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Statins for Prevention of Cardiovascular Events in a Low-Risk Population With Low Ankle Brachial Index

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ABSTRACT

BACKGROUND Evidence is lacking about the effectiveness of risk reduction interventions in patients with asymptomatic peripheral arterial disease.

OBJECTIVES This study aimed to assess whether statin therapy was associated with a reduction in major adverse cardiovascular events (MACE) and mortality in this population.

METHODS Data were obtained from 2006 through 2013 from the Catalan primary care system's clinical records database (SIDIAP). Patients age 35 to 85 years with an ankle-brachial index ≤0.95 and without clinically recognized cardiovascular disease (CVD) were included. Participants were categorized as statins nonusers or new-users (first prescription or represcribed after at least 6 months) and matched 1:1 by inclusion date and propensity score for statin treatment. Conditional Cox proportional hazards modeling was used to compare the groups for the incidence of MACE (myocardial infarction, cardiac revascularization, and ischemic stroke) and all-cause mortality.

RESULTS The matched-pair cohort included 5,480 patients (mean age 67 years; 44% women) treated/nontreated with statins. The 10-year coronary heart disease risk was low (median: 6.9%). Median follow-up was 3.6 years. Incidence of MACE was 19.7 and 24.7 events per 1,000 person-years in statin new-users and nonusers, respectively. Total mortality rates also differed: 24.8 versus 30.3 per 1,000 person-years, respectively. Hazards ratios were 0.80 for MACE and 0.81 for overall mortality. The 1-year number needed to treat was 200 for MACE and 239 for all-cause mortality.

CONCLUSIONS Statin therapy was associated with a reduction in MACE and all-cause mortality among participants without clinical CVD but with asymptomatic peripheral arterial disease, regardless of its low CVD risk. The absolute reduction was comparable to that achieved in secondary prevention. (J Am Coll Cardiol 2016;67:630–40) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Prescription of statins to prevent cardiovascular disease (CVD) is mainly a "high-risk" strategy focused on detection and intensive management of risk factors in individuals with a high probability of developing CVD (1). In the lipid management arena, this approach is grounded in the knowledge that the absolute risk reduction achieved with statin therapy improves with increasing CVD risk (2).

Detection of asymptomatic peripheral arterial disease (PAD) using the ankle-brachial index (ABI) in screening procedures is a potentially useful strategy to identify candidates for intensive risk-factor management (3) because low ABI values are associated with an increased risk of CVD and total mortality, independent of the CVD risk calculated by the Framingham function (4). Moreover, ABI measurement is reliable, simple, and inexpensive, and therefore suitable for target-population risk screening (5).

SEE PAGE 641

Unfortunately, the usefulness of this screening remains uncertain (6,7), and available guidelines offer heterogeneous recommendations (8). The American College of Cardiology, American Heart Association, and Inter-Society Consensus for the management of patients with PAD have recommended ABI screening, especially for certain groups of asymptomatic individuals (principally subjects age 50 to 69 years who also have diabetes or smoking history, and all patients age >70 years) (9). In contrast, the U.S. Preventive Services Task Force recommends against routine ABI screening in asymptomatic adults (8). One fundamental reason for this uncertainty is the lack of evidence about the effectiveness of risk reduction interventions when asymptomatic PAD is detected (10).

In this study, we aimed to assess whether statin use was associated with a reduction in incidence of CVD and mortality in individuals with asymptomatic PAD detected by ABI measurement.

METHODS

DATA SOURCE. The Information System for the Development of Research in Primary Care (SIDIAP) was created by the Catalan Institute of Health and the Jordi Gol Primary Care Research Institute. This anonymized database contains standardized, cumulated, clinical information about nearly 5 million patients attended by the 3,414 general practitioners (GPs) in the 274 primary care practices managed by the Catalan Institute of Health, consisting of approximately 80% of the Catalan population or 10% of the Spanish population (11). The records include demographic data; clinical diagnoses coded by International Classification of Diseases, 10th revision; referral and hospital discharge information (International Classification of Diseases-9th revision); laboratory tests; and treatments (drug prescriptions and drugs invoiced at any community pharmacy). All GPs follow the same clinical protocols for data recording, and completeness and continuity are assessed externally. A subset of records from GPs who surpass pre-defined data quality standards (12) constitute The Information System for the Development of Research in Primary Care, Quality (SIDIAP^{Q}), which provides anonymized data on approximately 2 million patients, attended by 1,365 GPs, yielding nearly 14 million person-years of clinical data for 2005 through 2013. The high quality of these data and its representativeness of the population of Catalonia in terms of geographic, age, and sex distributions has been previously documented (12), specifically for CVD and cardiovascular risk factors (13). Ethics approval for observational research using SIDIAP^{Q} data was obtained from a local ethics committee.

PARTICIPANTS AND STUDY DESIGN. A cohort study was designed for matched-pair analysis on the basis of study inclusion date and propensity score (PS) for statin treatment. All patients age 35 to 85 years with an ABI measurement recorded in SIDIAP^{Q} between April 2006 and December 2011 were eligible for inclusion. Follow-up lasted till December 2013, guaranteeing at least 2 years of data for each participant. Although individuals with an ABI between 0.91 and 0.95 can be considered to be at "borderline" cardiovascular risk (14), we used an ABI of ≤0.95 instead of 0.90 to identify individuals with asymptomatic PAD, as in a previous clinical trial with aspirin (15). This choice was made because the 0.95 cut-point covered a wider proportion of the population (16), with notably higher risk than patients with ABI between 1 and

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index
CHD = coronary heart disease
GP = general practitioner
MACE = major adverse cardiovascular event
NNT = number needed to treat
PAD = peripheral arterial disease
PS = propensity score
RCT = randomized clinical trial
SIDIAP^{Q} = The Information System for the Development of Research in Primary Care, Quality

authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Ramos and Garcia contributed equally to this work.

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1.1 (4). Although a proportion of the participants with ABI >1.4 (6.5% of those with an ABI measurement) could present with arterial obstruction, they were excluded from analysis because toe-brachial index measurements were not available to discard or confirm the diagnosis.

All ABI measurements were performed during outpatient examinations by each participant's GP in the primary care setting. For patients with more than 1 ABI measurement, the analysis used the first one taken. Exclusion criteria were any previous history of symptomatic PAD, coronary heart disease (CHD), stroke, or revascularization procedures. Symptomatic PAD was specifically ruled out by excluding: 1) patients with any primary care or hospital discharge diagnosis code suggesting clinically recognized PAD; 2) patients with any symptom of intermittent claudication detected by thorough revision of uncoded information (GP's free text notes); 3) patients who had been prescribed any drug related to intermittent claudication (cilostazol, pentoxifylline, buflomedil, or naftidrofuryl); and 4) patients with an ABI <0.4, even in the absence of any suggestive symptom.

STATIN EXPOSURE. To prevent survivor bias and covariate measurement bias, a "new-users design" was selected over prevalent statin users (17). New-users were defined as receiving statins (i.e., simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin, or atorvastatin) for the first time or after a hiatus of at least 6 months. The date of this new statin prescription was considered the index date. In descriptive analysis, we classified patients' statins exposure according to the drug's cholesterol reduction capacity as follows: low, <30%; moderate, 30% to 40%; high, 40% to 50%; and very high, >50% (18).

FOLLOW-UP AND OUTCOMES. Onset of vascular diseases during follow-up was identified from relevant SIDIAP^{Q} codes in both primary care and hospital discharge records. Primary outcomes were total mortality and major adverse cardiovascular event (MACE), a composite of hard CHD (myocardial infarction, cardiac revascularization, or coronary death) and stroke (fatal and nonfatal ischemic stroke). We also considered angina and coronary heart disease (a composite of angina and hard CHD) as secondary outcomes. Follow-up continued until the earliest date of a primary outcome, transfer out of the SIDIAP^{Q} database Catalan reference area, death, or censoring on December 31, 2011.

ADVERSE EFFECTS. Liver toxicity and myopathy were considered attributable to statins if they occurred within 12 months of initiating treatment. New-onset diabetes, cancer, and hemorrhagic stroke were considered more likely to be associated with long-term use, and thus were attributed to statins if the diagnosis occurred after 1 year (19).

DATA EXTRACTION RELATING TO POTENTIAL CONFOUNDERS. We explored the variables associated with statin prescription to determine candidate variables for the statin treatment PS. The following were obtained from SIDIAP^{Q}: age, sex, systolic and diastolic blood pressure, body mass index, vascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, smoking, and high alcohol consumption), other comorbidities at baseline (atrial fibrillation, lupus, arthritis, asthma, chronic obstructive pulmonary disease, hypothyroidism, depression, and cancer), other medication (nonstatin lipid-lowering drugs, diuretic agents, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, antidiabetic agents, psychoanaleptics, psycholeptics, anti-inflammatory drugs, aspirin, and oral corticosteroids), and laboratory tests (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, glycosylated hemoglobin, and glomerular filtration rate). For each participant, we also recorded a quality score for the GP's clinical practice derived from standard external evaluation procedures and a deprivation index (MEDEA index) (20). The CHD risk was calculated using the Framingham function adapted to the Spanish population, duly validated (21).

STATISTICAL ANALYSES. Categorical variables are presented as percentages and continuous variables as mean ± SD or median (1st and 3rd quartiles), both with 95% confidence intervals (CIs) when required. Validity of ABI measures was assessed by estimating the intraclass correlation coefficient of the SIDIAP^{Q} ABI measure with that recorded for the 134 patients who had also participated in a local epidemiological survey that used standardized measurement methods (16).

We used 10 multiple imputations by chained equations (22) to replace missing baseline values for total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, systolic and diastolic blood pressure, body mass index, and MEDEA deprivation index. In addition to incorporating the missing-at-random assumption, we compared complete-case only results with the multiple imputation as a sensitivity analysis.

Because of nonrandom treatment allocation, a logistic model on the basis of confounding covariates was used to calculate a statin therapy PS. Maximum cardinality matching of new-users and nonusers was

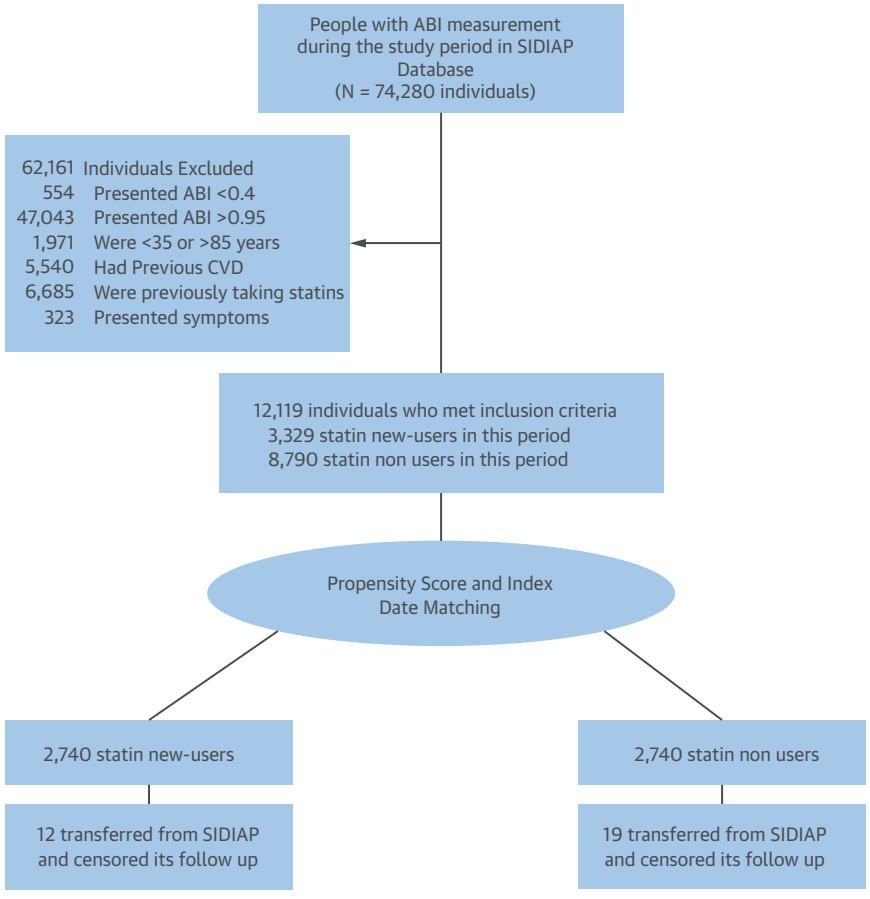
performed on a weighted bipartite graph on the basis of PS (to avoid confounding by indication bias) and on prescription time distribution (to avoid immortal time bias [23]). Matching was 1:1 within a caliper of one-quarter of the PS SD. Adequacy of matching was assessed by estimating the standardized differences between statin new-users and nonusers for all variables.

The hazard ratios of statin exposure were calculated for outcome events using conditional Cox proportional hazard regression models, and proportionality of hazards assumption was tested. Additional regression adjustments were performed after PS matching to prevent residual confounding in a sensitivity analysis. Variables not sufficiently balanced after PS matching and those associated with a worse prognosis were also included in the models. Absolute risk reductions and 1-year number needed to treat (NNT) for 1 additional patient to survive to this specific time point were calculated. We also carried out sensitivity analysis considering the exposure to statins as a time-varying covariate and compared the results with the intention-to-treat approach. Statistical analyses used R software version 3.2 (R Foundation for Statistical Computing, Vienna, Austria) (24,25).

RESULTS

During the study period, an ABI measurement was recorded in the SIDIAP[Q] database for 74,280 individuals. Of these, 12,119 fulfilled all inclusion criteria and 3,329 initiated statin therapy during the study period. The study included 5,480 participants (2,740 statin new-users and 2,740 control subjects) matched by PS and inclusion date. The study flow

FIGURE 1 Study Flow Chart



Participant selection in the study. ABI = ankle brachial index; CVD = cardiovascular disease; SIDIAP = Information System for the Development of Research in Primary Care.

chart is detailed in **Figure 1**. Median follow-up was 3.6 years (1st and 3rd quartiles, 4.9 and 7.8). Only 12 participants in the statin group and 19 in the non-statin group were lost to follow-up; all of them transferred out of the SIDIAP^{Q} reference area and were censored at their transfer date.

The proportion of missing data for incomplete variables and a comparison of the complete-case dataset and imputed dataset are shown in Online Table 1. The mean values of these variables remained similar after multiple imputations. The proportion of statin users matched with nonusers was 82.3% (Online Figure 1), and no significant clinical differences between matched and unmatched individuals were observed, although unmatched individuals were slightly younger, had a slightly lower CHD risk profile, and were less hyperlipidemic (Online Table 2).

Baseline characteristics for statin new-users and nonusers before and after PS matching are presented in **Table 1**. No significantly or clinically relevant standardized differences were observed. Women constituted 44% of both cohorts and the mean age was 67.2 ± 11.0 years. Diabetes was present in nearly 72% of participants, hypertension in 75%, smoking in 29%, and hypercholesterolemia in 56%; nonetheless, median 10-year CHD risk was low, at 6.9% (1st and 3rd quartiles, 3.9% and 11.9%), as expected in a Mediterranean country (26). Over 75% of new-users were treated with a statin of low and moderate LDL-reduction capacity (**Table 1**). The ABI measurements registered in SIDIAP^{Q} presented an intraclass correlation coefficient of 0.75 (95% CI: 0.62 to 0.84) with the 134 participants for whom an ABI measurement under standardized methods was available from an epidemiological study.

EFFECTIVENESS ENDPOINTS. A first MACE occurred in 201 and 245 participants, and death in 263 and 316 participants, in the new-users and nonusers groups, respectively.

Differences were observed in MACE and all-cause mortality rates (in events per 1,000 person-years): 19.7 (95% CI: 17.2 to 22.5) in new-users versus 24.7 (95% CI: 21.8 to 27.8) in nonusers (**Figure 2**) and 24.8 (95% CI: 22.0 to 27.8) in new-users versus 30.3 (95% CI: 27.2 to 33.6) in nonusers, respectively. Hazard ratios for primary endpoint events significantly differed between groups (**Table 2**). MACE decreased relatively by 20% (95% CI: 3% to 34%) and all-cause mortality by 19% (95% CI: 3% to 32%). The 1-year NNTs were for 200 MACE and 239 for all-cause mortality.

Comparisons of NNT with statins to prevent 1 event (MACE and all-cause mortality) during follow-up are shown in the **Central Illustration** by ABI cut-points and 10-year CHD risk categories. Briefly, NNT decreased with ABI cut-point.

The complete-case analysis showed no statistical or clinically relevant differences from the hazard ratios obtained in previously described analyses of the multiple imputations dataset (Online Table 3). Hazard ratios from the model with additional adjustment for hypertension, hypercholesterolemia, aspirin use, nonstatin lipid-lowering drug use, ABI, and 10-year coronary heart disease risk did not significantly differ from the PS matching model (Online Table 4). The hazard ratios obtained when considering statins as a time-varying covariate did not significantly differ from those of the intention-to-treat approach; the relative differences were <10% for all outcomes (Online Table 5). We observed no significant increase of adverse events attributable to statins (**Table 2**).

DISCUSSION

To our knowledge, this is the first study to report the association between statins and both MACE and mortality reduction among individuals free of clinical CVD, but with asymptomatic PAD identified by ABI. This reduction was observed regardless of 10-year CHD risk levels at baseline, which for most participants were well below the treatment threshold according to current prevention guidelines (27). Statin treatment produced an absolute reduction in MACE of about 5 per 1,000 individuals/year and in overall mortality of over 4 per 1,000 individuals/year. The absolute reduction in both MACE and all-cause mortality was notably higher than that reported in individuals at low risk in randomized clinical trials (RCTs) (28) and was comparable to that achieved in secondary prevention (29) or in individuals with symptomatic PAD (30). This is consistent with the idea that asymptomatic PAD (diagnosed through screening) and symptomatic PAD are associated with vascular events and mortality to a similar extent (31).

Furthermore, we observed that the degree of limb obstruction, estimated by the ABI value, was associated with noticeable changes in NNT, whereas changes in 10-year CHD risk produced no substantial effect, except for those individuals with 10-year CHD risk of ≤10%, in which case the NNT increased. This could suggest that the ABI value better predicts the benefit of statins than does the estimated risk on the basis of CVD risk charts (**Central Illustration**) in this population.

Our study results have 2 major implications. First, in the absence of clinically recognized CVD, asymptomatic ABI ≤0.95 might be sufficient to indicate

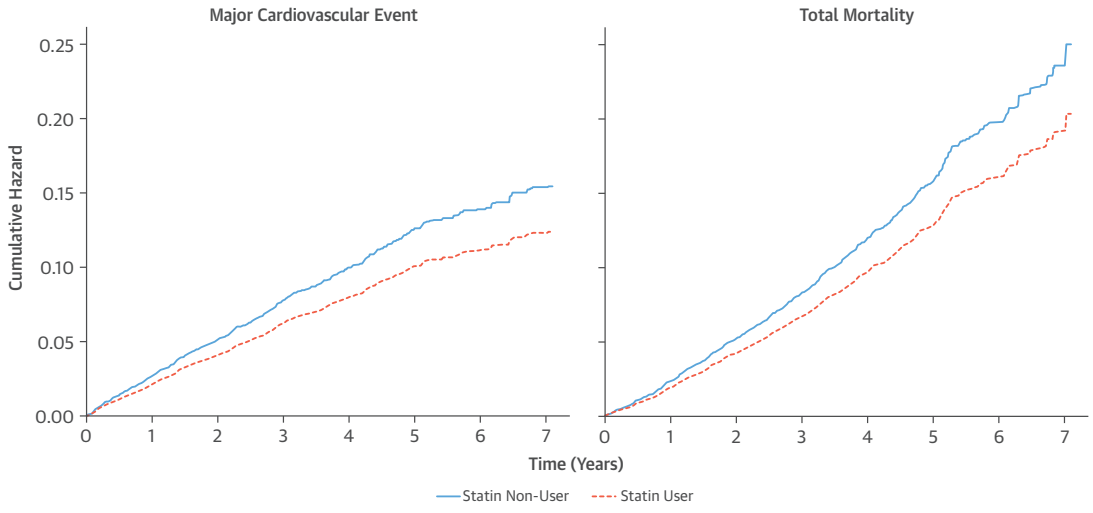
TABLE 1 Characteristics of Participants in Statin New-User and Nonuser Groups Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	Statin New-Users (n = 3,329)	Statin Nonusers (n = 8,790)	Standardized Difference	Statin New-Users (n = 2,740)	Statin Nonusers (n = 2,740)	Standardized Difference
Age, yrs	66.7 ± 10.7	66.2 ± 12.5	0.043	66.9 ± 10.7	67.5 ± 11.2	−0.061
Male	1,892 (56.8)	4,851 (55.2)	0.033	1,532 (55.9)	1,538 (56.2)	−0.004
ABI	0.80 ± 0.14	0.82 ± 0.12	−0.211	0.80 ± 0.14	0.81 ± 0.13	0.014
Smokers	1,027 (30.9)	2,294 (26.1)	0.105	801 (29.3)	798 (29.2)	0.002
Diabetes	2,434 (73.1)	5,670 (64.5)	0.187	1,983 (72.4)	1,977 (72.2)	0.005
Hypertension	2,528 (75.9)	5,909 (67.2)	0.194	2,042 (74.6)	2,077 (75.8)	−0.029
Hypercholesterolemia	2,062 (61.9)	2,491 (28.3)	0.717	1,516 (55.4)	1,543 (56.4)	−0.020
Obesity	1,616 (48.6)	4,210 (47.9)	0.013	1,347 (49.2)	1,355 (49.5)	−0.006
Body mass index, kg/m^2	29.8 ± 5.3	29.6 ± 5.4	0.038	29.9 ± 5.4	29.9 ± 5.2	0.002
Blood pressure						
Systolic, mm Hg	138.0 ± 17.0	137.0 ± 17.5	0.056	137.9 ± 17.0	137.6 ± 17.3	0.015
Diastolic, mm Hg	76.6 ± 10.1	76.6 ± 9.9	0.003	76.5 ± 10.1	76.4 ± 9.8	0.012
Total cholesterol, mg/dl	219.2 ± 38.0	197.0 ± 34.3	0.613	213.7 ± 35.5	213.4 ± 34.4	0.010
LDL cholesterol, mg/dl	137.1 ± 32.9	119.3 ± 29.1	0.573	132.5 ± 30.7	132.5 ± 29.5	0.002
HDL cholesterol, mg/dl	51.6 ± 13.9	52.6 ± 14.7	−0.070	51.7 ± 14.0	51.5 ± 13.9	0.016
Serum triglycerides, mg/dl	158.5 ± 97.6	137.6 ± 90.8	0.222	154.0 ± 93.6	155.5 ± 108.3	−0.014
Glycosylated hemoglobin, %*	7.4 ± 1.7	7.2 ± 1.6	0.061	7.4 ± 1.7	7.3 ± 1.7	0.003
Medication						
Aspirin	1,386 (41.6)	1,674 (19.0)	0.507	990 (36.2)	954 (34.9)	0.028
Diuretic	642 (19.3)	1,620 (18.4)	0.022	534 (19.5)	528 (19.3)	0.006
Beta-blocker	346 (10.4)	797 (9.0)	0.050	286 (10.4)	288 (10.5)	−0.003
ACE inhibitor/ARB	1,646 (49.4)	3,389 (38.6)	0.221	1,283 (46.9)	1,289 (47.1)	−0.004
Calcium-channel blocker	508 (15.3)	1,005 (11.4)	0.113	393 (14.4)	404 (14.8)	−0.011
Nonstatin lipid lowering	246 (7.4)	470 (5.4)	0.084	197 (7.2)	215 (7.9)	−0.025
Anti-inflammatory drugs	852 (25.6)	2,081 (23.7)	0.045	682 (24.9)	684 (25.0)	−0.002
Antidiabetic therapy	1,752 (52.6)	3,699 (42.1)	0.212	1,391 (50.8)	1,371 (50.1)	0.015
Statin by LDL reduction capacity						
Low (<30%)	98 (2.9)	–	–	80 (2.9)	–	–
Moderate (30%–40%)	2,449 (73.6)	–	–	2,042 (74.6)	–	–
High (40%–50%)	736 (22.1)	–	–	580 (21.2)	–	–
Very high (>50%)	36 (1.1)	–	–	28 (1.0)	–	–
10-yr CHD risk	9.13 ± 6.7	7.37 ± 6.1	0.274	8.8 ± 6.5	8.9 ± 6.8	−0.012
Comorbidities						
Atrial fibrillation	207 (6.2)	519 (5.9)	0.013	177 (6.5)	182 (6.6)	−0.006
CKD	572 (17.2)	1,251 (14.2)	0.034	467 (17.0)	465 (17.0)	0.001
COPD	393 (11.8)	955 (10.9)	0.030	316 (11.6)	329 (12.0)	−0.014
Arthritis	24 (0.7)	79 (0.9)	−0.020	22 (0.8)	26 (0.8)	−0.006
Asthma	117 (3.5)	316 (3.6)	−0.004	97 (3.6)	101 (3.7)	−0.007
Cancer	598 (18.0)	1,545 (17.6)	0.010	495 (18.1)	515 (18.8)	−0.019
Hypothyroidism	233 (6.8)	564 (6.4)	0.023	193 (7.1)	203 (7.4)	−0.014
Depression	107 (3.2)	252 (2.9)	0.020	86 (3.2)	83 (3.1)	0.005
Number of visits	6.4 ± 7.0	6.1 ± 6.9	0.054	6.2 ± 7.0	6.3 ± 7.0	−0.013
Socioeconomic status						
1 (most deprived)	638 (19.2)	1,788 (20.3)	−0.029	559 (20.4)	541 (19.8)	0.016
2	624 (18.8)	1,801 (20.5)	−0.044	530 (19.4)	563 (20.6)	−0.030
3	656 (19.7)	1,765 (20.1)	−0.009	541 (19.8)	552 (20.2)	−0.010
4	687 (20.7)	1,735 (19.8)	0.023	552 (20.2)	542 (19.8)	0.009
5 (less deprived)	721 (21.7)	1,699 (19.3)	0.058	555 (20.3)	538 (19.7)	0.016

Values are mean ± SD or n (%). *Calculated for all participants with diabetes mellitus.

ABI = ankle brachial index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease (glomerular filtration rate <60 ml/min/1.73 m^2); HDL = high-density lipoprotein; LDL = low-density lipoprotein.

FIGURE 2 Survival Cox Model



Cumulative hazard of major cardiovascular events and mortality by treatment and duration of follow-up.

statin use independently of the risk estimated by risk functions. Recent American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults suggest that ABI can be assessed as an additional factor to support statin therapy in patients at low 10-year coronary heart disease risk and with moderate LDL cholesterol blood level (27). Our results support such a strategy, because most patients in our study meet these characteristics.

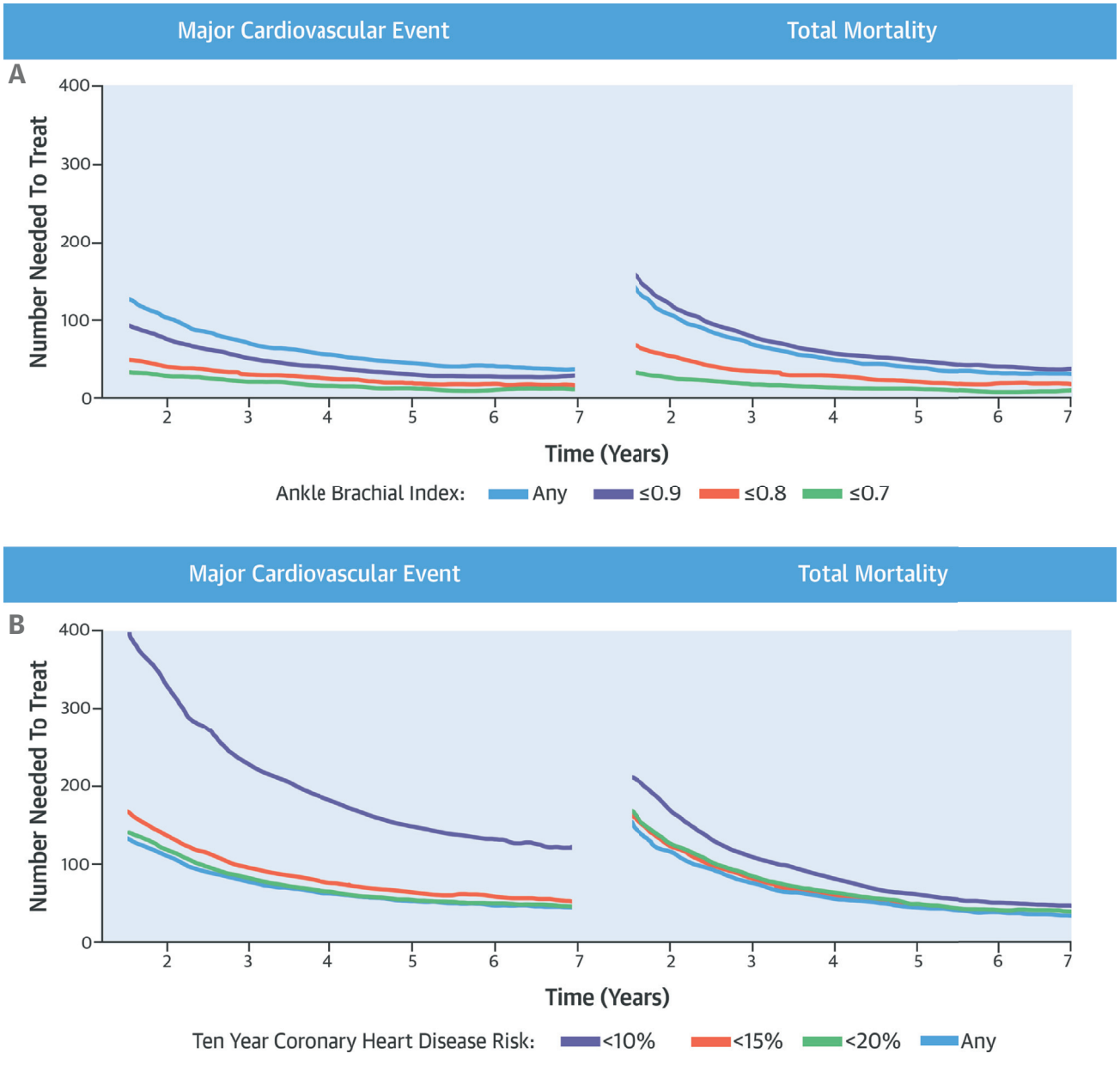
Second, and consequently, routine ABI screening for asymptomatic PAD in the targeted population could be a useful strategy (32) to identify candidates for statin therapy, most of whom would not be considered candidates solely on the basis of risk functions (16). A targeted population ABI screening could detect up to 85% of those individuals with

TABLE 2 Hazard Ratios of Incident Cardiovascular Events and Mortality and the 1-Year Number Needed to Treat to Prevent 1 Event by the Use of Statins: Intention-to-Treat Analysis

	Statin New-Users		Statin Nonusers			
	Events	Incidence Rate* (95% CI)	Events	Incidence Rate* (95% CI)	HR (95% CI)	NNT
Outcomes of interest						
Hard coronary heart disease	88	8.4 (6.8-10.4)	124	12.2 (10.2-14.5)	0.70 (0.52-0.94)	276
Angina	68	6.5 (5.1-8.2)	85	8.3 (6.7-10.2)	0.89 (0.69-1.16)	–
Coronary heart disease	123	11.9 (9.9-14.2)	162	16.1 (13.8-18.7)	0.74 (0.58-0.95)	233
Stroke	123	11.8 (9.9-14.1)	134	13.2 (11.1-15.6)	0.77 (0.54-1.12)	–
Major cardiovascular event	201	19.7 (17.2-22.5)	245	24.7 (21.8-27.8)	0.80 (0.66-0.97)	200
All-cause mortality	263	24.8 (22.0-27.8)	316	30.3 (27.2-33.6)	0.81 (0.68-0.97)	239
Adverse effects						
Cancer	154	22.2 (18.9-25.8)	140	20.6 (17.4-24.2)	1.08 (0.82-1.39)	–
Hemorrhagic stroke	37	4.7 (3.3-6.5)	36	4.7 (3.3-6.5)	1.01 (0.61-1.68)	–
Diabetes	82	34.8 (27.9-42.6)	68	30.3 (23.7-38.0)	1.16 (0.80-1.69)	–
Hepatotoxicity	3	–	1	–	–	–
Myopathy	3	–	2	–	–	–

*Per 1,000 person-years.
CI = confidence interval; HR = hazard ratio; NNT = number needed to treat.

CENTRAL ILLUSTRATION **Statins and Asymptomatic Low Ankle Brachial Index: Number Needed to Treat**



Ramos, R. et al. J Am Coll Cardiol. 2016; 67(6):630–40.

The number needed to treat to prevent 1 event over a 5-year follow-up by ankle brachial index **(A)** and by coronary heart disease risk at baseline **(B)**.

asymptomatic PAD (32). Patient characteristics in our study are similar to those observed in population-based studies of patients with low ABI (32,33), and could represent 5% to 17% of the general population, depending on age group (16,32,33).

These results, on the basis of observational data, may not provide enough evidence to establish clinical recommendations, but they do justify the performance of RCTs to further elucidate this question.

ADVERSE EFFECTS. No excess risk of serious adverse effects attributable to statin use was observed during follow-up. Excess risks of myopathy or liver toxicity were also absent among statins new-users. Although new-users presented a higher incidence of new

diabetes than nonusers (hazard ratio: 1.14), the difference was not significant. Limited statistical power might explain these results because there is evidence that statins slightly increase the incidence of new-onset diabetes (34). However, diabetes (35), myopathy (36), and hepatopathy (37) are more frequent in intensive regimens; in our study, approximately 80% of statin treatments were low-to medium-potency regimens. We also have to consider that mild myopathy or mild hepatopathy might be underestimated in electronic medical records.

We also observed no increased risk of cancer or hemorrhagic stroke among statins new-users, which is consistent with previous studies (38,39). We cannot discard the possibility that the incidence of diabetes, cancer, or hemorrhagic stroke could increase in this population with longer statin exposure.

STUDY CHARACTERISTICS THAT MERIT CONSIDERATION. When data are collected in well-designed, quality-assured databases and analyzed using appropriate methods, electronic medical records offer an outstanding opportunity to answer relevant questions related to medical treatments' effectiveness, close to actual clinical practice, and at a reasonable cost (40). This electronic database approach probably will be a noteworthy aspect of modern epidemiology in this 21st century (41). Researchers have demonstrated that such studies properly replicate the effects of statins observed in RCTs (42); it also has been suggested that observational studies could tend to overestimate the effect size of interventions (43) if several key points are not well addressed. First, a matching algorithm might fail to capture a broadly representative population. In our case, matched individuals were very similar to those who were not matched (Online Table 2, Online Figure 1) and also to those with low ABI in population-based epidemiological studies in the same population (32,33). The exception is the proportion of diabetes (twice as high in our study), which is probably due to diabetes guidelines strongly recommending ABI screening (44). We cannot discard that this might affect our results to some extent, but the general characteristics of our study participants support their representativeness of the asymptomatic PAD population, which provides external validity for targeted population screening (32).

Second, low data quality could generate misclassification. In this study, the presence of cardiovascular risk factors and outcomes were previously validated in SIDIAP (13), and the validity of ABI measurement was verified in a subgroup of 134 participants. Moreover, the validity of statin exposure in the medical records was confirmed by the official invoicing records from community pharmacies. Nevertheless, we cannot exclude some degree of under-reporting of outcomes, which could lead to a nondifferential misclassification; this would reduce statistical power, biasing results toward the null hypothesis.

Third, confounding indications can produce bias in observational studies. We used a new-users design to estimate confounding factors and then matched new-users with nonusers by PS and index date. The exposed (new-users) group was comparable with the nonexposed (nonusers) group for all relevant variables (**Table 2**). Furthermore, the hazard ratios obtained in a model with additional adjustments for relevant covariates did not vary significantly from the PS matching model. However, relative effect sizes of statins observed in our study were remarkably similar to those reported in RCTs, suggesting that we succeeded in overcoming potential confounders (28,29).

Fourth, the presence of missing data can influence the results. In our study, missing values did not exceed 30% for any variable, and the characteristics of the complete-case analysis did not differ from imputed data (Online Table 1) nor from individuals who also participated in a previous epidemiological study (32,33).

Fifth, immortal time bias can arise when the determination of an individual's treatment status involves a delay or waiting period during which, by design, death or the study outcome cannot be analyzed. To prevent this potential bias, in addition to PS we used prescription time-distribution matching (23). With this method, the overall distribution of the nonusers index date is matched to that of the users' time of first prescription. This prevents the imbalance of prescription time distribution between the 2 groups, which can generate a survival bias (23).

Sixth, discrepancies may occur when comparing statins as a time-varying covariate with the "intention-to-treat" approach. In the present study, this comparison yielded no significant differences.

If these results are confirmed, they could easily be applied in clinical practice and have a large effect on CVD prevention, because a non-negligible 5% to 17% of individuals have the characteristics reported here (16,32,33). Medical prescriptions in primary prevention account for part of the increasing economic burden of CVD in developed countries, so this strategy could be focused on actual high-risk individuals, ensuring cost-effectiveness (45). Our results on the basis of data from daily medical practice suggest this approach. Longer-term RCTs are needed to confirm our findings. Reliable cost-effectiveness estimates for the ABI screening strategy should also be obtained.

STUDY LIMITATIONS. The short follow-up period is a limitation of our study, restricting the possibility of performing subgroups analyses adequately such as a comparison of patients receiving high- versus moderate- to low-intensity statins. Another limitation is that we did not assess the association of statins with the incidence of adverse limb outcomes, which has been reported in secondary prevention of PAD in the REACH (Reduction of Atherothrombosis for Continued Health) study (46), and therefore did not measure this outcome in the follow-up.

CONCLUSIONS

Statin therapy was safely and significantly associated with a reduction in both MACE and total mortality in study participants without clinical CVD but with asymptomatic PAD. The absolute reduction was comparable to that achieved in secondary prevention. These results support the statin indication in asymptomatic patients when ABI is ≤0.95, regardless of CVD risk assessment.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: Regardless of other risk factors and in the absence of a clinical history of CVD, statin therapy in patients with asymptomatic PAD is associated with a reduction in MACE and all-cause mortality. The absolute risk reduction is comparable to that achieved in secondary prevention settings.

TRANSLATIONAL OUTLOOK: Prospective clinical trials should address the utility of systematic screening for PAD and implementation of statin therapy on the basis of measurement of the ABI alone as a population-based strategy for prevention of fatal and nonfatal cardiovascular events.

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APPENDIX For supplemental tables and a figure, please see the online version of this article.