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Statins in Familial Hypercholesterolemia

Consequences for Coronary Artery Disease and All-Cause Mortality

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ABSTRACT

BACKGROUND A statin-induced reduction of coronary artery disease (CAD) events and mortality has not been adequately quantified in patients with heterozygous familial hypercholesterolemia (FH).

OBJECTIVES This study estimated the relative risk reduction for CAD and mortality by statins in heterozygous FH patients.

METHODS The authors included all adult heterozygous FH patients, identified by the Dutch screening program for FH between 1994 and 2013, who were free of CAD at baseline. Hospital, pharmacy, and mortality records between 1995 and 2015 were linked to these patients. The primary outcome was the composite of myocardial infarction, coronary revascularization, and death from any cause. The effect of statins (time-varying) was determined using a Cox proportional hazard model, while correcting for the use of other lipid-lowering therapy, thrombocyte aggregation inhibitors, and antihypertensive and antidiabetic medication. The authors applied inverse-probability-for-treatment weighting (IPTW) to account for differences at baseline between statin users and never-users.

RESULTS The authors obtained medical records of 2,447 patients, of whom 888 were excluded on the basis of age <18 years or previous CAD. Simvastatin 40 mg and atorvastatin 40 mg accounted for 23.1% and 22.8% of all prescriptions, respectively. Statin users (n = 1,041) experienced 89 CAD events and 17 deaths during 11,674 person-years of follow-up versus statin never-users (n = 518), who had 89 CAD events and 17 deaths during 4,892 person-years (combined rates 8.8 vs. 5.3 per 1,000 person-years, respectively; $p < 0.001$). After applying IPTW and adjusting for other medications, the hazard ratio of statin use for CAD and all-cause mortality was 0.56 (95% confidence interval: 0.33 to 0.96).

CONCLUSIONS In patients with heterozygous FH, moderate- to high-intensity statin therapy lowered the risk for CAD and mortality by 44%. This is essential information in all cost-effectiveness studies of this disorder, such as when evaluating reimbursement of new lipid-lowering therapies. (J Am Coll Cardiol 2016;68:252-60)

Familial hypercholesterolemia (FH), a hereditary disorder of low-density lipoprotein (LDL) cholesterol metabolism, affects 1 in 250 persons and is characterized by greatly increased levels of LDL cholesterol (1-3). Patients with heterozygous FH are at 3- to 4-fold higher risk for coronary artery disease (CAD) and tend to develop CAD on average 10 years earlier in life than unaffected persons (3,4). Statins lower LDL cholesterol in patients with heterozygous FH (5), approximately to the same extent as in the general population (6). In the latter, the average relative risk reduction of statins for CAD is estimated to be 22% per mmol/l (6,7). Whether there is a comparable risk reduction in the setting of heterozygous FH

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is unknown, because it is considered unethical to withhold treatment from these patients. Randomized controlled trial data are therefore not available.

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There is a clear need to know to what extent statins reduce the risk for CAD and how large the residual CAD risk is in these patients because new classes of LDL cholesterol-lowering therapy (e.g., antibodies to proprotein convertase subtilisin/kexin type 9 [PCSK9]) will be evaluated for approval in heterozygous FH patients who do not reach treatment targets despite statin therapy. The objective of the current study was therefore to estimate the relative risk reduction for CAD and mortality by statins in heterozygous FH patients.

METHODS

For this retrospective cohort study, data were retrieved from the linkage between the database of the national FH cascade screening program in the Netherlands and the Pharmo Record Linkage System (RLS) (Pharmo Institute, Utrecht, the Netherlands) (8). An elaborate description of these databases is in the Online Appendix.

The database of the FH cascade screening program contains the following information, collected at the time of screening, of all subjects tested for FH: demographics, medical history, medication use, and lipid/lipoprotein levels. Data were collected during a single visit of a certified genetic field worker by means of a standardized questionnaire and a blood sample drawn for blood analysis.

The Pharmo RLS is a patient-centric data network of multiple health care databases. Relevant databases for our study include the national registries on mortality and hospitalization (Dutch National Medical Registration), as well as in- and outpatient pharmacies, representing virtually complete longitudinal follow-up of patients since January 1, 1995.

The initial linkage of patients was performed on April 7, 2013, and follow-up for linked patients was updated on April 22, 2015. All patients gave informed consent, and the study was approved by the medical ethical committee of the academic medical center in Amsterdam.

STUDY POPULATION. Participants were eligible if they were identified to be a heterozygous carrier of a deleterious FH mutation within the screening program between January 1, 1994, and April 7, 2013. Homozygous, compound heterozygous, and double heterozygous FH patients, as well as carriers of a nondeleterious mutation, were excluded. A list of nondeleterious mutations is provided in Online Table 1. We also excluded patients who reported at screening to have experienced CAD before their first observation in Pharmo RLS, as well as patients younger than 18 years at their first observation in Pharmo RLS.

PRIMARY OUTCOME. The primary outcome was the composite endpoint of first hospitalization for a CAD event and all-cause mortality. CAD was defined as myocardial infarction, angina pectoris, or other forms of atherosclerotic or ischemic heart disease (based on International Classification of Disease-9 codes 410 to 413, 4140, 4142, 4143, 4148, and 4149); or coronary artery bypass graft or percutaneous transluminal coronary angioplasty, based on the Dutch adaption (9) of the International Classification of Procedures in Medicine (10).

STATISTICAL ANALYSIS. Differences between statin users and never-users regarding descriptive characteristics were evaluated using logistic and linear regression for categorical and continuous variables, respectively. All regression analyses were performed using the generalized estimating equation method to account for family relations. The exchangeable correlation structure was used for these models.

The association between use of statins and time to the primary outcome was evaluated using Cox proportional hazard modeling. Statin use was based on the Anatomical Therapeutic Chemical Classification (ATC) codes C10AA, C10BA, and C10BX, and analyzed as a time-varying variable. Patients who discontinued statin use shortly after the first prescription (e.g., because of side effects) were classified as statin users for the remainder of the follow-up. To account for family ties, the Cox model was fitted with a random intercept per family. We used calendar time as time variable. Start of follow-up was defined as the first observation in Pharmo RLS (either filling of a prescription or hospitalization for a non-CAD event, such as pneumonia) for all patients. This could vary for each patient between January 1, 1995, and April 7, 2013. We therefore used a late-entry model in which patients were allowed to have delayed start of follow-up. End of follow-up was defined as the date of the primary endpoint or April 22, 2015, if the endpoint was not observed. Furthermore, we adjusted for age and other cardioprotective medication in a time-varying fashion. The following cardioprotective medication was considered: lipid-lowering medication other than statins (e.g., ezetimibe [ATC codes C10AB, C10AC, C10AC, and C10AX]), antidiabetic medication (ATC code A10B), antihypertensive agents

ABBREVIATIONS AND ACRONYMS

ATC = Anatomical Therapeutic Chemical Classification

CAD = coronary artery disease

CI = confidence interval

FH = familial hypercholesterolemia

HR = hazard ratio

IPTW = inverse-probability-of-treatment weighting

LDL = low-density lipoprotein

PCSK9 = proprotein convertase subtilisin/kexin type 9

RLS = Record Linkage System

(ATC codes starting with C01, C02, C03, C04, C07, C08, and C09), and thrombocyte aggregation inhibitors (ATC codes B01AC and B01AX).

Observational studies of effects of drugs are beset with problems of indication bias that results in patients on treatment often having worse outcomes than those not on treatment simply because they are sicker. To minimize bias resulting from imbalance in covariate distributions, we applied inverse-probability-of-treatment weighting (IPTW) (11). To do so, we first determined in each patient the propensity of being treated conditional on descriptive characteristics that were significantly different at baseline by means of a logistic regression analysis. In treated and untreated patients, the inverse of this propensity and the inverse of 1 minus this propensity, respectively, are applied as the individual weight. Consequently, untreated patients and treated patients with a low propensity contribute more weight, thereby balancing differences between treated and untreated patients. One limitation of IPTW, however, is inflation of the sample size, because the IPTW weight will be higher than 1 in most individuals. As a consequence, IPTW-weighted analyses tend to falsely reject the null hypothesis too often. To end up with a sum of weights close to the size of the original study population, we used stabilized IPTW as proposed by Cole and Hernán (11,12): that is, we divided the IPTW weights by the proportion of treated or untreated (as part of the whole population) for treated and untreated patients, respectively. These stabilized weights were included in linear regression models to obtain weighted estimates of the descriptive characteristics. An extensive description, as well as example codes in R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria), are described in the Online Appendix.

The logistic regression model for the propensity of being treated contained all descriptive characteristics that were significantly different between individuals using a statin and those who never used a statin during the total observation period. For continuous variables, we first explored which of 9 transformations (crude, $^{-2}$, $^{-1}$, $^{-0.5}$, $^{0.5}$, ^{2}, ^{3}, the natural logarithm, and the exponentiation to *e*) fit the data best based on the quasi-likelihood under the independence model criterion (13). This criterion is an adaption of Akaike's Information Criterion that can handle generalized estimating equation models. The best transformation was used in all subsequent analyses with stabilized IPTW.

Missing values were imputed based on all parameters using the aregImpute command from the Hmisc package in R (14). The p values were 2-sided, and significance level was set at <0.05. All analyses were carried out using the R statistical package version 3.2.0.

RESULTS

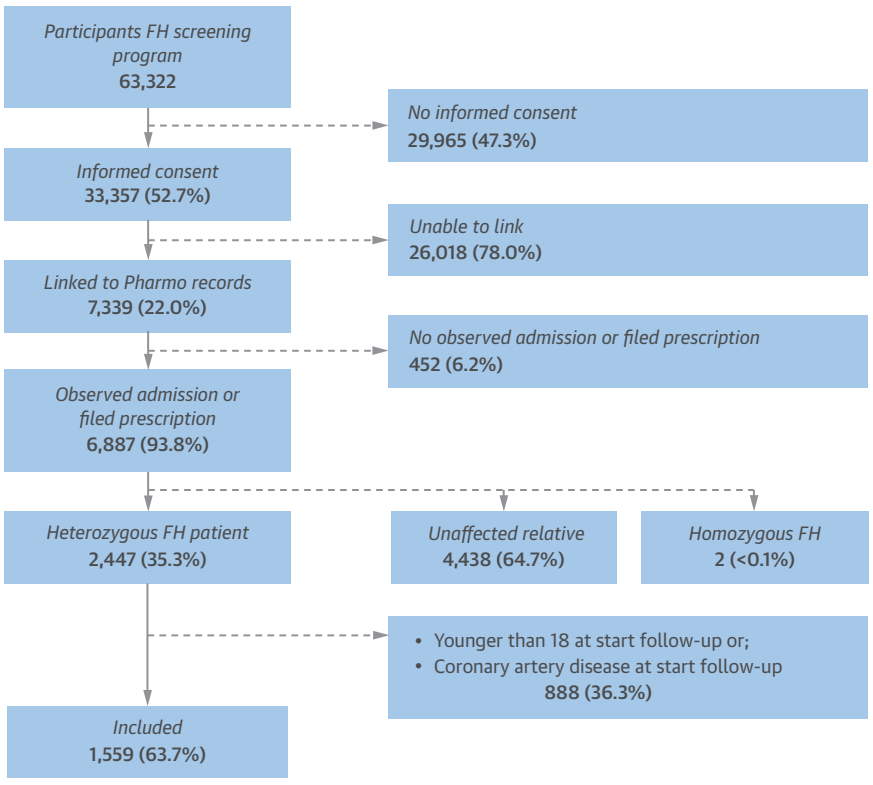
The selection of the study population is depicted in **Figure 1**. From January 1, 1994, until April 7, 2013, a total of 63,322 participants were enrolled in the screening program. Informed consent to collect health care data after the initial visit was provided by 33,357 (52.7%) individuals. Of these, 7,339 (22.5%) were identified in Pharmo RLS, and in 6,887 (93.8%), at least 1 filed prescription or hospital admission was observed. Of these, 1,559 (22.6%) were heterozygous FH patients 18 years and older and free of CAD at their first observation in Pharmo RLS. These subjects constituted our study population.

Included patients were compared with potentially eligible heterozygous FH patients of 18 years or older without CAD before 1995 who could not be linked in the Pharmo RLS (Online Table 2). On average, included patients showed a less favorable CAD risk profile (e.g., higher prevalence of smoking, hypertension, diabetes, and higher age) at screening and used a statin or other lipid-lowering therapy more often. Included and excluded patients were similar in regard to the hallmarks of the phenotype of FH, history of CAD and LDL-cholesterol level.

Patients who did use a statin were older at both start of observation in Pharmo RLS, as well as at screening, and had slightly higher levels of body mass index, LDL cholesterol, and triglycerides compared with those who never used a statin during follow-up (**Table 1**). We estimated stabilized IPTW weights for statin use based on these characteristics, and in the weighted comparison, all these covariates were well balanced as shown in **Table 2**. Compared with never-users, statin users more often were started on other lipid-lowering therapy, antihypertensive agents, antidiabetic medication, and thrombocyte aggregation inhibitors during follow-up, which were included as time-varying covariates in the Cox proportional hazard model.

EFFECT OF STATINS ON CAD AND MORTALITY. The 2 most prescribed statins were simvastatin 40 mg and atorvastatin 40 mg (8,001 filed prescriptions [23.1%] and 7,892 [22.8%] of 34,618, respectively) (Online Table 3). Simvastatin 40 mg is considered a moderate-intensity dose and atorvastatin 40 mg a high-intensity dose of statin according to the American College of Cardiology/American Heart Association guidelines, which provides intensity levels of additional doses of statins (15).

FIGURE 1 Study Population



From a total of 63,322 patients screened for familial hypercholesterolemia (FH), 1,559 met the criteria to be included in this retrospective cohort study.

Statin users (n = 1,041) had 89 CAD events and 17 deaths during 11,674 person-years versus never-users (n = 518) who experienced 22 CAD events and 9 deaths during 4,892 person-years (combined rates 8.8 vs. 5.3 per 1,000 person-years, respectively; $p < 0.001$) (Table 1). After applying IPTW, 72 statin users experienced a CAD event, and 14 died during 11,187 patient-years, whereas 37 never-users experienced a CAD event, and 31 died during 5,412 patient-years (event rates 7.5 per 1,000 patient-years vs. 11.9 per 1,000 patient-years, respectively; $p = 0.002$) (Table 2).

We assessed the association between statin use and time to CAD and mortality using Cox proportional hazards models, and the results are summarized in Table 3. In an unweighted model, statin use was associated with an increased risk for CAD and all-cause mortality (hazard ratio [HR]: 1.65; 95% confidence interval [CI]: 1.06 to 2.57). Using stabilized IPTWs (model 2), statin use tended to be associated with a decreased risk (HR: 0.62; 95% CI: 0.37 to 1.04). Also in the model with statin exposure as a time-varying variable, the HR decreased substantially after applying stabilized IPTWs (Table 3). After additional adjustment for other cardioprotective medication (time-varying), the HR for statins was found to be protective for CAD and all-cause mortality in the unweighted model (HR: 0.96; 95% CI: 0.58 to 1.59), which was even more pronounced in the weighted model (HR: 0.56; 95% CI: 0.33 to 0.96).

The HR for CAD and all-cause mortality tended to decrease with increasing tertile of age- and sex-specific LDL-cholesterol percentile at time of screening, although the p value for interaction between statin use and LDL-cholesterol percentile was not significant (Table 4). In line with this, the effect of statins seemed to be more pronounced in carriers of LDL-receptor (*LDLR*) mutations compared with apolipoprotein B (*APOB*) mutation carriers, although the p value for interaction was not significant.

DISCUSSION

In this large cohort of patients with heterozygous FH, moderate- to high-intensity statin therapy was

TABLE 1 Statin Users Versus Never-Users

	Statin Users				
	Statin at Baseline	Statin Initiation During Follow-Up	All	Never-Users	p Value (Statin Users vs. Never-Users)
Patients	391 (25.1)	650 (41.7)	1,041 (66.8)	518 (33.2)	
Male	207 (52.9)	279 (42.9)	486 (46.7)	243 (46.9)	0.937
Year of screening	2008 (2006–2010)	2008 (2006–2010)	2008 (2006–2010)	2008 (2006–2010)	0.2955
Birth year	1957 (1947–1966)	1961 (1950–1970)	1960 (1948–1969)	1969 (1959–1979)	<0.001
Age, yrs	51.2 ± 14.7	48.2 ± 14.9	49.4 ± 14.9	40.5 ± 14.2	<0.001
BMI*	26.0 ± 4.1	26.0 ± 4.6	26.0 ± 4.4	25.1 ± 4.4	<0.001
Smokers*	139 (35.9)	229 (35.6)	368 (35.7)	181 (35.3)	0.8747
Alcohol users	232 (59.3)	356 (54.8)	588 (56.5)	293 (56.6)	0.9484
Index patients	9 (2.3)	7 (1.1)	16 (1.5)	3 (0.6)	0.1186
Affected gene					0.2685
APOB	207 (19.9)	97 (18.7)	207 (19.9)	97 (18.7)	
LDLR	833 (80.0)	418 (80.7)	833 (80.0)	418 (80.7)	
PCSK9	1 (0.1)	3 (0.6)	1 (0.1)	3 (0.6)	
Lipid profiles at screening					
LDL-C, mg/dl*†	238 ± 68	221 ± 75	227 ± 73	183 ± 61	<0.001
HDL-C, mg/dl*	46 ± 14	45 ± 14	46 ± 15	46 ± 15	0.498
Triglycerides, mg/dl*	93 (66–148)	108 (71–158)	104 (71–154)	94 (64–143)	0.0161
Description of follow-up					
Age at start of follow-up, yrs	47 ± 13.7	42.5 ± 14.7	44.2 ± 14.5	37 ± 13.4	<0.001
CAD during follow-up‡	37 (9.5)	52 (8.0)	89 (8.5)	22 (4.2)	0.0031
Deceased during follow-up	5 (1.3)	12 (1.8)	17 (1.6)	9 (1.7)	0.8957
Total follow-up, yrs	4,019.2 (24.3)	7,655 (46.2)	11,674.1 (70.5)	4,891.8 (29.5)	
Event rate§	10.4	8	7.6	5.3	<0.001
Start of medication during follow-up					
Statin intensity‖					
Low	12 (3.1)	30 (4.6)	42 (4.0)		
Moderate	234 (59.8)	410 (63.1)	644 (61.9)		
High	145 (37.1)	210 (32.3)	355 (34.1)		
Other LLT	151 (38.6)	208 (32.0)	359 (34.5)	10 (1.9)	<0.001
Antihypertensive medication	176 (45.0)	274 (42.2)	450 (43.2)	79 (15.3)	<0.001
Antidiabetic medication	29 (7.4)	55 (8.5)	84 (8.1)	4 (0.8)	<0.001
Thrombocyte aggregation inhibitor	118 (30.2)	153 (23.5)	271 (26.0)	32 (6.2)	<0.001

Values are n (%), median (interquartile range), or mean ± SD, unless otherwise indicated. *Variables with missing values: BMI (3.3%); smokers (1%); LDL-C (7.1%); HDL-C (5.3%); and triglycerides (5.3%). †Off-treatment LDL-cholesterol. ‡CAD is defined as myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty. §Rates of CAD and mortality per 1,000 person-years of follow-up. ‖Statin intensity is based on the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on cholesterol treatment (15).

APOB = apolipoprotein B; BMI = body mass index; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; *LDLR* = low-density lipoprotein receptor; LLT = lipid-lowering therapy; *PCSK9* = proprotein convertase subtilisin/kexin type 9.

associated with a relative risk reduction of approximately 44% for the primary prevention of CAD and all-cause mortality (**Central Illustration**). Furthermore, a nonsignificant positive association between off-treatment LDL-cholesterol levels and relative risk reduction was observed.

The efficacy of statin therapy in patients with FH was previously evaluated in a retrospective cohort study (16). The authors of that study reported a relative risk reduction of 76%, much higher than the relative reduction of 44% in our study. The main reason for this discrepancy might be found in the high untreated LDL-cholesterol levels of their study population as compared with our study population (309 mg/dl vs. 213 mg/dl). In fact, prior studies have shown that the higher the baseline LDL cholesterol, the greater the relative risk reduction with statin therapy (17,18). The latter is consistent with our other findings as well. Furthermore, the baseline LDL level in our study was similar to that in large population-based cohorts of patients with heterozygous FH (200 to 236 mg/dl) (19,20). We therefore deemed the relative risk reduction of 44% to be applicable to heterozygous FH patients in general.

In line with the association between baseline LDL-cholesterol level and the extent of relative risk

TABLE 2 Weighted Comparison: Statin Users Versus Never-Users

	Statin Users				
	Statin at Baseline	Statin Initiation During Follow-Up	All	Never-Users	p Value (Statin Users vs. Never-Users)
Patients	368 (23.6)	658 (42.2)	1,026 (65.8)	533 (34.2)	
Male	197 (53.5)	279 (42.4)	476 (46.4)	268 (50.3)	0.133
Year of screening	2008 ± 0	2008 ± 0	2008 ± 0	2008 ± 0	0.903
Birth year	1959 ± 1	1963 ± 1	1962 ± 0	1961 ± 1	0.322
Age, yrs	48.6 ± 0.8	45.4 ± 0.6	46.6 ± 0.5	47.4 ± 0.7	0.442
BMI, kg/m^2	25.8 ± 0.2	25.6 ± 0.2	25.7 ± 0.1	25.4 ± 0.2	0.348
Smokers	127 (34.4)	234 (35.5)	360 (35.1)	198 (37.1)	0.642
Alcohol users	214 (58.2)	362 (55.1)	576 (56.2)	309 (58.0)	0.452
Index patients	8 (2.3)	6 (0.9)	14 (1.4)	4 (0.8)	0.292
Affected gene					0.147
APOB	54 (14.6)	159 (24.2)	213 (20.8)	95 (17.9)	
LDLR	314 (85.4)	498 (75.7)	812 (79.2)	436 (81.8)	
PCSK9	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.3)	
Lipid profiles at screening					
LDL-C, mg/dl*	227 ± 4	206 ± 3	213 ± 2	217 ± 3	0.461
HDL-C, mg/dl	46 ± 1	45 ± 1	46 ± <1	45 ± 1	0.378
Triglycerides, mg/dl	116 ± 8	127 ± 8	123 ± 3	127 ± 4	0.215
Description of follow-up					
Age at start of follow-up, yrs	44.9 ± 0.8	40.1 ± 0.6	41.9 ± 0.5	42.7 ± 0.7	0.641
CAD during follow-up†	30 (8.2)	42 (6.4)	72 (7.0)	37 (7.0)	0.956
Deceased during follow-up	4 (1.1)	10 (1.5)	14 (1.4)	31 (5.8)	<0.001
Total follow-up, yrs	3,632.4 (21.9)	7,555 (45.5)	11,187.4 (67.4)	5,411.6 (32.6)	
Event rate‡	9.4	6.6	7.5	11.9	
Start of medication during follow-up					
Statin intensity§					
Low	11 (3.0)	31 (4.7)	42 (4.1)		
Moderate	223 (60.6)	430 (65.4)	653 (63.7)		
High	134 (36.4)	197 (29.9)	331 (32.2)		
Other LLT	134 (36.3)	187 (28.4)	321 (31.2)	17 (3.2)	<0.001
Antihypertensive medication	149 (40.5)	240 (36.5)	389 (38)	120 (22.5)	<0.001
Antidiabetic medication	25 (6.8)	47 (7.2)	72 (7.0)	13 (2.5)	<0.001
Thrombocyte aggregation inhibitor	99 (26.8)	129 (19.6)	227 (22.2)	69 (13.0)	<0.001

Values are n (%) or mean ± SE unless otherwise indicated. *Off-treatment LDL-cholesterol. †CAD is defined as myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty. ‡Rates of CAD and mortality per 1,000 person-years of follow-up. §Statin intensity is based on the ACC/AHA guidelines on cholesterol treatment (15).

Abbreviations as in Table 1.

reduction is the lower HR of statin use for CAD and all-cause mortality in *LDLR* mutation carriers compared with *APOB* mutation carriers. However, caution is warranted because the CIs of these HRs are wide and include 1.00, and the p value for interaction is far from significant. Nonetheless, it might be suggested that *LDLR* mutation carriers profit more from statin use, on the basis of their higher baseline LDL level and therefore their absolute LDL-cholesterol reduction.

In absolute terms, the lifetime risk for first CAD event in untreated patients with heterozygous FH is estimated to be 103 per 100,000 person-years in the Netherlands (21). In theory, statins would lower this risk by 44% to 58 per 100,000 person-years. This is certainly an improvement, but a substantial residual risk remains in these patients compared with CAD event rates in their unaffected family members (29 per 100,000 person-years) (21).

CLINICAL RELEVANCE. The increased risk for premature CAD in heterozygous FH, in conjunction with its high prevalence of around 1:250 (1,3,22), has an important impact on public health. Moreover, it is estimated that 80% of these patients will not reach LDL-cholesterol levels <100 mg/dl despite efficacious therapy (23). Currently, new lipid-lowering modalities, such as PCSK9 inhibitors, are being evaluated by authorities for reimbursement for these patients. An important aspect in this decision is the potential for the prevention of CAD events by statins at a

population level; therefore, it is important to quantify the residual CAD risk in statin-treated patients. The relative risk reduction by statins is key information in this estimation. In fact, it is fundamental information in all cost-effectiveness studies in this disorder, such as when evaluating screening programs (24,25).

STUDY LIMITATIONS. Some methodological aspects of our study merit discussion. First, the aim of our study was to assess the effect of statin treatment on CAD risk in patients with FH. Because of the observational nature of our study, indication bias will arise from the imbalance between statin users and never-users regarding characteristics that influence the decision to initiate statin treatment. As a consequence, observed differences may simply reflect underlying differences between the groups rather than effects caused by statin treatment. Therefore, we applied IPTW, a powerful tool to balance covariates across treatment groups to mimic a randomized controlled trial. Using this statistical approach, the possibility of residual confounding by unmeasured factors remained; however, because the most important indications for statin use (e.g., LDL-cholesterol level and age) were measured, we expect that the impact of residual confounding on our effect estimates will be minimized.

The HR of statins for CAD and all-cause mortality changed substantially after applying IPTW. We explored which of the variables that constitute the IPTW weights had the most impact on this change. To do so, we determined new IPTW weights using the individual variables only and constructed new Cox proportional hazard models based on these IPTW weights (Online Table 4). It appeared that year of birth and age at time of screening influenced the effect of statin use on CAD and all-cause mortality the most.

Additionally, in the majority of patients, the first observation in the Pharmo database preceded the visit in the screening program. It is possible that the CAD risk profile might have changed during the period following the first observation in Pharmo, but more likely for the better than the worse, because these patients were under the attention of a physician. This potential improvement in risk profile would reduce the probability of statin initiation and thus influence the IPTW weights. In statin users, IPTW weights are the inverse of the probability of statin initiation, and in this case, the estimated weights could be an overestimation of the true weights. In never-users, the weights are the inverse of 1 minus the probability of statin initiation and are, thus, an underestimation of the true weights.

TABLE 3 Statin Use for CAD and All-Cause Mortality

Model	Hazard Ratio (95% CI)
1: Statin use yes/no*	1.51 (1.05–2.17)
2: Statin use yes/no*, IPTW weighted†	1.09 (0.71–1.68)
3: Statin use time-varying	3.23 (2.10–4.98)
4: Statin use time-varying, IPTW weighted†	1.31 (0.76–2.29)
5: Statin use time-varying with adjustment‡	0.96 (0.58–1.59)
6: Statin use, time-varying, IPTW weighted† with adjustment‡	0.56 (0.33–0.96)

*Statin use (yes/no) at start of follow-up. †Stabilized IPTW weight based on logistic regression modeling. ‡Adjusted for age, other LLT, antihypertensive medication, antidiabetic medication, and thrombocyte aggregation inhibitor medication (all time-varying).

CI = confidence interval; IPTW = inverse-probability-of-treatment weighting; other abbreviations as in Table 1.

Overestimation and underestimation of the IPTW weights in, respectively, statin users and never-users probably also overestimate and underestimate the weight of CAD events in these subgroups, respectively. Together, they could result in an underestimation of the true effect of statins. We expect this underestimation to be small, because one of the factors determining the IPTW weights (age) cannot be altered, and another important factor (LDL-cholesterol level) is probably mostly influenced by medication versus lifestyle intervention.

Furthermore, misclassification of statin use could have underestimated the effect on CAD and all-cause mortality, because events that occurred in patients who discontinued their statin shortly after initiation were incorrectly attributed to statin users. We expect this misclassification bias to be minimal, because the median duration of statin use was 7.3 years, and only 86 persons (5.5%) used a statin <1 year.

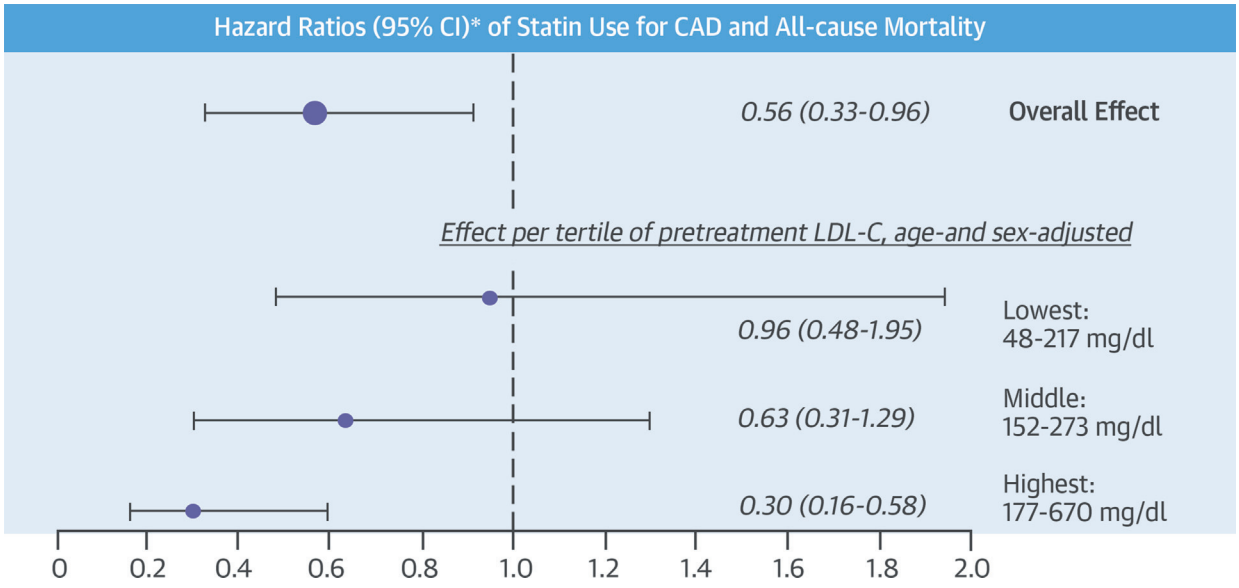
TABLE 4 Stratified Analyses of Statin Use for CAD and All-Cause Mortality

	Hazard Ratio* (95% CI)
Age- and sex-specific LDL-C percentile at time of screening	
Tertile 1 (48–217 mg/dl)	0.96 (0.48–1.95)
Tertile 2 (152–273 mg/dl)	0.63 (0.31–1.29)
Tertile 3 (177–670 mg/dl)	0.30 (0.16–0.58)
p value for interaction (statin use × LDL-C tertile)	0.1451
Affected gene	
LDLR	0.46 (0.29–0.74)
APOB	0.92 (0.32–2.58)
p value for interaction (statin use × affected gene)	0.8296

*Hazard ratios were determined by means of a Cox proportional hazard model with stabilized IPTW, analyzing statin use as time-varying variable and adjusting for age, other LLT, antihypertensive medication, antidiabetic medication, and thrombocyte aggregation inhibitor medication (all time-varying).

Abbreviations as in Tables 1 and 3.

CENTRAL ILLUSTRATION **Statins in FH: Consequences for CAD and All-Cause Mortality**



Besseling, J. et al. J Am Coll Cardiol. 2016;68(3):252-60.

Retrieving data from patients identified by the Dutch screening program for familial hypercholesterolemia (FH), this retrospective cohort study sought to estimate the relative risk reduction for coronary artery disease (CAD) and mortality by statins in heterozygous FH patients. Moderate- to high-intensity statin therapy was associated with a relative risk reduction of approximately 44% for the primary prevention of CAD and all-cause mortality. *Derived from a Cox proportional hazard model analyzing statin use as a time-varying variable, while applying stabilized inverse-probability-of-treatment weighting (IPTW) and adjusting for age, other lipid-lowering therapy, antihypertensive medication, antidiabetic medication, and thrombocyte aggregation inhibitors (all-time varying). Variables included in the final model: statin use, age, lipid-lowering therapy, antidiabetic medication, antihypertensive medication, thrombocyte aggregation inhibitors (all-time varying) as well as IPTW weights based on age at screening and start of follow-up, birth year, body mass index, low-density lipoprotein cholesterol (LDL-C), and triglycerides. CI = confidence interval.

Finally, cause of death was not specified in our data. It could be insightful to have estimates of the effect of statins on cause-specific mortality. Nonetheless, in meta-analyses, as well as in individual studies, CAD and all-cause mortality were considered important outcomes (6,7,26,27). Therefore, we felt that the composite outcome of nonfatal CAD and all-cause mortality was of most interest in these patients.

A strength of the current study is the linkage with institutional health care registries, which resulted in virtually complete follow-up regarding mortality, hospitalization, and medication prescriptions. In combination with IPTW weighting, we feel that this is currently the best possible attempt to mimic a randomized controlled trial on the efficacy of statins in patients with heterozygous FH.

CONCLUSIONS

Medium- to high-intensity statin therapy lowered the risk of CAD and all-cause mortality by approximately 44% in patients with heterozygous FH.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients in the Netherlands with heterozygous familial hypercholesterolemia, statin therapy lowers the risk of coronary artery disease and mortality by 44%.

TRANSLATIONAL OUTLOOK: Registries of patients with familial hypercholesterolemia in other countries should be analyzed to assess the generalizability of this magnitude of risk reduction to other populations.

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KEY WORDS intensity, inverse-probability-of-treatment-weighting, lipid lowering

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this article.