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

Pauliina Tuomikoski[a], Veikko Salomaa[b], Aki Havulinna[b], Juhani Airaksinen[c], Matti Ketonen[d], Heli Koukkunen[e], Olavi Ukkola[f], Y. Antero Kesäniemi[f], Heli Lyytinen[a], Olavi Ylikorkala[a], Tomi S. Mikkola (MD PhD)[a,g,*]

[a] University of Helsinki and Helsinki University Hospital, Department of Obstetrics and Gynecology, 00029 Helsinki, Finland
[b] THL-National Institute for Health and Welfare, PO BOX 30, 00271 Helsinki, Finland
[c] Heart Center, Turku University Hospital and Department of Clinical Medicine, University of Turku, Turku, Finland
[d] Central Hospital of North Karelia, Joensuu, Finland
[e] University of Eastern Finland, Kuopio, Finland
[f] Research Institute of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
[g] Folkhälsan Research Center, Biomedicum, 00029 Helsinki, Finland

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.

* Corresponding author at: Helsinki University Hospital, Department of Obstetrics and Gynecology, Haartmaninkatu 2, PO Box 140, FIN–00029 HUS, Helsinki, Finland.
E-mail address: tomi.mikkola@hus.fi (T.S. Mikkola).

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

Table 2
Age-adjusted fatality rates (%) and odds ratios of death after the first acute coronary syndrome in relation to ever-use of postmenopausal hormone therapy (HT).

	Hormone therapy use		Odds ratio (95% confidence interval)
	Yes	No	
Pre-hospital (0-1 days)	22.1%, n = 113	25.8%, n = 1963	0.77 (0.62–0.96), p = 0.023
2–28 days	18.5%, n = 67	24.7%, n = 1496	0.68 (0.51–0.90), p = 0.007
29–365 days	12.5%, n = 21	17.0%, n = 649	0.56 (0.38–0.83), p = 0.004
Within 1 year	42.4%, n = 211	51.7%, n = 4108	0.62 (0.52–0.76), p < 0.001

Table 3
0–28-day mortality after first acute coronary syndromes compared in women with and without a history of postmenopausal hormone therapy (HT) use.

	Women (% death[a])	Odds ratio[b] (95% confidence interval)	p-value
No HT	6633 (43.4%)	1	Not applicable
Ever HT use	625 (35.7%)	0.70 (0.57–0.86)	p < 0.001
Exposure <5 years	415 (38.4%)	0.79 (0.63–1.00)	p = 0.051
≥5 years	210 (29.8%)	0.52 (0.37–0.75)	p < 0.001

[a] Age-adjusted.
[b] Adjusted for age, diabetes, hypertension, hyperlipidemia, study area, and study year.

Table 4
0–28-day mortality due to first acute coronary syndrome in relation to the age at the initiation of postmenopausal hormone therapy (HT) or timing of HT use.

	Number of women	Odds ratio[a](95% confidence interval)	p-value
HT started ≤60 years			
Ever use	324	0.65 (0.48–0.88)	p = 0.006
Current use[b]	189	0.44 (0.29–0.67)	p < 0.001
HT started >60 years			
Ever use	301	0.73 (0.57–0.94)	p = 0.016
Current use[b]	106	0.47 (0.30–0.74)	p = 0.001
HT started at any age			
Ever use	625	0.74 (0.60–0.90)	p = 0.002
Current use[b]	295	0.47 (0.34–0.63)	p < 0.001

[a] Adjusted for age, diabetes, hypertension, hyperlipidemia, study area, and study year.
[b] Last purchase ≤6 months prior to event.

study the use of HT was accompanied with comparable ACS death risk reductions if initiated before or after 60 years of age. Thus, the reduction in cardiac mortality in Finnish HT users [12] may not only be a reflection of decreased incidence of CHD, but could be, at least in part, caused by a reduced case fatality after the ACS, as shown by our present data.

We cannot deduce which components of HT, estradiol alone, progestins or a combination of them contributed to the death risk reductions after an ACS. However, it is likely that estradiol was the causative agent, since it has been associated with beneficial cardiovascular effects [5,6]. Estradiol, which is exclusively used in HT regimens in Finland, is more beneficial to the cardiovascular system than conjugated equine estrogens, used commonly in the USA [13,14]. Moreover, estradiol lowers cholesterol levels and reduces the risk of diabetes [2,15]. A lower prevalence of diabetes was present in HT users in our series, perhaps due to the effect of estradiol, although a healthy women bias cannot be excluded. Furthermore, estradiol induces beneficial alterations in antioxidant and apoptotic properties of blood vessels that may enhance myocyte survival and limit myocardial damage after coronary artery occlusion [5,6]. Estradiol also increases the release of vasoactive substances, such as nitric oxide and prostacyclin [16], which increase vasodilatation and thus enhance blood flow to the injured area. Prostacyclin is also a potent inhibitor of platelet aggregation arresting thrombus formation and growth, thus limiting the degree of coronary artery occlusion and consequent myocardial damage [4,17,18]. Moreover, decreased heart rate variability after ACS is associated with a risk of sudden cardiac death [19], and the use of HT stabilizes heart rate variability, and thus possibly protects against fatal cardiac arrhythmias [20]. All these mechanisms of estradiol action may have contributed to the death risk reduction after ACS seen in our study.

Only 56 women continued the use of HT after an ACS in our study. This patient group was so small that it was not feasible to analyze the impact of the continued use of HT on the recurrence risk of ACS. Some data imply that the de novo start of HT after ACS increases the risk of recurrence [21], while other data speak for the safety of the continuation of HT after the first ACS [22–25].

Our data warrant some caution. First, the number of women with ACS and HT use was rather small limiting definite conclusions. Second, as in all observational data, a “healthy women” bias may have been present, i.e. more health-conscious women may choose to use HT. Such a possible bias may primarily concern the incidence of ACS, but perhaps also the death risk to some degree. Moreover, the patients who had used HT were younger at the time of ACS than patients who had been classified as non-users. It is possible that some older women had used HT regimens before our register opening. However, we know with certainty that no patients classified as HT non-users had used any HT between 1995 and 2009. Failure to record possible HT use before 1995 should not cause any major error, since all our death risk comparisons were carried out as age-adjusted. Third, HT is reimbursed by the state in Finland, and Finnish HT users have shown to be rather comparable to non-users [26]. Access to primary and secondary care of ACS is also basically free of charge, and thus, no bias should arise in the availability of treatment before or after incident ACS. Finally, our patient series was too small to allow comparisons between different HT regimens or routes of administration.

The strengths of our study include accurate and reliable data on both HT use and the outcomes of ACS. The ACS register is supervised by cardiologists and the National Institute for Health and Welfare.

During the last few decades, CHD mortality in women has markedly decreased in Finland [7]. This is due to improvements in treatment of risk factors, such as hypertension and hypercholesterolemia, but also due to developments in ACS treatments. However, our 15-year study period covers improvements in acute and secondary ACS treatments, which are similar in both HT users and non-users.

5. Conclusion

The use of HT is accompanied with reduced mortality risk after primary ACS. This may be a result of estradiol-induced cardiac benefits before and/or during ACS event.

Conflicts of interest

T.M. has been a speaker and/or received consulting fees from Mylan and Novo Nordisk. P.T. has been a speaker and/or received consulting fees from Mylan and Orion, and received funding for congress trips from Mylan. The other authors report no conflicts of interest.

Funding

This work was supported by a special governmental grant for health sciences research (grant to Tomi S Mikkola), the Finnish Foundation for Cardiovascular Research (grant to Veikko Salomaa), and an unrestricted grant from the 1.3 milj. klubi-klubben (grant to Pauliina Tuomikoski).

Ethical approval

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).

Contributors

PT, VS, HL, OY and TSM made substantial contributions to the conception, design and interpretation of data for the work.

AH, JA, MK, HK, OU, and YAK made substantial contributions to the acquisition, analysis, and interpretation of data for the work.

All authors drafted the work and revised it critically for important intellectual content; and gave a final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

[1] H.N. Hodis, W.J. Mack, Hormone replacement therapy and the association with coronary heart disease and overall mortality: clinical application of the timing hypothesis, J. Steroid. Biochem. Molec. Biol. 142 (2014) 68–75.
[2] J.E. Manson, R.T. Chlebowski, M.L. Stefanick, et al., Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials, JAMA 310 (2013) 1353–1368.
[3] A. Pines, Post-myocardial infarction hormone therapy revisited, Climacteric 15 (2012) 538–541.
[4] R.A. Khalil, Estrogen vascular estrogen receptor and hormone therapy in postmenopausal vascular disease, Biochem. Phamacol. 86 (2013) 1627–1642.
[5] J.R. Bell, G.B. Bernasochi, U. Varma, A.J. Raaijmakers, L.M. Delbridge, Sex and sex hormones in cardiac stress–mechanistic insights, J. Steroid. Biochem. Mol. Biol. 137 (2013) 124–135.
[6] M.E. Mendelsohn, R.H. Karas, Molecular and cellular basis of cardiovascular gender differences, Science 308 (2005) 1583–1587.
[7] V. Salomaa, A.S. Havulinna, H. Koukkunen, et al., Aging of the population may not lead to an increase in the numbers of acute coronary events: a community surveillance study and modelled forecast of the future, Heart 99 (2013) 954–959.
[8] R.V. Luepker, F.S. Apple, R.H. Christenson, et al., Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA council on epidemiology and prevention; AHA statistics committee; world heart federation council on epidemiology and prevention; the european society of cardiology working group on epidemiology and prevention; centers for disease control and prevention; and the national heart, lung, and blood institute, Circulation 108 (2003) 2543–2549.
[9] M.G. Shlipak, B.G. Angeja, A.S. Go, et al., Hormone therapy and in-hospital survival after myocardial infarction in postmenopausal women, Circulation 104 (2001) 2300–2304.
[10] A.H. Tackett, A.L. Bailey, J.M. Foody, et al., Hormone replacement therapy among postmenopausal women presenting with acute myocardial infarction: insights from the GUSTO-III trial, Am. Heart J. 160 (2010) 678–684.
[11] L.L. Schierbeck, L. Rejnmark, C.L. Tofteng, et al., Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial, BMJ 345 (October (9)) (2012) e6409.
[12] T.S. Mikkola, P. Tuomikoski, H. Lyytinen, et al., Estradiol-based postmenopausal hormone therapy and the risk for cardiovascular and all cause mortality, Menopause 22 (2015) 976–983.
[13] C.L. Shufelt, C.N. Bairey Merz, R.L. Prentice, et al., Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the women's health initiative observational study, Menopause 21 (2013) 260–266.
[14] N.L. Smith, M. Blondon, K.L. Wiggins, et al., Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens, JAMA Intern. Med. 174 (2014) 25–31.
[15] V. Salomaa, J. Rasi, E. Pekkanen, et al., Association of hormone replacement therapy with hemostatic and other cardiovascular risk factors the FINRISK hemostasis study, Arterioscler. Thromb. Vasc. Biol. 15 (1995) 1549–1555.
[16] T. Mikkola, P. Turunen, K. Avela, A. Orpana, L. Viinikka, O. Ylikorkala, 17 beta-estradiol stimulates prostacyclin, but not endothelin-1, production in human vascular endothelial cells, J. Clin. Endocrinol. Metab. 80 (1995) 1832–1836.
[17] V.M. Miller, S.P. Duckles, Vascular actions of estrogens: functional implications, Pharmacol. Rev. 60 (2008) 210–241.
[18] E. Murphy, Estrogen signaling and cardiovascular disease, Circ. Res. 109 (2011) 687–696.
[19] R.E. Kleiger, P.K. Stein, J.T. Bigger Jr., Heart rate variability: measurement and clinical utility, Ann. Noninvasive Electrocardiol. 10 (2005) 88–101.
[20] H. Lantto, P. Haapalahti, P. Tuomikoski, et al., Vasomotor hot flashes and heart rate variability: a placebo-controlled trial of postmenopausal hormone therapy, Menopause 19 (2012) 82–88.
[21] K.P. Alexander, K. Newby, A.S. Hellkamp, et al., Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up, J. Am. Coll. Cardiol. 38 (2001) 1–7.
[22] R.B. Heckbert, R.C. Kaplan, N.S. Weiss, et al., Risk of recurrent coronary events in relation to use and recent initiation of postmenopausal hormone therapy, Arch. Intern. Med. 161 (2001) 1709–1713.
[23] N. Cherry, K. Gilmour, P. Hannaford, et al., Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial, Lancet 360 (2002) 2001–2008.
[24] D.M. Bretler, P.R. Hansen, R. Sørensen, et al., Discontinuation of hormone replacement therapy after myocardial infarction and short term risk of adverse cardiovascular events: nationwide cohort study, BMJ 344 (March (27)) (2012) e1802.
[25] E. Windler, P. Stute, O. Ortmann, A.O. Mueck, Is postmenopausal hormone replacement therapy suitable after a cardio- or cerebrovascular event? Arch. Gynecol. Obstet. 291 (2015) 213–217.
[26] P. Topo, R. Luoto, E. Hemminki, A. Uutela, Declining socioeconomic differences in the use of menopausal and postmenopausal hormone therapy in Finland, Maturitas 32 (1999) 141–145.