Hormone therapy and risk of myocardial infarction: a national register study

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Aim	To assess the risk of myocardial infarction (MI) as a result of hormone therapy (HT), with focus on the influence of age, duration of HT, various regimens and routes, progestagen type, and oestrogen dose.
Methods and results	All healthy Danish women ($n = 698\,098$, aged 51–69) were followed during 1995–2001. On the basis of a central prescription registry, daily updated national capture on HT was determined. National Registers identified 4947 MI incidents. Poisson regression analyses estimated rate ratios (RRs). Overall, we found no increased risk [RR 1.03 (95% CI: 0.95–1.11)] of MI with the current HT compared with women who never used HT; age-stratified RR among women aged 51–54, 55–59, 60–64, and 65–69 years were 1.24 (1.02–1.51), 0.96 (0.82–1.12), 1.11 (0.97–1.27), and 0.92 (0.80–1.06), respectively. An increasing risk with longer duration was found for younger women, which was not observed with older age groups. In all age groups, the highest risk of MI was found with continuous HT regimen. No increased risk was found with unopposed oestrogen, cyclic combined therapy, or tibolone. Significantly lower risk was found with dermal route than oral unopposed oestrogen therapy ($P = 0.04$). No associations were found with progestagen type or oestrogen dose.
Conclusion	In a National cohort study, we found that HT regimen and route of application could modify the influence of HT on the risk of MI.
Keywords	Hormone therapy • Hormone replacement therapy • Myocardial infarction • Coronary heart disease • Ischaemic heart disease • Oestrogen

Background

Postmenopausal use of hormones was widely used in the western world until 2002, when the largest randomized clinical trial (RCT), the Woman's Health Initiative (WHI), investigating the health effects of continuous combined hormone therapy (HT) was prematurely terminated due to overall increased morbidity with HT.[1] This finding was unexpected, as a primary preventive effect of HT on cardiovascular diseases was predicted to outbalance the perceived increased risk of breast cancer and venous thrombo-embolism. These expectations were based on observational studies;[2] however, the WHI found an increased risk of both coronary heart disease and stroke.[1,3] These findings were

in accordance with an earlier RCT that tested the effect of HT on re-event after coronary heart disease (the HERS study[4]).

Following the study termination, part of the WHI testing unopposed oestrogen vs. placebo among women without uterus was also prematurely stopped, as no cardio-protective was observed, and an increased risk of stroke was instead found.[5] The discrepant findings from the RCT and observational literature were the topic of much debate. The observational studies could be influenced by a 'healthy user' bias,[2] and the WHI was criticized for not being applicable for healthy younger perimenopausal women.[6,7] Recently, the RCT and observational results have been found to be more in agreement if time since HT initiation was controlled for these studies was found to be in closer agreement.[8]

The WHI trial tested two hormone therapies: oral continuous combined therapy with conjugated equine oestrogen 0.625 and 2.5 mg/day medroxyprogesterone acetate vs. placebo for women with an intact uterus, which HERS also tested, and oral unopposed equine oestrogen 0.625 mg/day vs. placebo for women who had a hysterectomy. After termination of the WHI, no other randomized studies testing other hormone therapies have been initiated, despite positive results with lower oestrogen dosages from a pilot study.[9] Studies exploring the overall increased risk of venous thrombo-embolism with hormone therapy indicate a lower risk with unopposed oestrogen therapy[10] and potentially with dermal application.[11]

In the observational literature, little focus has been placed on the significance of various potentially important factors concerning the risk of myocardial infarction (MI) associated with hormone therapy, i.e. regimens as oestrogen monotherapy or combined oestrogen–progestagen therapy in cyclic or continuous combination; oral, dermal, or vaginal route of administration; chemical structure of the progestagen and dosages of oestrogen and progestagen.

In studies in Danish populations, we previously found that women using HT could not be characterized as 'healthy users',[12,13] and in the Danish nurse cohort study, we found no overall protective effect of HT on MI, but instead found a harmful interaction between diabetes and hormone therapy.[12]

The purpose of this study was to assess the risk of MI associated with HT using the National registry information on all Danish women; specifically, we assessed the influence of duration of use, various regimens, routes of administration, progestagen types, and oestrogen dose, and also investigated the potential interactions between HT and register-recorded risk factors for cardiovascular diseases.

Methods

The Danish Sex Hormone Register Study (DaHoRS) is based on five National registers that are merged through an individual personal registration number given to Danish citizens at birth or at immigration, and hereafter replaced by a random number to ensure anonymity. The registers include the following: (i) the Civil Registration System (CRS) that registers all Danish inhabitants' age and address, (ii) the National Register of Patients (NRP) that collects diagnoses from all hospitalizations in Denmark, (iii) the Cause of Death register, which has information from death certificates, (iv) The National Register of Medicinal Product Statistics, which records all prescriptions reimbursed on Danish pharmacies, and (v) Statistics Denmark that delivers information about the individual's education.

Study base

In the CRS, a National cohort of all Danish women aged at least 51 years by 1 January 1995 or reaching 51 years during the period from 1 January 1995 to 31 December 2001 were identified. In order to focus the analysis on postmenopausal women, we used a cut off age of 51 years, as this was the average age at menopause in Denmark. Women were excluded from the cohort when they turned 70 years old. This open cohort included 748 324 women.

Exclusion criteria

We aimed to establish a cohort of healthy women; consequently, women recorded in the NRP with cardiovascular diseases or hormone-related cancers prior to entrance were excluded. The

NRP has collected discharge diagnoses and surgical codes on all hospitalized patients since 1976, coded according to WHO's international classification of diseases (version ICD-8 until end of 1993 and ICD-10 from 1 January 1994). The specific diseases leading to exclusion were previous ischaemic heart disease (ICD-8: 410–414; ICD-10: DI20–25), stroke (ICD-8: 430–31; ICD-10: 433–434; 436/DI60–64), venous thrombo-embolism (ICD-8: 450–4; ICD-10: DI26, DI80–82), breast cancer (ICD-8: 174; ICD-10: DC50), cancer of female genitals (ICD-8: 180, 182–184; ICD-10: DC53–57), colorectal cancer (ICD-8: 153–54; ICD-10: DC180–211) and haematological malignancy (ICD-8: 200–207; ICD-10: DC81–85, DC88, DC90–96).

In total, 23 657 and 25 342 women were excluded due to previous cardiovascular and malignant diseases, respectively, 1135 due to both, and 92 women were excluded due to only one day of observation, leaving 698 098 women in the cohort. These women were followed until the end of 2001, corresponding to 2 987 068 woman-years of observation.

A woman was excluded from the study if diagnosed with any of the diseases (except MI, which was considered an event) during the study period. Additionally, women were excluded upon emigration or death from reasons other than MI, or at turning 70 years of age.

Exposure

Exposure to HT was recorded from the National Register of Medicinal Product Statistics (NRM), which has collected data on redeemed prescriptions by Danish citizens since January 1994, and is considered complete as of 1 January 1995.

In NRM, all prescriptions on hormone products were recorded by Anatomical-Therapeutical-Chemical (ATC) codes. The date the prescription was redeemed, pack size, number of packs, the defined daily doses, and administration form were available. The included ATC codes are described in detail in earlier publications;[14] briefly, HT was categorized into six main groups according to regimen, 25 subgroups according to chemical compounds, and 45 detailed groups according to the route of administration, and type and dose of oestrogen and progestagen.

For the cardiovascular analyses, women were grouped based on the type of hormone used most recently. Detailed information is available at www.dachre.dk. The exposures of these hormones were updated daily for each individual through the study period, and at the expiration of the prescription, the women used the hormones for four additional months to account for individual variation in prescription pattern and diagnostic delay in the NRP. HT exposure was thereafter considered a time-varying covariate in the statistical model. Exposure to hormones before age 51 but within the 6 year study period was also recorded and used in the calculation of duration of HT.

End points

The first event of MI was recorded (ICD-10 code DI21–22) in either the NPR or cause of death registry receiving information from death certificates. In total, 4947 events of MI were identified during the follow-up period.

Confounders

Ages were calculated from birth dates, which were extracted from the individual person's registration number.

Information on education was recorded from the Statistics Denmark integrated database for labour market research. Potential confounders included the most recently completed education recorded at the start of study period in 1995: (i) elementary school/high school, (ii) occupational practice, (iii) short-term/middle term/longer education, or

(iv) unknown. Information on surgical procedures, oophorectomy, and hysterectomy were determined from the NRP. Actual address at study entry was determined from the CRS and categorized into four regions: East Zealand and Bornholm (capital area), the remaining Zealand, Funen and Southern Jutland, and the remaining Jutland.

From the NRM, four time-varying indicator variables were recorded as positive upon the prescription of a minimum of 100 defined daily doses for one of four medical conditions: diabetes [A10A (insulin)/ A10B (oral anti-diabetics)], cardiac arrhythmia [C01 (anti-arrhythmic)], hypertension [C02 (antihypertensive)/C03 (diuretics)/C07 (beta-blockers)/C08 (calcium antagonists)/C09 (drugs affecting renin−angio-tensin system)] and hypercholesterolaemia [C10 (lipid lowering)]. These were used as updated confounders in the main analyses.

In total, 4388 had missing values on one of the confounders, leaving 693 710 women for analyses.

Statistical analysis

Data were analysed according to eight pre-specified time-varying hormone exposure definitions: (a) *the hormone status*: never used HT, previous HT, and current HT; (b) *length of current therapy*: short term (<1 year), middle term (1−4 years), long term (>4 years); (c) *hormone regimen*: oestrogen only therapy, cyclic combined oestrogen/ progestagen therapy, long-cycle combined oestrogen/progestagen therapy (i.e. simultaneous redemption of 7−14 times more DDD oestrogen than DDD progestogen), continuous combined oestrogen/ progestagen therapy, tibolone, and raloxifene; (d) *route of adminis-tration*: oral oestrogen, oral combined oestrogen/progestagen, dermal oestrogen, dermal combined oestrogen/progestagen, hormone-IUD, hormone-IUD, and oral oestrogen, hormone-IUD and dermal oestro-gen, and local oestrogen; (e) *type of progestagen*: Norethisterone acetate (NETA), Medroxyprogesterone (MPA), Levonorgestrel (Lng), Cyproterone acetate (CPA); (f) *dose of progestagen*; cyclic combined, continuous low dose (0.5 mg NETA or 2.5 mg MPA), continuous high dose (≥1 mg NETA or ≥5 mg MPA); (g) *type of oestrogen*: conjugated equine oestrogen, non-conjugated oestrogen; (h) *dose of oestrogen* (only non-conjugated): low (<1 mg), middle (1−2 mg), and high (>2 mg).

When data were recorded, the person years and events with various levels of (f) *progestagen dose* and (g) *oestrogen type* were too few to determine the estimates for these pre-specified HT definitions. In addition, the following categories of variables had too little exposure and few MI to determine estimates: Raloxifene in (c) *hormone regimen*, hormone-IUD combinations in (d) *route of administration*, and CPA in (e) *type of progestagen*.

In the analysis of the axes, (a) *hormone status* and (b) *length of therapy* women never on systemic HT in the same age band was the reference group. Analysing the axis, the (c) *hormone regimen*, no HT (including vaginal treatment) group was used as the reference since local treat-ment was one of the levels in this axis.

Included confounders were crude model including age and calendar year, the adjusted models, including additionally education and four geo-graphical areas, and the fully adjusted model, including also medication vari-ables on diabetes, anti-arrhythmic, anti-hypertensive, and lipid-lowering medicine. Finally, duration adjusted models in which the various levels of exposure in the (c−h) definitions mentioned above were additionally sub-categorized according to the duration of the therapy.

Data was analysed by Poisson regression analysis on a data set con-sisting of risk time (women-years) and number of MI events for each combination of exposure axis, age band, and included confounders. Age was used as the timescale in the analyses, and women were divided into 5 year age bands (51−54, 55−59, 60−64, and 65−69 years), assuming constant risk of MI within each band.

As a model control, each model was checked for significance of an interaction between age (51−54, 55−59, 60−64, and 65−69 years) and exposure-axis as well as between age and each of the confounders. To eliminate random findings due to multiple testing, we lowered the *P*-value to 0.01 in the interaction testing. In some of the models, the interaction between age and exposure definitions was found to be sig-nificant in simple adjusted models, and consequently the results con-cerning these axes are presented in 5 year age bands.

Interactions between HT exposure and concomitant use of other medications (anti-diabetics, anti-arrhythmic, anti-hypertensive, and lipid-lowering medicine) were calculated.

Rate ratio estimates and 95% confidence intervals were calculated for each model. The statistical software used for the analysis was SAS, version 8.2.

Results

The 698 098 women in the cohort resulted in 2 952 635 women-years of observation; 74% did not use HT during the observation period, 7% were previous users, and 19% were current users of hormones at censoring.

The risk of MI was associated with age, lower education, anti-hypertensive, and anti-diabetic medication, with taking anti-arrhythmic and lipid-lowering medicine (*Table 1*). The use of HT was positively associated with antihypertensive medication and gynaecological surgery, and inversely associated with the use of anti-diabetic medicine (*Table 1*).

Hormone status and risk of myocardial infarction

Compared with women who never used HT, the relative risk of MI with current use of HT among women aged 51−70 was 1.03 (95% CI: 0.95−1.11) and with past use was 0.81 (95% CI: 0.71−0.93). The risk associated with the use of hormones varied across age groups, as there was a significant interaction between age groups and HT status in the crude model (*P* = 0.005); however, this inter-action was not significant in the fully adjusted model (*P* = 0.10). In the age group 51−54 years, the current use of hormones was associated with an increased risk of MI [RR 1.24 (1.02−1.51)]. In the older age groups, the relative risk was 0.92 (0.80−1.06) (*Table 2*). In women of 60−69 years of age, the previous use was associated with a decreased risk of MI. Exclusion of women who had an oophorectomy did not change the risk in women of 51−54 years of age [RR 1.26 (1.04−1.53)], nor did it influence the estimates of the older women (data not shown).

Duration of hormone therapy

Compared with women who never used HT, the risk according to the duration of HT was 1.06 (0.92−1.23), 1.03 (0.93−1.14), and 0.99 (0.85−1.16) for short-term (<1 year), middle term (1−4 years), and long-term (>4 years) use, respectively (*P* = 0.016). In the younger age groups, we observed an increased risk of MI with increasing duration of systemic HT, which was not observed in the older age groups (*Table 2*). There was significant interaction between age groups and duration of HT in the crude model (*P* = 0.007); this interaction, however, was not significant in the fully adjusted model (*P* = 0.12). In the analyses of the various axes

Table I Distribution of person years among healthy Danish women aged 51–70 years observed from 1995 to 2000

	Year of birth	Women-years	%	MI	Rate	Women 1 January 2000	Current	Previous	Never
Age	1925–1929	250 838	8.4	856	3.4	*	*	*	*
	1930–1934	610 737	20.5	1740	2.8	95 524	13.9	7.1	79.0
	1935–1939	728 707	24.4	1221	1.7	114 925	19.3	10.1	70.6
	1940–1944	919 428	30.8	847	0.9	150 293	23.2	12.4	64.4
	1945–1949	477 359	16.0	283	0.6	149 093	20.3	11.0	68.7
Education	Elementary School	1 570 921	52.6	3454	2.2	249 738	17.4	10.2	72.4
	Occupational practice	901 304	30.2	1071	1.2	164 007	21.4	10.8	67.8
	Further education	458 301	15.3	319	0.7	86 881	23.6	10.5	65.9
	Unknown	56 542	1.9	103	1.8	9209	16.7	10.6	72.7
Geographical area	Metropolitan and Bornholm	1 040 257	34.8	1489	1.4	178 282	22.4	11.3	66.3
	Other Zealand	327 634	11.0	664	2.0	55 282	17.9	10.4	71.7
	Funen and Southern Jutland	537 581	18.0	851	1.6	91 207	20.5	10.7	68.8
	Other Jutland	1 081 596	36.2	1943	1.8	185 064	17.4	9.6	73.0
Medication	No lipid lowering	2 946 890	98.7	4720	1.6	499 721	19.8	10.5	69.7
	Lipid lowering	40 178	1.4	227	5.6	10 114	16.8	11.4	71.8
	No anti-arrhythmic	2 950 837	98.8	4489	1.5	503 688	19.4	10.5	70.1
	Antiarrhythmic	36 231	1.2	458	12.6	6147	20.3	10.9	68.8
	No anti-hypertensive	2 235 800	74.9	2036	0.9	367 769	18.5	9.8	71.7
	Anti-hypertensive	751 268	25.2	2911	3.9	142 066	23.0	12.2	64.8
	No anti-diabetic	2 922 307	97.8	4466	1.5	497 405	20.0	10.5	69.5
	Anti-diabetic	64 761	2.2	481	7.4	12 430	11.4	8.8	79.8
Gynaecological operation	No hysterectomy	2 727 946	91.3	4619	1.7	451 278	17.5	9.9	72.6
	Hysterectomy	259 122	8.7	328	1.3	58 557	37.4	14.8	47.8
	No oophorectomy	2 921 899	97.8	4850	1.7	496 673	18.8	10.4	70.8
	Oophorectomy	65 170	2.2	97	1.5	13 162	54.3	15.1	30.6

Myocardial infarctions (absolute and rate per 1000 women years) and hormone therapy (%) at 1 January 2000 according to the various background variables in analyses.
*Not included in the cohort 1 January 2000 due to inclusion of women aged 51–70 years.

categorized according to the duration of therapy, no consistent association with duration was found (data not shown).

Hormone regimen

The highest risk of MI was found with continuous combined therapy when compared with women who never used HT [RR 1.35 (1.18–1.53)] (*Table 2*), whereas the risk associated with cyclic combined regimen was 0.92 (0.81–1.05) and with tibolone was 0.80 (0.54–1.20). The difference in risk between women on continuous combined therapy vs. women on cyclic combined therapy, and vs. women on tibolone was significant, with *P*-values of <0.001 and 0.007, respectively. Unopposed oestrogen was not associated with the risk of MI and was not significantly different from the risk with cyclic combined therapy (*P* = 0.39).

The *P*-value for the interaction between age and HT regimen in the fully adjusted model was 0.09. For all age groups, the highest risk was found with continuous combined regimens (*Figure 1*).

Route of administration

There was a significantly decreased risk of MI [RR 0.62 (0.42–0.93)] with dermal unopposed oestrogen compared with women who never used HT (*Table 2*). The risk associated with dermal unopposed oestrogen was significantly lower than for oral

unopposed oestrogen use (*P* = 0.04). In women on combined therapy, no difference was detected between whether the treatment was administered orally or dermal (*P* = 0.33).

Vaginal oestrogen was associated with a significantly decreased risk of MI [RR 0.56 (0.44–0.71)].

Oestrogen dose

There was no overall indication of an increased risk of MI with increasing oestrogen dose (*Table 2*).

Progestagen type

Norethisterone acetate was the only progestagen administered with the continuous combined regimen. Consequently, NETA-containing regimens were subdivided as to whether they were administered in a continuous or cyclic combined regimen. For cyclic combined regimens, no indication of a differential effect with various progestagen types was detected (*Table 2*).

Interaction between hormone therapy and other medications

There were no significant interactions between the use of hormones and concomitant medications for diabetes, anti-arrhythmic, anti-hypertensives, or lipid-lowering medicine (*Figure 2*).

Table 2 Risk of myocardial infarction (MI) in the various hormone therapy (HT) categories

HT Status	Age	Women-years	MI	Rate per 1000 women year	Crude RR	95% CI		Adjusted RR	95% CI	
Systemic HT status (*P* < 0.0001)										
Never	51–54	610 880	374	0.61	1.00			1.00		
	55–59	569 331	660	1.16	1.00			1.00		
	60–64	510 796	1110	2.17	1.00			1.00		
	65–69	488 409	1598	3.27	1.00			1.00		
Previous	51–54	66 689	38	0.57	0.95	0.68	1.33	0.84	0.60	1.18
	55–59	70 228	76	1.08	0.96	0.76	1.22	0.94	0.74	1.19
	60–64	43 800	67	1.53	**0.72**	**0.57**	**0.93**	**0.74**	**0.57**	**0.94**
	65–69	27 338	64	2.34	**0.73**	**0.57**	**0.94**	**0.77**	**0.60**	**0.99**
Current	51–54	177 340	143	0.81	**1.32**	**1.09**	**1.60**	**1.24**	**1.02**	**1.51**
	55–59	192 103	207	1.08	0.93	0.80	1.09	0.96	0.82	1.12
	60–64	120 247	274	2.28	1.06	0.93	1.21	1.11	0.97	1.27
	65–69	75 473	211	2.80	0.86	0.75	0.99	0.92	0.80	1.06
Duration systemic HT (*P* < 0.0001)										
<1 year	51–54	54 291	42	0.77	1.21	0.88	1.67	1.18	0.86	1.63
	55–59	41 516	42	1.01	0.82	0.60	1.13	0.84	0.61	1.15
	60–64	23 297	69	2.96	**1.27**	**1.00**	**1.63**	**1.33**	**1.04**	**1.70**
	65–69	15 717	50	3.18	0.91	0.69	1.21	0.95	0.72	1.27
1–4 years	51–54	101 337	78	0.77	1.28	1.00	1.63	1.20	0.94	1.53
	55–59	108 221	115	1.06	0.93	0.76	1.14	0.96	0.79	1.17
	60–64	64 511	148	2.29	1.07	0.90	1.28	1.13	0.95	1.35
	65–69	40 547	111	2.74	0.85	0.70	1.03	0.91	0.75	1.11
>4 years	51–54	21 672	23	1.06	**1.81**	**1.19**	**2.77**	**1.59**	**1.04**	**2.44**
	55–59	42 366	50	1.18	1.06	0.79	1.07	1.07	0.80	1.44
	60–64	32 439	57	1.76	0.85	0.65	1.11	0.89	0.68	1.16
	65–69	19 209	50	2.60	0.83	0.63	1.11	0.89	0.67	1.19
Regimen[a] (*P* < 0.0001)										
Never any HT		2 082 277	3596	1.73	1.00			1.00		
Oestrogen		179 742	288	1.60	0.97	0.86	1.09	0.94	0.83	1.06
Long cycle combined		26 097	34	1.30	1.98	0.70	1.37	1.07	0.76	1.50
Cyclic combined		220 121	244	1.11	0.85	0.75	0.97	0.92	0.81	1.05
Continuous combined		118 135	244	2.07	**1.28**	**1.13**	**1.46**	**1.35**	**1.18**	**1.53**
Tibolone		19 457	24	1.23	0.70	0.47	1.05	0.80	0.54	1.20
Route[a] (*P* < 0.0001)										
Never any HT		2 082 277	3596	1.73	1.00			1.00		
Oral oestrogen		148 388	264	1.78	1.02	0.90	1.16	0.98	0.67	1.12
Dermal oestrogen		31 354	24	0.77	**0.61**	**0.41**	**0.91**	**0.62**	**0.42**	**0.93**
Oral combined		358 615	523	1.46	1.01	0.92	1.11	1.08	0.98	1.19
Dermal combined		25 196	23	0.91	0.82	0.54	1.23	0.95	0.63	1.43
Vaginal		68 723	69	1.00	**0.54**	**0.42**	**0.68**	**0.56**	**0.44**	**0.71**
Oestrogen dose[a] (*P* < 0.0001)										
Never any HT		2 082 277	3596	1.73	1.00			1.00		
Unopposed low		35 979	51	1.42	0.91	0.69	1.20	0.91	0.69	1.20
Unopposed medium		114 381	202	1.77	1.03	0.90	1.19	1.00	0.87	1.16
Unopposed high		17 463	25	1.43	0.87	0.59	1.30	0.82	0.55	1.21
Cont comb low		6195	10	1.61	1.14	0.61	2.13	1.30	0.70	2.42
Cont comb medium		111 939	234	2.09	**1.29**	**1.13**	**1.47**	**1.35**	**1.18**	**1.54**
Cont comb high		21 116	39	1.85	1.35	0.98	1.85	1.36	0.99	1.86

Continued

Table 2 *Continued*

HT Status	Age	Women-years	MI	Rate per 1000 women year	Crude RR	95% CI		Adjusted RR	95% CI	
Progestagen type[a] (*P* < 0.0001)										
Never any HT		2 082 277	3596	1.73	1.00			1.00		
NETA continuous		118 134	244	2.07	**1.28**	**1.13**	**1.46**	**1.35**	**1.18**	**1.53**
NETA cyclic		131 167	154	1.17	0.89	0.76	1.05	0.95	0.81	1.12
MPA cyclic		42 905	46	1.07	0.90	0.67	1.21	0.98	0.73	1.31
LEVO cyclic		32 451	33	1.02	0.72	0.51	1.01	0.78	0.56	1.10

The crude analyses were adjusted for age and calendar year. The adjusted analyses are additionally adjusted for education, employment status, habitation, and medication for hypertension, heart conditions, hyperlipidaemia, or diabetes. *P*-values for the significance of the various hormone therapy categories are in brackets. Significant results are in bold. NETA, Norethisterone acetate; MPA, Medroxy progesterone acetate; LEVO, Levonorgestrel.

[a]The reference group was never any systemic HT (excluding vaginal administration).

Discussion

On the basis of national observational data, overall we found no association between HT and MI. We found an increased risk of MI among younger women on HT, which was correlated to the duration of use; no such correlation was found in older women on HT.

For all age groups, the highest risk was found with combined regimens. For the regimen equivalent to the WHI regimen, we found comparable estimates despite differences in design. The hazard ratio for unopposed oestrogen in the WHI was 0.95 (0.79–1.16); our estimate 0.94 (0.83–1.06). For combined regimens, WHI found an HR of 1.24 (1.00–1.54), while we calculated an RR of 1.35 (1.18–1.53).

Our age-stratified estimates were higher for the youngest age groups compared with the WHI results. Of note, our study had no information on menopausal status, although the majority in the young age group were postmenopausal due to the cut off at 51 years. However, the group who never used HT includes premenopausal women, and as late menopause possibly protects against ischaemic heart disease, suggesting that the risk estimate associated with HT in this group will be elevated.

Women oophorectomized at a young age have early menopause and are therefore at an increased risk of MI. To what extent HT decreases the risk of MI in these women is not known. Excluding these women from the group who never used HT should increase our risk estimate. On the other hand, excluding them from the current user group should not necessarily decrease the estimates, as HT may counteract the increased risk of MI in these oophorectomized women. We conducted analyses in which we excluded the oophorectomized women and found no change in these elevated risks among younger women. With these considerations, our data do not support the timing hypotheses that perimenopausal hormone therapy is associated with a reduced risk of cardiovascular disease.[15,16]

We found lower risk with cyclic combined than with continuous combined therapy. Cyclic regimens were not previously tested in randomized designs, and previous observational studies had limited power to test the differences between various combined regimens.[12,17] Unfortunately, the available data did not allow us to test whether this is due to the differential dose of progestagen or whether it is based on the regimen *per se*. When cyclic regimens were considered, we found no significant difference in risk

between HT with MPA, used in the USA, and NETA, which is mostly used in the Scandinavian countries. We found lower risk associated with dermal application, especially of unopposed oestrogen, in accordance with other studies.[18] This interesting finding may possibly be explained by reduced activation of the haemostatic system due to the avoidance of the first pass hepatic effect.[19–21] We found a surprisingly low risk of MI with vaginal oestrogen, which should have little or no systemic effect. A biological effect here may be possible. Alternatively, this may be caused by residual confounding. This finding should be confirmed from other studies before clinical recommendations are given.

We were not able to test the effect of conjugated estrogens vs. 17 β-estradiol, as conjugated estrogens are infrequently used in Denmark. We found no clear association between oestrogen dose and risk of MI.

We do not believe that a healthy user bias was in effect for several reasons. First, previous studies have no evidence of such a bias.[12,13] Secondly, we adjusted for education, and thirdly, women taking hormones were more frequently on medication against hypertension and cardiac arrhythmia, although more seldom on anti-diabetics.

We found no indication that women with pre-existing medically treated diabetes, hypercholesterolemia, hypertension, or heart arrhythmics had increased risk with HT, in contrast to our previous finding from the Danish Nurse Cohort Study in which diabetic women had a higher relative risk with hormones than those without diabetes.[12] However, our data did not include the potential important confounders, weight and body fat distribution, both are potential confounders.[22]

Among the strengths of our study were the National unselected data. Denmark has free access to medical care and, to some extent, public refunds of medical expenses. Consequently, HT is generally not associated with a healthy user lifestyle.[13] The data were collected before the results from the WHI were published, implying stable exposure during the study period. We had daily updated information on HT exposure and complete records of all hospitalized events from the NRP with high validity.[23]

Several limitations should be noted. Information on HT exposure is based on whether prescriptions are redeemed. In a previous validation study, we found high agreement between self-reported
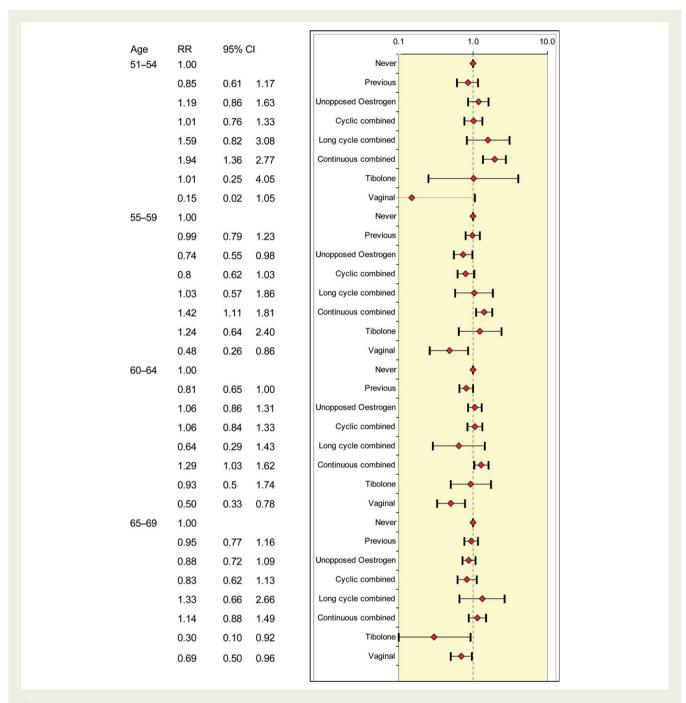
Figure 1 The age-stratified risk of myocardial infarction with various hormone therapy regimens from multivariable model. Rate ratios (RR) with 95% confidence intervals (95% CI) are presented.

HT use and redeemed prescriptions.[24] In contrast to classical cohort studies, the time window used in this study could result in exposure misclassification due to truncation of the database in 1995; this allowed older women who used HT in their 50s to be misclassified as having never used HT instead of as classification as previous users of HT. However, the influence of HT on coronary heart disease seems to be quite immediate.[25] Consequently, this circumstance should have minimal influence on our cardiovascular analyses. Also, no information was available on individual risk factors such as physical activity, smoking, and alcohol habits, which could result in residual confounding. However, we do have individual information on education level and habitation, as well as the use of other medication for medical conditions that under other circumstances might be considered intermediate variables.

Conclusion

Our study found risk estimates of MI comparable with estimates in randomized clinical studies. Our data suggest a lower risk with cyclic combined than with continuous combined therapy, and low risk with dermal or vaginal application of oestrogen.
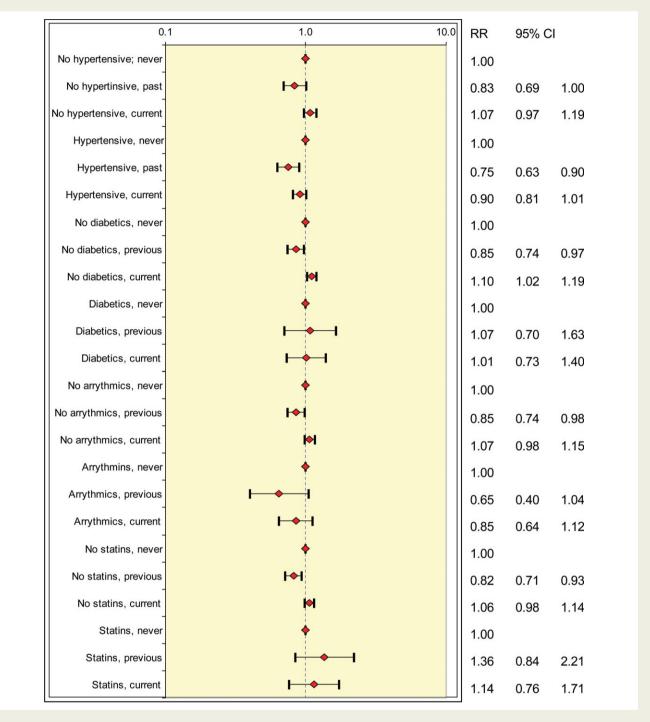
Figure 2 Rate ratios (RR) with 95% confidence intervals (95% CI) of the risk of myocardial infarction with current and previous use of hormone therapy compared with no HT use stratified by concomitant use of various medications. *P*-values from interaction terms between hormone status and medical variable was, respectively, 0.07 for anti-hypertensive, 0.51 for anti-diabetic, 0.17 for anti-arrhythmic, and 0.17 for lipid-lowering in full model adjusting for all significant covariates (education, habitation, and calendar year).

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