Maturitas 94 (2016) 106–109

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Decreased mortality risk due to first acute coronary syndrome in women with postmenopausal hormone therapy use

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ARTICLE INFO

Article history:
Received 19 July 2016
Received in revised form
26 September 2016
Accepted 27 September 2016

Keywords:
Estrogen
Myocardial infarction
Case fatality

ABSTRACT

Objectives: The role of postmenopausal hormone therapy (HT) in the incidence of acute coronary syndrome (ACS) has been studied extensively, but less is known of the impact of HT on the mortality risk due to an ACS.
Study design and main outcome measures: We extracted from a population-based ACS register, FINAMI, 7258 postmenopausal women with the first ACS. These data were combined with HT use data from the National Drug Reimbursement Register; 625 patients (9%) had used various HT regimens. The death risks due to ACS before admission to hospital, 2–28, or 29–365 days after the incident ACS were compared between HT users and non-users with logistic regression analyses.
Results: In all follow-up time points, the ACS death risks in HT ever-users were smaller compared to non-users. Of women with HT ever use, 42% died within one year as compared with 52% of non-users (OR 0.62, $p < 0.001$). Most deaths (84%) occurred within 28 days after the ACS, and in this group 36% of women with ever use of HT (OR 0.73, $p = 0.002$) and 30% of women with ≥5 year HT use (OR 0.54, $p < 0.001$) died as compared to 43% of the non-users. Age ≤60 or >60 years at the HT initiation was accompanied with similar reductions in ACS mortality risk.
Conclusions: Postmenopausal HT use is accompanied with reduced mortality risk after primary ACS.

1. Introduction

Abundant data exist on the role of postmenopausal hormone therapy (HT) in the incidence of coronary heart disease (CHD), often manifesting as acute coronary syndrome (ACS) [1,2]. In contrast, less is known of the possible impact of HT use on the mortality risk due to primary ACS [3]. Such an effect appears plausible, since coronary arteries express estrogen receptors [4]. These receptors are also present in the cardiac rhythmic conducting system, perhaps preventing life-threatening arrhythmias that are prone to occur in association with ACS [5]. Moreover, estrogen triggers the release of vasodilatory and antiaggregatory substances, such as nitric oxide and prostacyclin from the coronary endothelium [4], which may stabilize atherosclerotic plaques and limit hypoxic myocardial damage after ACS [6]. It is also possible that a number of indirect vascular benefits of estrogen use before ACS, such as improvements in profiles of lipids, lipoproteins, inflammatory mediators and matrix metalloproteinases, may contribute to plaque stabilization and smaller myocardial damage. Thus, it is possible that the positive vascular effects of estrogen are of importance during and after ACS and may contribute to the outcome of ACS. We therefore compared the mortality risk due to primary ACS in women with and without HT use.

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http://dx.doi.org/10.1016/j.maturitas.2016.09.015
0378-5122/

2. Methods

The FINAMI register, founded in 1993, is targeted to characterize ACS in Finland [7]. It operates in the southwestern (city of Turku), eastern (cities of Kuopio and Joensuu, and some adjacent rural areas), and northern districts (city of Oulu) Finland. The FINAMI register aims at recording every ACS event in the monitored populations. The FINAMI register in practice represents the situation in the urban areas of the whole country, while the coverage of rural areas may be limited.

All patients who died of ACS (both in and out of hospital deaths) in the study districts can be identified from this register. These data have been collected from hospital files, death certificates, autopsy reports and medico-legal documents by trained nurses under the control of register physicians, using standardized protocols. The ACS as a cause of death was confirmed by changes seen in premortal electrocardiograms and biomarkers reflecting myocardial necrosis, using the AHA 2003 case definitions [8]. Deaths were entered into the register with ICD-10 codes I20–I25, I46, R96, R98 or ICD-9 codes 410–414, 798 (not 798A). The ACS event was considered as first for the particular patient ("incident") if there was no history of a clinically recognized ACS. The data were sent to a coordinating center at the National Institute for Health and Welfare and checked against the national hospital discharge register and the national causes of death register using a personal identification code, to ensure the complete coverage of all ACS events.

We identified 7258 women with their first ACS during 1995–2009. The use of HT at >40 years of age by these patients was assessed from the National Drug Reimbursement Register. In Finland, HT is available only by a doctor's prescription, and a part of the price of the HT (42–50% during the study period) is reimbursed by the national health insurance. Thus, all Finnish women buying HT since 1994 (=opening year for this register) have been entered into this register. Because we could not know exactly whether the first HT purchase in the opening year 1994 was really the first one for a given woman, we included only those who bought their first HT on 1.1.1995 or later. Women must visit the pharmacy at three month intervals to get their HT regimens; all of these HT purchases are entered into the register. Thus, a woman failing to purchase additional HT regimens was judged to have discontinued her HT regimen. Because women often discontinue the use of HT gradually, we set the date of discontinuation as the date of the last HT purchase plus six months. Therefore, the last eligible date for a HT purchase in this study was 30.6.2009.

The HT regimens used in Finland contain exclusively estradiol, and the cumulative days of estradiol exposure were calculated based on the type of HT regimen (oral or transdermal). Non-hysterectomized women used progestin as a 10–14 day course in 1–3 month intervals (=sequential combination therapy) or every day (continuous combination therapy). The identification and classification of HT used were based on the trade names of the commercial products. Exposure days to HT were added up for each woman regardless of the order these exposures accumulated. Due to the limited number of cases, various types of systemic HT (estradiol-only and estradiol-progestin therapy) regardless of the route of administration were analyzed as one group. Possible use of vaginal estrogens, alone or concomitantly with systemic HT was not considered as a confounding factor.

The models were adjusted for age, diabetes, hypertension and hyperlipidemia. Other clinical factors for ACS, such as smoking, was not available for women who died before reaching the hospital. The analyses were also adjusted for study area and study year. Pre-hospital mortality was defined as death before hospitalization or in the emergency room (<1 day from ACS). After the ACS, the follow-up consisted of 2–28 and 29–365 days. As most deaths (84%) occurred within 0–28-days (including pre-hospital and 2–28 days) after ACS, different HT exposures and different ages at the HT initiation were analyzed solely in this group.

The research committee at the Helsinki University Central Hospital approved the study. Approvals to use confidential register data in scientific research were obtained from the following authorities: 1. the National Institute for Health and Welfare (THL/1370/5.05.00/2010), 2. Statistics Finland (TK-53-1560-10), and 3. Social Insurance Institution of Finland (KELA 40/522/2014).

Table 1
Background characteristics of women with or without postmenopausal systemic hormone therapy use who had experienced their first-ever myocardial infarction during 1995–2009.

	Hormone therapy use		p-value
	Yes	No	
Number of women	625	6633	N/A
Age in years (mean ± SD)	68.8 (10.2)	80.4 (10.2)	<0.001
Diabetes(%)	21.3	28.1	<0.001
Smoking[b] (%)	28.0	14.2	<0.001
Treated hypertension	24.3	26.8	0.19
Total cholesterol[a] millimoles/l (mean ± SD)	4.8 (1.0)	5.1 (1.4)	<0.001
Hyperlipidemia	25.9	17.6	<0.001

[a] Information on clinical characteristics is more complete in patients who survived to hospital.
[b] Information on smoking was available only for 50% of patients.

3. Results

Of the 7258 women with their first ACS, 625 (9.0%) had used HT (Table 1). Women with HT use were younger than non-users at the time of the first ACS. Despite of having a diagnosis of hyperlipidemia more often than non-users, HT users had lower levels of total cholesterol and suffered more seldom from diabetes than did non-HT users. As regards treated hypertension, the study groups were comparable (Table 1). Smoking was more prevalent in HT users, but data was missing from 50% of the women. Only 56 of the HT users (9.0%) who survived ACS continued to use HT (data not shown).

In all follow-ups, the ACS death risks in ever-users of HT were lower compared to non-users (Table 2). Within the first post-ACS year, 42.4% of women with HT use died as compared to 51.7% of the non-users ($p < 0.001$).

Most deaths (84%) occurred within 0–28-days after ACS, and in this group 35.7% of women with HT ever use (OR 0.70, $p < 0.001$) and 29.8% of women with ≥5 year HT use (OR 0.52, $p < 0.001$) died as compared to 43.4% of the non-users (Table 3). The ACS death risk was comparable in HT users who had initiated HT <60 or ≥60 years of age (Table 4).

4. Discussion

We compared the mortality risk due to the first ACS in postmenopausal women who had been exposed to HT for various time periods to that of women without any HT use. Both previous and current HT use were accompanied with comparable decreases in ACS mortality. This finding is in line with previous reports showing better in-hospital survival [9] and post-hospital survival rates after ACS [10] in HT users compared with non-users. The HT-use related reductions in ACS death risk were seen for ever-HT users in the total series, but in more detailed analyses, the risk reduction was most significant if HT use had exceeded five years. Our findings may be in line with randomized data showing that only long-term HT exposure is accompanied by reductions both in the incidence and mortality of ACS [11], whereas a shorter HT duration, such as in the Women's Health Initiative –study [2], did not affect ACS mortality. It has been also suggested that HT has cardiac benefit only if initiated before 60 years of age ("window theory") [1], but in our