and expected expenditures with a hypothetical universal provision of simvastatin 20 mg/day

The Italian National Health System purchases simvastatin 20 mg at 10.02 € for 28 pills (daily price 0.35786 €), resulting in a 6-year cost for an individual of 783.71 €. Providing universal prescriptions of simvastatin 20 mg daily would result in total health expenditures of 802,356,962 €, far more expensive than the current expenditure of 142,895,869 € (Table 2). This overall unfavorable balance is present for both men (observed expenditures 120,157,950 € against estimated expenditures of 420,671,297 €) and women (observed expenditures 22,737,919 € against estimated expenditures of 381,685,665

Table 2 Observed and estimated total hospital expenditures (€) for CVEs with universal provision of simvastatin at National Italian Health System price and at the International Drug Price Indicator median, according to gender and age categories

	Observed costs (National Italian Health System)			Estimated costs (National Italian Health System)			Estimated costs (International Drug Price Indicator)		
	All subjects	Men	Women	All subjects	Men	Women	All subjects	Men	Women
All CV events									
<45 years (y)	17,282,673	14,210,201	3,072,472	210,029,600	102,721,603	107,307,997	22,952,651	14,690,328	8,262,323
≥45 and <50 y	26,638,934	22,546,623	4,092,311	186,191,164	94,121,739	92,069,425	27,158,024	19,192,775	7,965,248
≥50 and <55 y	31,949,723	27,735,166	4,214,556	162,452,575	87,184,478	75,268,097	28,935,005	21,900,359	7,034,645
>55 y	67,024,538	55,665,958	11,358,579	243,683,621	136,643,476	107,040,145	54,896,174	41,663,701	13,232,472
All ages	142,895,869	120,157,950	22,737,919	802,356,962	420,671,297	381,685,665	133,941,854	97,447,164	36,494,689
MI									
<45 years	12,643,658	11,303,343	1,340,315	205,237,674	99,511,790	105,725,884	19,280,329	12,217,898	7,062,430
≥45 and <50 y	20,839,699	18,593,872	2,245,826	179,573,120	89,601,205	89,971,914	22,293,090	15,669,904	6,623,186
≥50 and <55 y	25,825,020	23,025,977	2,799,043	154,474,136	81,887,547	72,586,588	23,558,546	17,667,537	5,891,008
>55 y	50,763,454	43,465,875	7,297,578	224,043,407	124,920,053	99,123,354	41,550,771	31,578,235	9,972,535
All ages	110,071,831	96,389,068	13,682,763	763,328,339	395,920,597	367,407,742	106,682,737	77,133,576	29,549,160
Stroke									
<45 years	3,815,569	2,303,996	1,511,572	201,084,530	94,968,272	106,116,257	14,816,466	7,365,667	7,450,798
≥45 and <50 y	4,700,623	3,099,137	1,601,485	171,543,895	81,602,841	89,941,054	13,699,996	7,149,999	6,549,997
≥50 and <55 y	4,033,062	2,957,091	1,075,970	143,162,065	71,310,644	71,851,420	11,514,125	6,430,692	5,083,433
>55 y	11,073,156	7,882,209	3,190,947	204,131,063	106,661,450	97,469,613	20,321,130	12,155,492	8,165,638
All ages	23,622,410	16,242,434	7,379,976	719,921,554	354,543,208	365,378,345	60,351,719	33,101,851	27,249,868
PVD									
<45 years	859,011	601,009	258,001	57,671,036	28,199,169	29,471,867	12,554,013	6,062,547	6,491,466
≥45 and <50 y	1,668,671	1,319,224	349,447	48,000,173	23,449,862	24,550,310	11,141,282	5,535,479	5,605,803
≥50 and <55 y	2,677,748	2,274,481	403,267	40,659,305	20,899,712	19,759,593	10,399,724	5,790,325	4,609,399
>55 y	7,907,213	6,851,539	1,055,674	59,620,944	32,209,311	27,411,632	17,320,036	10,652,097	6,667,938
All ages	13,112,645	11,046,255	2,066,390	205,951,459	104,758,055	101,193,404	51,415,056	28,040,448	23,374,607

Table 3 Incidence rates observed and expected with universal provision of low-dose statin

|	All observed	All expected	95 % CI	Men observed	Men expected	95 % CI	Women observed	Women expected	95 % CI
All CV events									
<45 years	12.44	7.96	7.22–8.83	21.18	13.56	12.28–15.04	4.68	3.00	2.71–3.32
≥45 and <50 y	20.87	13.36	12.11–14.82	35.70	22.85	20.71–25.35	7.67	4.91	4.45–5.45
≥50 and <55 y	30.12	19.28	17.47–21.39	51.00	32.64	29.58–36.21	10.13	6.48	5.88–7.19
>55 y	45.38	29.04	26.32–32.22	72.11	46.15	41.82–51.20	18.32	11.73	10.63–13.01
All ages	27.28	17.46	15.82–19.37	45.53	29.14	26.41–32.33	10.19	6.52	5.91–7.24
MI									
<45 years	8.78	5.18	4.57–5.88	16.24	9.58	8.45–10.88	2.19	1.29	1.14–1.47
≥45 and <50 y	15.97	9.42	8.30–10.70	28.94	17.08	15.05–19.39	4.47	2.64	2.32–3.00
≥50 and <55 y	23.23	13.71	12.08–15.56	40.60	23.95	21.11–27.20	6.50	3.84	3.38–4.36
>55 y	32.55	19.21	16.93–21.81	52.44	30.94	27.27–35.14	11.72	6.92	6.09–7.85
All ages	19.99	11.79	10.40–13.39	34.69	20.47	18.04–23.24	6.12	3.61	3.18–4.10
Stroke									
<45 years	2.95	2.30	2.10–2.48	3.90	3.04	2.77–3.28	2.10	1.64	1.49–1.76
≥45 and <50 y	3.92	3.06	2.78–3.29	5.30	4.13	3.76–4.45	2.70	2.11	1.92–2.27
≥50 and <55 y	4.92	3.84	3.49–4.13	7.02	5.48	4.98–5.90	2.87	2.24	2.04–2.41
>55 y	9.94	7.75	7.06–8.35	13.61	10.62	9.66–11.43	6.05	4.72	4.30–5.08
All ages	5.52	4.31	3.92–4.64	7.71	6.01	5.47–6.48	3.44	2.68	2.44–2.89
PVD									
<45 years	0.82	0.63	0.52–0.75	1.26	0.97	0.79–1.16	0.42	0.32	0.27–0.39
≥45 and <50 y	1.40	1.08	0.88–1.29	2.17	1.67	1.37–2.00	0.71	0.55	0.45–0.65
≥50 and <55 y	2.82	2.17	1.78–2.59	4.66	3.59	2.94–4.29	1.04	0.80	0.66–0.96
>55 y	5.28	4.07	3.33–4.86	8.92	6.87	5.62–8.21	1.52	1.17	0.96–1.40
All ages	2.63	2.03	1.66–2.42	4.43	3.41	2.79–4.08	0.92	0.71	0.58–0.85
CV death									
<45 years	0.28	0.22	0.19–0.26	0.43	0.34	0.29–0.40	0.15	0.12	0.10–0.14
≥45 and <50 y	0.41	0.32	0.28–0.38	0.64	0.50	0.43–0.59	0.21	0.16	0.14–0.19
≥50 and <55 y	0.76	0.59	0.51–0.70	1.08	0.84	0.72–0.99	0.44	0.34	0.30–0.41
>55 y	2.07	1.62	1.39–1.90	2.93	2.28	1.96–2.70	1.17	0.91	0.78–1.08
All ages	0.91	0.71	0.61–0.84	1.35	1.05	0.91–1.24	0.49	0.38	0.33–0.45
Non-CV death									
<45 years	12.86	11.19	10.03–12.22	16.54	14.39	12.90–15.71	9.59	8.34	7.48–9.11
≥45 and <50 y	18.19	15.83	14.19–17.28	23.53	20.47	18.35–22.35	13.42	11.68	10.47–12.75
≥50 and <55 y	29.44	25.61	22.96–27.97	38.69	33.66	30.18–36.76	20.44	17.78	15.94–19.42
>55 y	55.82	48.56	43.54–53.03	73.75	64.16	57.53–70.06	36.81	32.03	28.71–34.97
All ages	29.43	25.60	22.96–27.96	39.47	34.34	30.79–37.50	19.87	17.29	15.50–18.88

€). No age group (either male or female) gains an equitable balance between observed and predicted costs with the universal provision of statins at current prices (Table 2 and Fig. 2a, b).

However, if simvastatin was available at the prices of the International Drug Price Indicator (the buyer median price of simvastatin 20 mg is 0.0213880 € per tablet or capsule), universal provision would be both clinically effective and economically attractive in men (observed expenditures 120,157,

950 € against estimated expenditures of 97,447,164.4 €, with positive balance for men older than 45 years) but not in women (observed expenditures 22,737,919 € against estimated expenditures of 36,494,689.8 €) (Figs. 1d and 2c and Table 4).

Potential severe adverse effects

During follow-up, there were 10 hospitalizations with discharge diagnosis of rhabdomyolysis (0.21 cases/
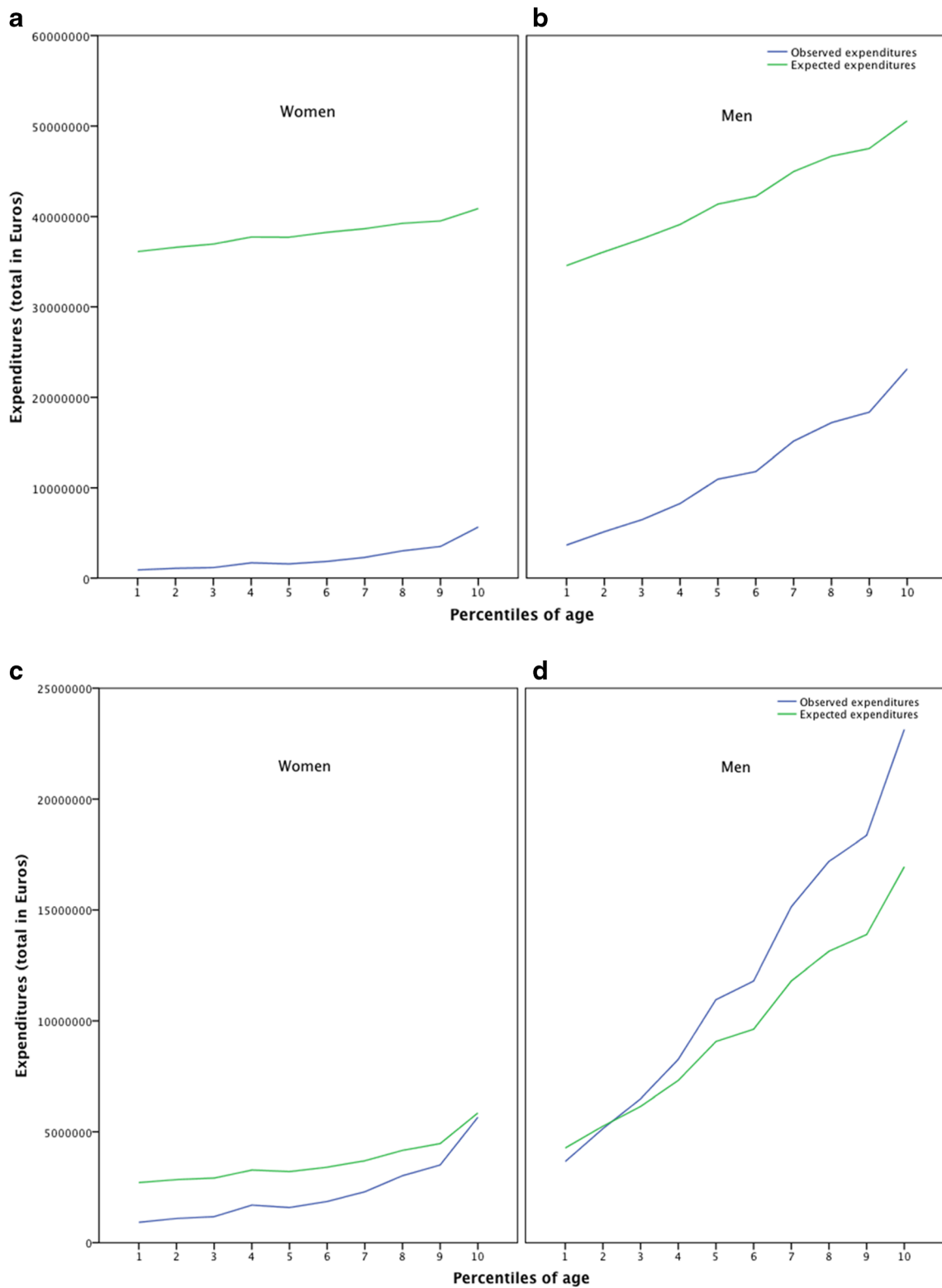
Fig. 2 Observed (*blue lines*) and expected (*green lines*) expenditures for cardiovascular events by gender for current statins costs (**a, b**) and for International Drug Price Indicator costs (**c, d**).

100.00 PY; 95 % CI 0.11−0.39), lower than reported with simvastatin 20–39 mg/day, and no case fatalities [22]. These events had a median cost of € 9347 (interquartile range € 5265 to € 14763).

Table 4 Observed and estimated (with universal provision of low-dose statin) expenditures with International Drug Price Indicator

	All subjects Actual	Men Actual	Women Actual	All subjects Statin	Men Statin	Women Statin
All CV events						
<45 years	17,282,673.8	14,210,201.5	3,072,472.4	22,952,651.0	14,690,328.0	8,262,323.0
≥45 and <50 y	26,638,934.3	22,546,623.0	4,092,311.2	27,158,024.0	19,192,775.8	7,965,248.2
≥50 and <55 y	31,949,723.0	27,735,166.9	4,214,556.1	28,935,005.1	21,900,359.3	7,034,645.8
>55 y	67,024,538.4	55,665,958.7	11,358,579.7	54,896,174.0	41,663,701.2	13,232,472.8
All ages	142,895,869.5	120,157,950.1	22,737,919.4	133,941,854.2	97,447,164.4	36,494,689.8
MI						
<45 years	12,643,658.4	11,303,343.2	1,340,315.2	19,280,329.4	12,217,898.9	7,062,430.5
≥45 and <50 y	20,839,699.1	18,593,872.3	2,245,826.9	22,293,090.3	15,669,904.3	6,623,186.0
≥50 and <55 y	25,825,020.1	23,025,977.0	2,799,043.0	23,558,546.7	17,667,537.8	5,891,008.9
>55 y	50,763,454.0	43,465,875.7	7,297,578.3	41,550,771.1	31,578,235.9	9,972,535.2
All ages	110,071,831.6	96,389,068.2	13,682,763.4	106,682,737.5	77,133,576.9	29,549,160.6
Stroke						
<45 years	3,815,569.1	2,303,996.6	1,511,572.5	14,816,466.0	7,365,667.5	7,450,798.5
≥45 and <50 y	4,700,623.1	3,099,137.5	1,601,485.6	13,699,996.7	7,149,999.1	6,549,997.6
≥50 and <55 y	4,033,062.0	2,957,091.3	1,075,970.8	11,514,125.8	6,430,692.4	5,083,433.4
>55 y	11,073,156.7	7,882,209.1	3,190,947.5	20,321,130.7	12,155,492.1	8,165,638.6
All ages	23,622,410.8	16,242,434.4	7,379,976.4	60,351,719.2	33,101,851.2	27,249,868.0
PVD						
<45 years	859,011.5	601,009.8	258,001.7	12,554,013.2	6,062,547.0	6,491,466.2
≥45 and <50 y	1,668,671.7	1,319,224.3	349,447.5	11,141,282.3	5,535,479.0	5,605,803.3
≥50 and <55 y	2,677,748.7	2,274,481.6	403,267.1	10,399,724.6	5,790,325.0	4,609,399.7
>55 y	7,907,213.7	6,851,539.3	1,055,674.4	17,320,036.5	10,652,097.8	6,667,938.7
All ages	13,112,645.6	11,046,255.0	2,066,390.6	51,415,056.6	28,040,448.7	23,374,607.9

Sensitivity analyses

Our overall findings were stable under hypothetical settings with different hospital and statin costs, including some unfavorable for statin strategy as the combined reduction in direct hospital costs and an increase in statin costs (Supplemental Table).

Discussion

This study found that in a large population considered to be at low to very low cardiovascular risk, the actual number of CVE and direct costs related to these were considerable. We also found that hypothetical universal provision of low-dose simvastatin would result in a reduction of CVE, yet direct costs could be reduced only among men >44 years of age only when simvastatin could be provided at the price suggested by International Drug Price Indicator. In other words, low-dose simvastatin results in cost savings only when generic prices become available.

This analysis identified a population with a low to very low risk of CVE who did not reach the threshold for recommendation of pharmacological prescription for primary prevention. The incidence rates of premature events in this otherwise "low risk" population indicates consideration of opportunities to implement safe and effective interventions to improve global health are warranted, although the most appropriate strategy to do so is not clear. Obviously, the first and only recommendation should be counseling the adoption of a healthy lifestyle [23]. A better lifestyle, including not smoking, 30 min or more of daily exercise, having a body mass index of 25 kg/m^2 or less, following an ideal diet with no or modest alcohol consumption are all prudent recommendations. Still, few people effectively achieve these habits, and responsibility must not reside entirely with the single citizen [5, 8, 24, 25].

This burden of disease had another important consequence. The total hospital expenditures for the treatment of CVE totaled nearly 140 M € in a 6-year period in only one Italian region. This amount should be interpreted as a conservative estimate of total costs because it does not consider ambulatory treatments (drugs and visits), nor social and economic consequences from loss of productivity following events (indirect costs). Yet, the present analysis found that the (measured)

economic benefits of providing statins (to men over 44 years but not to women) outweigh the (measured) economic costs, several limitations of these results should also be taken into account. As the analysis did not account for indirect costs that occur outside the hospital, the cost-offset may be underestimated. Additionally, since no clinical trial provide empirical evidence that treating persons at low risk effectively reduces all-cause mortality and morbidity, we cannot conclude that—if applied—this strategy would have a significant net effect on the desired outcomes. Furthermore, it would not be appropriate to conclude that the least expensive alternative (in this case simvastatin 20 mg at the International Drug Price Indicator's prices) is the best alternative. Also, the duration of follow-up that could be considered short, notwithstanding that a clear cost saving effect was evident with International Drug Price Indicator's simvastatin price. Finally, we have no data on non-severe adverse events, which could be relevant when considering a pharmacological prevention strategy at population level.

Recent NICE guidelines stress the absence of evidence of benefit of treatment for most population, the cost-effectiveness advantages of non-pharmacologic approaches for risk management, and the uncertainty of benefit/harm balance due to the possibility of higher than reported adverse effects incidence [26]. Considering the aforementioned uncertainties, our analyses should not be interpreted as evidence for recommendation of mass medication with statins, but only as a contribution to other existing data on this issue.

Although universal provision of low-dose statins to persons above 50 years has been proposed as an alternative or complement to (a failed) primary prevention [1], this strategy faces several challenges. The main being that universal provision without risk discrimination has not been demonstrated to be associated with any reduction of CVE. However, the lack of clinical trials does not necessarily mean that there are no data to support a benefit. It is hard to conceive that reducing LDL-cholesterol in a "healthy" population would not translate into a clinical benefit of a similar proportion of what has been observed in the context of secondary prevention. In fact, favorable risk factor levels in middle age are associated with a lower lifetime risk for cardiovascular mortality, increased survival, and improved quality of life [27]. Our analysis indicates a high total number of events in a low-risk population, and also that nearly 10 events would be avoided for each 10,000 PY (15 in men and 4 in women) with statin treatment. Assuming this effect, the second challenge with the universal provision strategy is related to cost. The present analysis confirms that universal provision of statins would be extremely expensive and certainly much more expensive than current spending as far as direct costs of treating the CVE that occur. However, the analysis also suggest that if the Italian government would decide to buy (or to produce) statins not at a market price but at the one suggested in the International

Drug Price Indicator Guide, universal provision of generic statins would not only reduce CVE but also be a cost-saving strategy for all men above 44 years of age [21]. The analyses failed to demonstrate economic benefit in women up to 60 years, driven by the low number of CVE. Sensitivity analyses, showing stability of the cost-saving with statins even under the unfavorable relation of lower direct hospital costs and higher statin prices, extend our findings to other health settings with different costs. These analyses also suggest that in settings were mean direct hospital costs for CVE are higher, as is the case of US, savings associated with this strategy could potentially be higher [28].

The potential implications of these findings are medical and political. From a government policy perspective, support for prevention policies and the necessary appropriations that support prevention can be difficult to garner when resources are limited. Political decisions are usually made for clear and immediate gains, while long-term savings or savings that cannot be accurately measured are less persuasive [29]. For this reason, the mathematical models that have been published on this topic have not been terribly convincing to politicians [30, 31]. Our analysis does not make mathematical assumptions of cost but reports real ones, confirming and extending previous findings [30, 31].

In conclusion, our results suggest that universal provision of low dose simvastatin at generic prices would result in a reduction of CVE and their related direct costs men >44 years of age.

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