

Hormone therapy and risk of cardiovascular outcomes and mortality in women treated with statins

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Abstract

Objective: This work aims to study the effects of hormone therapy (HT) on the risk of cardiovascular outcomes and all-cause mortality in women treated with statins.

Methods: We included women aged 40 to 74 years and living in Sweden who filled a first statin prescription between 2006 and 2007. Women were categorized as HT users or as nonusers. Information on dispensed drugs, comorbidity, cardiovascular outcomes, and all-cause mortality was obtained from national health registers.

Results: A total of 40,958 statin users—2,862 (7%) HT users and 38,096 nonusers—were followed for a mean of 4.0 years. In total, 70% of the women used statins as primary prevention. Among HT users, there were five cardiovascular deaths per 10,000 person-years. The corresponding rate among nonusers was 18, which yielded a hazard ratio of 0.38 (95% CI, 0.12-1.19). The all-cause mortality rates were 33 and 87, respectively, and the hazard ratio was 0.53 (95% CI, 0.34-0.81). There were no associations with cardiovascular events. A similar pattern was found for both primary and secondary prevention.

Conclusions: HT is associated with a reduced risk of all-cause mortality in women treated with statins. Although confounding factors, such as lifestyle and disease severity, might have influenced the results, HT does not seem to be detrimental to statin-treated women.

Key Words: Cohort – Population-based – Hormone therapy – Statins – Cardiovascular disease.

Hormone therapy (HT) has been subjected to continued debate, and two large randomized clinical trials (the Women's Health Initiative study and the Heart and Estrogen/progestin Replacement Study) have had a major impact on recommendations concerning use of HT.^{1,2} Before the publication of the trials, HT was believed to be protective against cardiovascular disease.^{3,4} However, the picture changed

and, mainly based on the findings from these studies, the European Medicines Agency and the US Food and Drug Administration currently recommend that HT be restricted to the minimal effective dose for the shortest duration and that women with a history of cardiovascular disease abstain from HT.^{5,6} These regulatory recommendations do not, however, consider different base risks. The restrictive prescription policy attributable to fear of cardiovascular disease among women at risk for cardiovascular disease may cause impaired quality of life and lack of beneficial therapy effects.^{1,7-9} Prevention of cardiovascular disease has increasingly important health implications as the population ages and, currently, as many as 10% of the adult Swedish female population is treated with statins.¹⁰ Benefits and risks of HT have not been thoroughly explored for women treated with statins. The aim of the present work was to study associations between HT and cardiovascular events and mortality in women treated with statins, using population-based data.

METHODS

Study design and population

In a register-based cohort study, we included incident female statin users aged 40 to 74 years and living in Sweden (Fig.). Women who filled a prescription for statins between July 2006 and July 2007 and had no previous fillings of statins within a 12-month period before that were included. Twelve months after statin initiation, they were included in the study cohort as HT users or nonusers.

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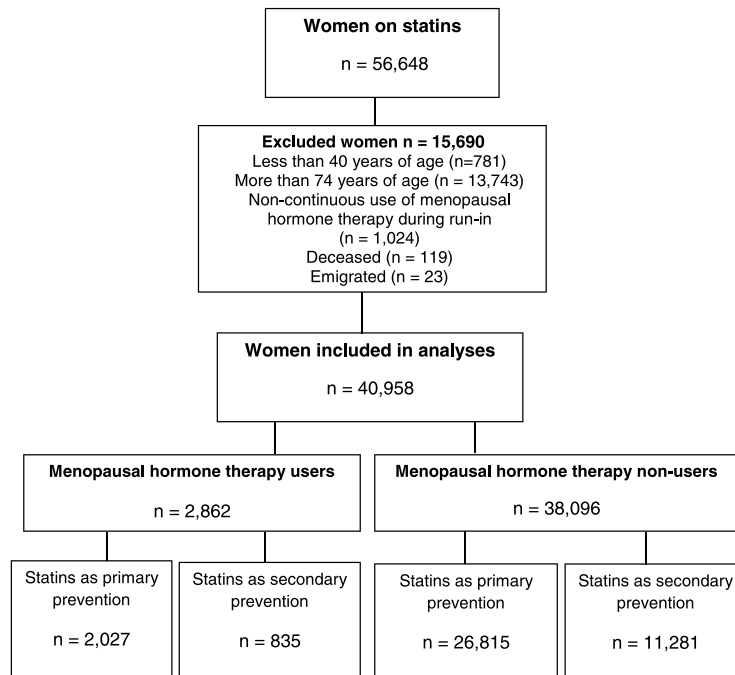


FIG. Study flow chart.

Data collection

Information on filled prescriptions, comorbidity, cardiovascular events, and mortality was obtained from the Swedish national registers. Individual record linkage between the registers was possible through the unique personal identification number assigned to all Swedish residents.¹¹ The registers are nationwide and cover all residents. The Swedish Prescribed Drug Register comprises information on the formulation and date of all filled prescriptions, including their Anatomical Therapeutic Chemical Classification System (ATC) codes since July 2005. Drugs administered in hospitals are not covered in the register.

The Swedish National Patient Register holds information on primary and secondary diagnoses from all hospitalizations (nationwide since 1987) and outpatient hospital visits (since 2001). Diagnoses are recorded by the *International Classification of Diseases* (ICD) system. The current version is the 10th revision, which has been used since 1997. The register also holds information on the Nordic Classification of Surgical Procedures. The Cause of Death Register holds data on the dates and causes of death of all Swedish residents, and diagnoses are recorded by ICD-10 codes. The Register of the Total Population holds information on migration, education, and income.

Exposure to HT

HT users were defined as women who continuously filled prescriptions for HT within 12 months of statin initiation. For each woman, information on number of dispensed packages and package size was obtained from the Prescribed Drug Register. Doses were assumed to be one unit dose (tablet/patch/gel) per day. Exposure length was defined as the number of packages multiplied by package size. All dispensed unit doses were assumed to be used, and excessive unit doses were included in

exposure length. Continuation of HT was assessed using the permissible gap method.¹² Gaps are periods in which no medication is available to the patient, and treatment was considered continued if the gap between the previous filled prescription's last date of supply and the subsequent refill was less than 180 days. The ATC was used to identify HT, such as semisynthetic estrogens (ATC code G03CA), combinations of progestogen and estrogen (ATC codes G03FA and G03FB), and selective estrogen receptor modulators (ATC code G03XC01). Only estrogens with systemic effects were considered in the analyses. Of the 40,958 statin users eligible for inclusion, 1,024 women with noncontinuous use of HT during run-in were excluded from further analyses.

Outcomes

We investigated associations between HT and cardiovascular events, cardiovascular deaths, and all-cause mortality. The outcomes were defined using information on primary diagnoses by ICD-10, Nordic Classification of Surgical Procedures, and ATC codes, as presented in Table 1. The cardiovascular events included were myocardial infarction, ischemic stroke/transient ischemic attack, peripheral arterial disease, or ischemic heart disease. Only incident ischemic heart disease or peripheral arterial disease (ie, without a previously recorded diagnosis of ischemic heart disease or peripheral arterial disease) was considered as outcome. Analyses were performed for all women, for women categorized by reason for statin therapy (primary or secondary prevention), and for incident and prevalent users of HT. Secondary prevention was defined as a previously recorded diagnosis of myocardial infarction, other ischemic heart disease, ischemic stroke/transient ischemic attack, or peripheral arterial disease at statin initiation. Women without any of these

TABLE 1. Cardiovascular outcomes, comorbidity, and other covariates identified by ICD-10, Nordic Classification of Surgical Procedures, and ATC codes

Diagnosis	ICD-10 ^a	Nordic Classification of Surgical Procedures codes	ATC codes ^b
Myocardial infarction	I21, I22, I23, I241, I252	NA	NA
Ischemic heart disease	I20, I24, I25 (except I241, I252, I253, and I254)	FNA, FNB, FNC, FND, FNE, FNF, FNG	C01D
Stroke/transient ischemic attack	G45, G46, I63-I66, I693, I694	NA	NA
Peripheral arterial disease	I70, I71, I739, I74, K55	PAE, PAF, PAH, PAP, PAQ, PBE, PBF, PBH, PBP, PBQ, PCE, PCF, PCH, PCP, PCQ, PDE, PDF, PDH, PDP, PDQ, PEE, PEF, PEH, PEP, PEQ, PFE, PFF, PFH, PFP, PFQ	B01AC30
Atrial fibrillation	I48	NA	NA
Congestive heart failure	I50, I099, I11-I13, I15, I34, I35, I420, I425-I429, I43-I47	NA	NA
Essential hypertension ^c	I10	NA	C02, C07, C08, C09, C03A, C03B
Diabetes	E10, E11	NA	A10A, A10B
Diabetes without complications	E100, E101, E106 (except E106D), E108, E109, E110, E111, E116 (except E116D), E118, E119	NA	NA
Diabetes with complications	E102-E105, E107, E116D, E112-E115, E117, E106D	NA	NA
Dementia	F00-F03, G30, G311, F051		
Chronic obstructive pulmonary disease	J40-J47, J60-J67, I278, I279, J684, J701, J703	NA	NA
Rheumatic disease	M05, M06, M32-M34, M315, M351, M353, M360	NA	NA
Peptic ulcer disease	K25-K28	NA	NA
Mild liver disease	B18, K73, K74, K700-K703, K709, K713-K715, K717, K760, K762-K764, K768, K769, Z944	NA	NA
Moderate or severe liver disease	K704, K711, K721, K729, K765, K766, K767, I850, I859, I864, I982	NA	NA
Renal disease	N18, N19, N052-N057, N250, I120, I131, N032-N037, Z490-Z492, Z940, Z992	NA	NA
Cancer	C00-C09, C10-C19, C20-C26, C30-C34, C37-C39, C40, C41, C43-C49, C50-C58, C60-C69, C70-C76, C81-C84, C85, C88, C90-C97	NA	NA
Metastatic solid tumor	C77, C78, C79, C80	NA	NA
Nicotine therapy	NA	NA	N07BA
Obesity	E65, E66	NA	NA

ICD-10, *International Classification of Diseases 10th Revision*; ATC, Anatomical Therapeutic Chemical Classification System; NA, not applicable.

^aDiagnosis or procedure codes within 8 years of the statin index date recorded in the National Patient Register.

^bA filled prescription recorded in the Prescribed Drug Register within 1 year of the statin index date used to define statin use as secondary prevention. Statin users without these diagnoses, procedure codes, and drugs were categorized as primary prevention.

^cIndividuals using an antihypertensive drug without a recorded diagnosis of stroke/transient ischemic attack, ischemic heart disease, peripheral arterial disease, atrial fibrillation, congestive heart failure, or diabetes with complications.

diagnoses at statin initiation were considered to be using statins for primary prevention and were categorized accordingly. Women who filled a prescription for HT and had no previous fillings during the 12-month period before the start of statins were considered as incident hormone users. All other women were categorized as prevalent HT users.

Covariates

We included as covariates those conditions occurring before inclusion in the study (Table 1), which could be considered as confounders or effect modifiers: HT, myocardial infarction, ischemic heart disease, stroke/transient ischemic attack, peripheral arterial disease, essential hypertension, congestive heart failure, atrial fibrillation, diabetes with or without complications, dementia, chronic obstructive pulmonary disease,

peptic ulcer disease, rheumatic disease, renal disease, mild liver disease, moderate or severe liver disease, any cancer, metastatic cancer, level of income and education, nicotine therapy, and adherence to statin therapy. The diseases were classified by ICD-10 codes and categorized as disease (yes or no). Both primary and secondary diagnoses were considered for the covariates. Education was categorized into three categories, and income was categorized by quartiles (Table 2).

Follow-up period

All women were followed up from 12 months after the date of the first filled prescription for statins to the end of the study (December 31, 2011), emigration, cardiovascular event, death, or change of HT. Nonusers were censored at the first filled

TABLE 2. Baseline characteristics of women on statins by use of HT at the start of follow-up

Characteristics	Primary or secondary prevention		Primary prevention		Secondary prevention	
	HT users	Nonusers	HT users	Nonusers	HT users	Nonusers
Total	2,862 (100)	38,096 (100)	2,027 (100)	26,815 (100)	835 (100)	11,281 (100)
Age						
40-54 y	451 (16)	6,858 (18)	345 (17)	5,253 (20)	106 (13)	1,605 (14)
55-64 y	1,529 (53)	15,244 (40)	1,118 (55)	11,318 (42)	411 (49)	3,926 (35)
65-74 y	882 (31)	15,994 (42)	564 (28)	10,244 (38)	318 (38)	5,750 (51)
Number of comorbidities						
At least one of the morbidities below	2,244 (78)	30,572 (80)	1,409 (70)	19,291 (72)	835 (100)	11,281 (100)
Cardiovascular disease						
Myocardial infarction	153 (5)	2,335 (6)	9 (0)	117 (0)	144 (17)	2,218 (20)
Ischemic heart disease	439 (15)	4,708 (12)	56 (3)	618 (2)	383 (46)	4,090 (36)
Ischemic stroke/transient ischemic attack	179 (6)	3,021 (8)	12 (1)	205 (1)	167 (20)	2,816 (25)
Peripheral arterial disease	116 (4)	1,429 (4)	18 (1)	169 (1)	98 (12)	1,260 (11)
Congestive heart failure	178 (6)	2,663 (7)	15 (1)	200 (1)	163 (20)	2,463 (22)
Atrial fibrillation	86 (3)	1,480 (4)	9 (0)	113 (0)	77 (9)	1,367 (12)
Essential (primary) hypertension	988 (35)	12,734 (33)	988 (49)	12,734 (47)	0 (0)	0 (0)
Other diseases						
Diabetes	402 (14)	7,203 (19)	269 (13)	4,596 (17)	133 (16)	2,607 (23)
Without long-term complication	228 (8)	4,126 (11)	127 (6)	2,104 (8)	101 (12)	2,022 (18)
With long-term complication	70 (2)	1,480 (4)	5 (0)	153 (1)	65 (8)	1,327 (12)
Dementia	1 (0)	87 (0)	1 (0)	47 (0)	0 (0)	40 (0)
Chronic obstructive pulmonary disease	189 (7)	2,021 (5)	85 (4)	948 (4)	104 (12)	1,073 (10)
Rheumatologic disease	87 (3)	961 (3)	43 (2)	512 (2)	44 (5)	449 (4)
Peptic ulcer disease	32 (1)	481 (1)	16 (1)	258 (1)	16 (2)	223 (2)
Mild liver disease	21 (1)	244 (1)	13 (1)	149 (1)	8 (1)	95 (1)
Moderate or severe liver disease	4 (0)	31 (0)	2 (0)	17 (0)	2 (0)	14 (0)
Renal disease	17 (1)	328 (1)	2 (0)	125 (0)	15 (2)	203 (2)
Obesity	58 (2)	998 (3)	30 (1)	554 (2)	28 (3)	444 (4)
Any malignancy	37 (1)	1,297 (3)	16 (1)	824 (3)	21 (3)	473 (4)
Metastatic solid tumor	2 (0)	135 (0)	1 (0)	80 (0)	1 (0)	55 (0)
Education						
≤9 y	726 (25)	11,852 (31)	468 (23)	7,851 (29)	258 (31)	4,001 (35)
>9-12 y	1,369 (48)	17,282 (45)	969 (48)	12,290 (46)	400 (48)	4,992 (44)
>12 y	761 (27)	8,725 (23)	585 (29)	6,529 (24)	176 (21)	2,196 (19)
Missing	6 (0)	237 (1)	5 (0)	145 (1)	1 (0)	92 (1)
Income						
Missing	0 (0)	2 (0)	0 (0)	2 (0)	0 (0)	0 (0)
Low quartile	464 (16)	7,922 (21)	303 (15)	5,224 (19)	161 (19)	2,698 (24)
Middle-low quartile	531 (19)	8,204 (22)	327 (16)	5,276 (20)	204 (24)	2,928 (26)
Middle-high quartile	810 (28)	10,682 (28)	557 (27)	7,656 (29)	253 (30)	3,026 (27)
High quartile	1,057 (37)	11,286 (30)	840 (41)	8,657 (32)	217 (26)	2,629 (23)
Adherence to statin ^a						
High adherence (≥80%)	1,684 (59)	22,301 (59)	1,179 (58)	15,478 (58)	505 (60)	6,823 (60)
Nicotine therapy	110 (4)	973 (3)	66 (3)	512 (2)	44 (5)	461 (4)
Previous menopausal HT ^b						
No	231 (8)	37,279 (98)	178 (9)	26,261 (98)	53 (6)	11,018 (98)
Yes	2,631 (92)	817 (2)	1,849 (91)	554 (2)	782 (94)	263 (2)

Data are presented as n (%).

Start of follow-up was 1 year after statin initiation. Women are presented by reason for statin use (primary or secondary prevention).

HT, hormone therapy.

^aAdherence to statin treatment was estimated as proportion of days (%) covered by statin therapy during the first year since statin initiation.

^bA filled prescription for HT on the year before the statin index date.

prescription for HT, and users were censored 180 days after the end of exposure to hormones.

Adherence to statins

To assess the influence of adherence to statins, we performed analyses including adherence categorized as high or low by the proportion of days covered by statin therapy during the first year after the statin index date. Adherence was categorized as "high" when the proportion of days covered was 80% or more and as "low" when the proportion of days covered was less than 80%.

Statistical methods

All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC). Descriptive statistics are presented as numbers and proportions. Observed person-years were calculated separately for users and nonusers as the sum of years during the follow-up period. Rates are presented as number of events per 10,000 person-years. Using multiple Cox regression, we estimated hazard ratios for cardiovascular events, cardiovascular deaths, or all-cause mortality for women using HT (users) versus women not using HT (nonusers). Time to first cardiovascular event, death from cardiovascular disease, or all-cause mortality

was used as an independent variable (survival time) in the models. Cox regression models were adjusted for age (model 1) and age together with other covariates (model 2). Hazard ratios for cardiovascular events, cardiovascular deaths, and all-cause mortality were also estimated by primary or secondary prevention and for incident or prevalent users of HT. In additional analyses, change in estimate of hazard ratio was tested for each of the confounders or effect modifiers and calculated relative to hazard ratios derived from model 1. None of the confounders or effect modifiers changed the estimate by more than 10%. Furthermore, the influence of adherence to statin therapy was investigated by examining the hazard ratios for low versus high adherence, applying model 2 for the total cohort, incident HT users, and prevalent HT users.

Ethical approval

The study was approved by the Regional Ethical Review Board at Karolinska Institutet (Stockholm, Sweden; 2010/2:11).

RESULTS

Baseline characteristics of the study population are presented in Table 2. We included 40,958 women (2,862 HT users and 38,096 nonusers) who were followed up for 3.5 years at least and 4.5 years at most (mean, 4.0 y). In total, 70% of the women used statins as primary prevention. The mean (interquartile range) age of HT users was 61 (57-66) years, and that of nonusers was 62 (57-68) years. A similar proportion of HT users and nonusers had been recorded, at baseline, with at least one diagnosis of cardiovascular disease or other chronic disease (78% vs 80%; Table 2). The rates per 10,000 person-years, together with hazard ratios for associations between HT and cardiovascular events, cardiovascular deaths, and all-cause mortality, are presented in Table 3. The rates of cardiovascular events were 250/10,000 person-years among HT users and 267/10,000 person-years among nonusers. The adjusted hazard ratio (95% CI) was 1.04 (0.88-1.22). The corresponding rates of cardiovascular deaths were 5/10,000 person-years among users and 18/10,000 person-years among nonusers, yielding an adjusted hazard ratio (95% CI) of 0.38 (0.12-1.19). The all-cause mortality rates were 33/10,000 person-years among users and 87/10,000 person-years among nonusers, and the adjusted hazard ratio (95% CI) was 0.53 (0.34-0.81).

Similar patterns of conformity were found when women were categorized by reason for statin treatment (ie, as primary or secondary prevention). For women who used statins as primary prevention, there were no effects on risk of cardiovascular events (adjusted hazard ratio, 1.07; 95% CI, 0.87-1.32). The rates of cardiovascular death were 2/10,000 person-years and 10/10,000 person-years among users and nonusers, respectively, yielding an adjusted hazard ratio (95% CI) of 0.31 (0.04-2.22). The corresponding rates of all-cause mortality were 25/10,000 person-years and 59/10,000 person-years, and the adjusted hazard ratio (95% CI) was 0.58 (0.32-1.06). For women who used statin treatment as secondary prevention, there was no association between HT use and cardiovascular events (adjusted hazard ratio, 0.98; 95% CI, 0.76-1.27). The rates

TABLE 3. Numbers, proportions, and hazard ratios for cardiovascular events, cardiovascular deaths, and all-cause mortality by use of HT among women on statins

	HT users			Nonusers			Model 1 ^a			Model 2 ^b		
	n (%)	Person-years	Events/10,000 person-years	n (%)	Person-years	Events/10,000 person-years	Hazard ratio	95% CI	Hazard ratio	95% CI		
Total	2,862 (100)			38,096 (100)								
Cardiovascular events												
Primary or secondary prevention	152 (5.3)	6,073	250	3,693 (9.7)	138,239	267	0.95	0.81-1.12	1.04	0.88-1.22		
Secondary prevention	60 (7.2)	1,760	341	1,588 (4)	39,671	400	0.84	0.65-1.09	0.98	0.76-1.27		
Primary prevention	92 (4.5)	4,313	213	2,105 (7.9)	98,569	214	1.03	0.84-1.27	1.07	0.87-1.32		
Cardiovascular deaths												
Primary or secondary prevention	3 (0.10)	6,296	5	266 (0.70)	145,447	18	0.31	0.10-0.96	0.38	0.12-1.19		
Secondary prevention	2 (0.24)	1,856	11	166 (1.5)	42,758	39	0.32	0.08-1.28	0.43	0.11-1.73		
Primary prevention	1 (0.05)	4,441	2	100 (0.37)	102,689	10	0.27	0.04-1.94	0.31	0.04-2.22		
All-cause mortality												
Primary or secondary prevention	21 (0.73)	6,296	33	1,264 (3.3)	145,447	87	0.44	0.28-0.67	0.53	0.34-0.81		
Secondary prevention	10 (1.2)	1,856	54	657 (5.8)	42,758	154	0.38	0.21-0.72	0.47	0.25-0.88		
Primary prevention	11 (0.54)	4,441	25	607 (2.3)	102,689	59	0.48	0.27-0.88	0.58	0.32-1.06		

Hazard ratios with 95% CI were estimated for HT users versus nonusers.

HT, hormone therapy.

^aAdjusted for age.

^bAdjusted for age, myocardial infarction, ischemic heart disease, stroke/transient ischemic attack, peripheral arterial disease, essential hypertension, congestive heart failure, atrial fibrillation, paraplegia or hemiplegia, diabetes with or without complications, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, rheumatic disease, renal disease, liver disease (mild/moderate or severe), any cancer, metastatic solid cancer, education (three levels), income (quartiles), nicotine therapy, and adherence to statins (high adherence [$\geq 80\%$ of days covered by statin therapy during the first year since statin initiation] vs low adherence).

of cardiovascular death were 11/10,000 person-years and 39/10,000 person-years among users and nonusers, respectively (adjusted hazard ratio, 0.43; 95% CI, 0.11-1.73). The corresponding rates of all-cause mortality were 54/10,000 person-years and 154/10,000 person-years, yielding an adjusted hazard ratio (95% CI) of 0.47 (0.25-0.88).

The hazard ratios for estimated cardiovascular outcomes were lower for incident users than for prevalent users of HT, though with imprecise CIs. For cardiovascular events, the adjusted hazard ratio (95% CI) was 0.49 (0.18-1.31) for incident users and 1.07 (0.90-1.26) for prevalent users. For cardiovascular deaths, hazard ratios could not be estimated for incident users because there were no deaths among them. Among prevalent users, the adjusted hazard ratio (95% CI) for cardiovascular death was 0.40 (0.13-1.27). The corresponding adjusted hazard ratio (95% CI) for all-cause mortality was 0.87 (0.22-3.51) among incident users and 0.51 (0.32-0.80) among prevalent users. The proportion of women with high adherence to statin treatment was 59% both among HT users and among nonusers.

DISCUSSION

In this nationwide cohort study including women treated with statins, HT was associated with a reduced risk of all-cause mortality, and we found no association with occurrence of cardiovascular events. Point estimates of cardiovascular death among hormone users suggested a reduced risk, but CIs were imprecise. The results were consistent whether the women had statins for primary or secondary prevention. There may be several explanations for the discrepancy between the findings in the Women's Health Initiative study,¹ the findings in the Heart and Estrogen/progestin Replacement Study,² and the findings in our study, such as differences in study population and statin use. We included all women aged 40 to 74 years who were recently considered to be at risk for cardiovascular disease. Although the Women's Health Initiative study cohort included women of similar age, they were mainly healthy, and only 7% of the women were statin users at baseline. The results of the Women's Health Initiative study are not necessarily applicable to women on statin treatment. The Heart and Estrogen/progestin Replacement Study² included women with previous coronary heart disease. Despite the fact that all of the women had previous coronary heart disease, only 45% used lipid-lowering drugs at baseline. The Heart and Estrogen/progestin Replacement Study found that HT increased the risk of recurrent coronary events in the short term, but of coronary benefits in the long term. These somewhat controversial findings were also found in the secondary analyses of the Nurses' Health Study¹³ and have been explained by the fact that estrogens seem to prevent the development of atherosclerosis but have an opposite effect on established atherosclerosis.¹⁴⁻¹⁶ Although we had limited information on duration of hormone use before statin initiation and time of menopause, our findings of similar risk reductions for cardiovascular mortality among incident and prevalent hormone users would speak against a differential effect by time of use. In our study, all of the women used semi-natural 17 β -estradiol, as conjugated estrogens are not sold in

Sweden. In the Women's Health Initiative study and the Heart and Estrogen/progestin Replacement Study, all women used conjugated estrogens. Although the findings reported from previous studies have been ambiguous, estradiol might be less thrombotic or atherosclerogenic than conjugated estrogens, which may explain the more beneficial effect of HT in the present study.¹⁷⁻²⁰ A possible beneficial effect is supported by the findings in a recent follow-up of a clinical trial, where women initially were randomized to HT with 17 β -estradiol and compared with nonusers.²¹ In that study and in accordance with our findings, HT was reported to reduce the risks of mortality and myocardial infarction. There may be a positive interaction between statins and HT. A substudy from the Heart and Estrogen/progestin Replacement Study suggested that statins attenuate the early increased risk of coronary heart events associated with HT.²² Previous basic studies implied that 17 β -estradiol may increase atherosclerotic plaque instability, for example, by up-regulating mediators.^{23,24} Concurrent use of statins, which inhibit 17 β -estradiol up-regulation of mediators, may prevent increased atherosclerotic plaque instability and thus prevent early coronary heart events. Several factors may contribute to the lower risk of cardiovascular death among HT users compared with nonusers. HT users might have closer medical attention than nonusers, which could increase the possibilities for other preventive interventions and thereby reduce the risk of cardiovascular disease. It should also be acknowledged that the absolute number of cardiovascular deaths among HT users was low; therefore, the results should be interpreted cautiously. Death from any cause may be considered less prone to bias or interpretation, and the decrease in all-cause mortality was mainly driven by the decrease in cardiovascular death. Except for diabetes, which was more common among nonusers, there were no major differences in the prevalence of cardiovascular diseases or other chronic diseases between users and nonusers. However, upon assessment of the influence of diabetes on the risks of cardiovascular outcomes and mortality, risk estimates were hardly affected. Lifestyle may also influence the results, and previous studies have indicated that women who receive HT may generally be healthier than those not receiving HT.²⁵ High socioeconomic status (assessed as high education and high income), which is associated with a healthier lifestyle, was slightly more common among users. Adjusting for level of education and income had, however, only minor effects on risk estimates. We had no direct information on smoking, but we used chronic obstructive pulmonary disease diagnoses and smoking cessation drugs as surrogate measures for smoking. HT users were slightly more often diagnosed with chronic obstructive pulmonary disease (7% among users vs 5% among nonusers). In Sweden, most cases of chronic obstructive pulmonary disease are related to tobacco smoking,²⁶ and recording of this disorder should reflect the extent of smokers in our study. The number of women who filled a prescription for smoking cessation drugs was equally distributed among users and nonusers. In addition, education may be used as a surrogate measure for smoking.²⁷ Adjusting for chronic obstructive pulmonary disease, smoking cessation drugs, and education had

only minor influence on the results. Although the lack of ability to assess smoking as such is a limitation, smoking-related factors had no major influence on the estimates. Adherence to statin treatment most probably affects cardiovascular outcomes and may also be regarded as a proxy for a healthier lifestyle.²⁸ It should be noted that high adherence was equally common (59%) among HT users and nonusers, and there was no change in the risks of cardiovascular outcomes and all-cause mortality when adjusting for adherence to statin treatment. We considered as users all women on continuous HT during the year after the statin index date. Some nonusers may have previously used HT, as drug use before July 2005 could not be assessed. However, if anything, these presumptive misclassifications would have diluted the effect of therapy. In addition, as the outcomes were based on codes recorded in the registers, some misclassification of the outcome may have occurred, as diagnoses and procedures could have been wrongly recorded or not recorded at all. Such misclassifications would presumably be nondifferential in relation to HT and of subordinate importance, considering the good quality of the registers.^{29,30}

Strength and limitations

A major strength of this study is the ability to follow up a well-defined large cohort of women. The use of a nationwide population-based cohort, including all female incident statin users taking or not taking HT, ensures the generalizability of the study results. However, this study does not include women at risk for cardiovascular disease but not taking statin treatment; thus, the results are not applicable to all women at risk for cardiovascular disease. The use of filled prescriptions as a measure of drug use eliminates recall bias, and although the Prescribed Drug Register holds nearly complete data regarding all fillings, we acknowledge that filled prescriptions do not necessarily imply the use of a drug. The lack of information on disease severity and the scarce information on body mass index (as only those with a diagnosis of obesity recorded in the registers were captured) could be considered as additional limitations. In the present study, 7% of the women at risk for cardiovascular disease used HT. Most of these women probably had used HT for several years because half of HT users were older than 61 years and the mean age at menopause is around 52 years. The current recommendations imply that some women at risk for cardiovascular disease, which have disabling symptoms related to menopause, may unnecessarily be denied hormone use.^{7,8,13,31,32} In light of the current prevention strategies for cardiovascular diseases, such as statin use and lifestyle interventions, it should be valuable to reflect on the restricted use of HT in women treated with statins.

CONCLUSIONS

HT is associated with a reduced risk of all-cause mortality and no increased risk of cardiovascular disease. Although other factors, such as lifestyle and disease severity, may have influenced the results, HT does not seem to be detrimental to statin-treated women.

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