Piret Veerus

The Impact of Postmenopausal Hormone Therapy on Health and Use of Health Services

Experience from the Estonian Postmenopausal Hormone Therapy (EPHT) Trial

National Research and Development Centre
for Welfare and Health

Research Report 168

Electronic dissertation
Acta Electronica Universitatis Tamperensis 669
ISBN 978-951-44-7134-6
ISSN 1456-954X
http://acta.uta.fi

The research presented in this series has been approved for publication after undergoing a formal referee evaluation process.

Translations of the abstract: Done Information Oy

Cover design: Harri Heikkilä
Layout: Christine Strid

ISBN 978-951-33-2024-9
ISSN 1236-0732

Gummerus Printing
Vaajakoski 2007

Abstract

Piret Veerus. The Impact of Postmenopausal Hormone Therapy on Health and Use of Health Services: Experience from the Estonian Postmenopausal Hormone Therapy (EPHT) Trial. STAKES, Research Report 168. Helsinki, Finland 2007.
ISBN 978-951-33-2024-9

Introduction: At the time of starting the trial, knowledge of the long-term effects of hormone therapy (HT) was based on non-experimental studies, but the use of HT was rapidly increasing. The main anticipated long-term benefits of HT were to be prevention of osteoporosis and related fractures and a possible prevention of cardiovascular diseases. In addition to studying the long-term health effects of HT, the aim of the EPHT trial was to ascertain the effect of HT on health-related quality of life, symptoms of menopause, on the use of health services and health care costs.

From 1993 to 1998, the Women's Health Initiative (WHI) trial recruited participants in the United States into a randomised HT trial with a planned duration of 8.5 years. In 1999, the European Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) trial was started in the United Kingdom. It was planned that EPHT trial would be carried out in co-operation with the WISDOM trial, with the duration of the EPHT trial being five years. However, due to the premature stopping of the WHI trial and its findings, the WISDOM trial was cancelled at an early stage. Trial treatment in the EPHT trial was also stopped preterm, the decision being based on the published results of the WHI trial.

Objective: The aims of this study were to use the framework of a randomised preventive trial to study the effects of continuous combined HT among healthy women on the incidence of coronary heart disease, cerebrovascular disease, total cancer and bone fractures over time; to study the effect of HT on quality of life and symptom reporting; to study the use of health services and health care costs related to HT; and to study the use of prescription medication by HT users versus non-users.

Material and methods: 1 823 postmenopausal women aged 50 to 64 years at the time of sampling were recruited into a randomised preventive trial in Estonia between 1999 and 2001. In order to study the utilization of health services and to determine the health care costs due to postmenopausal hormone therapy, a non-blind sub-trial was used in parallel to the blind one. Altogether, 796 women were recruited into the blind sub-trial and allocated either to active treatment or placebo, and 1 027 women were recruited into the non-blind sub-trial and allocated either to open-label hormone therapy or no treatment.

The drug in oral daily use in the treatment arms contained 0.625 mg of conjugated oestrogens and 2.5 mg of medroxyprogesterone acetate or matched placebo. In the non-blind control arm, women used no treatment. Women who had been in menopause for less than three years received daily orally 0.625 mg of oral conjugated oestrogens and 5.0 mg of medroxyprogesterone acetate or placebo in the treatment arms. The rate of women using more than 80% of allocated trial treatment dropped approximately 50% during the first trial year, and remained nearly the same throughout the trial. Less than 10% of women started taking prescribed HT in the non-blind control arm. The trial treatment was planned for five years, but after the release of the results from the WHI trial the Data Monitoring Committee recommended to stop trial treatment, which was completed preterm by May 2004.

The minimal follow-up time was 2.00 years and maximal 4.97 years. The mean follow-up time was 3.43 years for the ascertainment of clinical outcomes and use of health services, 3.60 years for analysing the effect of HT on health-related quality of life and menopausal symptoms and 4.40 for the analysis of prescription medication usage during the trial. Women were followed by annual questionnaires and annual linkages to the Estonian Cancer Registry, to the Estonian Health Insurance Fund and to the Estonian Mortality Database. The response rate was 75% to the first annual survey, 69% to the second annual survey, 68% to the third annual survey, and 81% to the final survey mailed at the end of the trial. There was no difference in the annual response rates between the trial arms. Follow-up through registries is assumed to have been complete.

Results: The combined hazard ratio for coronary heart disease after adjustment by blinding, age at recruitment and former oral contraceptive use in the HT arms was 1.12 (95% CI: 0.90–1.40). The adjusted hazard ratio in the HT arms for cerebrovascular disease was 1.24 (95% CI: 0.85–1.82) and for total cancer 1.36 (95% CI: 0.73–2.52). The adjusted hazard ratio for bone fractures in the HT arms was 0.61 (95% CI: 0.42–0.89).

There were less women in the HT arms reporting hot flushes (OR 0.54; 95% CI: 0.41–0.71) and sweating (OR 0.74; 95% CI: 0.58–0.93), but more women reporting vaginal bleeding (OR 8.40; 95% CI: 3.27–27.43) at the end of the trial. HT also alleviated sleeping problems, but had a negative effect on backache. There was no difference in the prevalence of other symptoms or quality of life scores between the trial arms over time.

Within the non-blind sub-trial, the number of all health care visits was 10% higher and the number of visits to family practitioners 16% higher per person-year in the HT arm. Per person-year, the number of vaginal sonograms was 14% and the number of electrocardiograms 19% higher in the HT arm of the non-blind sub-trial. Outpatient health care costs and drug expenses were higher in the

non-blind HT arm. In the blind sub-trial, the number of gynaecologic operations, vaginal sonograms and total health care costs was higher in the HT arm.

The proportion of women using any prescription medication besides HT did not differ between the arms. The type of prescribed drugs varied between the arms. After combining data from both HT arms, the combined hazard ratio was 1.26 (95% CI: 1.05–1.53) for the use of calcium channel blockers, 1.48 (95% CI: 1.10–1.99) for local vaginal treatment, 0.70 (95% CI: 0.50–0.99) for hypnotics and sedatives and 0.77 (95% CI: 0.60–0.99) for selective serotonin reuptake inhibitors (SSRIs).

Conclusions: According to the results from the EPHT trial, combined HT reduced bone fractures in healthy women. The trial provided no evidence of benefits from combined HT for coronary heart disease, cerebrovascular disease, or total cancer. The results are consistent with the findings from the WHI trial.

Combined HT alleviated vasomotor symptoms and sleeping problems, but added bleeding episodes and backache among postmenopausal women, and had no effect on quality of life among participants of the EPHT trial.

Postmenopausal HT increased expenses on drugs and outpatient health care. The increase in outpatient health care costs was due to additional health care visits and medical procedures in the HT arms. HT did not increase the overall use of prescription medication other than hormone therapy, but the types of drugs used in hormone therapy and non-therapy arms varied, with increased use of calcium channel blockers for hypertension and local vaginal treatments for vaginal candidiasis and decreased use of hypnotics, sedatives and selective serotonin reuptake inhibitors in the HT arms.

Key-words: postmenopausal hormone therapy; randomised preventive trial; health effects; use of health services and prescription medication; health care costs; quality of life; symptoms of menopause

Summary in Finnish

Piret Veerus. The Impact of Postmenopausal Hormone Therapy on Health and Use of Health Services: Experience from the Estonian Postmenopausal Hormone Therapy (EPHT) Trial [Vaihdevuosien jälkeisen hormonihoidon vaikutus terveyteen ja terveyspalveluiden käyttöön: kokemuksia Virossa suoritetusta vaihdevuosihormonihoitokokeesta]. STAKES, Research Report 168. Helsinki 2007.
ISBN 978-951-33-2024-9

Johdanto: Tutkimusta aloitettaessa tiedot hormonihoidon pitkäaikaisvaikutuksista perustuivat ei-kokeellisiin tutkimuksiin, mutta silti hormonihoito yleistyi nopeasti. Pitkäaikaisen hormonihoidon odotettiin ehkäisevän osteoporoosia ja siihen liittyviä luunmurtumia sekä mahdollisesti myös sydän- ja verisuonitauteja. Pitkäaikaisten terveysvaikutusten lisäksi EPHT-tutkimuksessa pyrittiin selvittämään hormonihoidon vaikutuksia elämänlaatuun, vaihdevuosioireisiin, terveyspalveluiden käyttöön ja terveydenhuollon kustannuksiin.

Yhdysvalloissa rekrytoitiin vuosina 1993–1998 osallistujia satunnaistettuun WHI (Women's Health Initiative) hormonihoitokokeeseen, jonka oli suunniteltu kestävän 8,5 vuotta. Vuonna 1999 Isossa-Britanniassa puolestaan aloitettiin eurooppalaisten naisten vaihdevuosien hormonihoidon vaikutuksia tutkiva WISDOM-tutkimus (European Women's International Study of Long Duration Oestrogen after Menopause). Viisivuotiseksi suunniteltu EPHT-tutkimus oli tarkoitus toteuttaa yhteistyössä WISDOM-tutkimuksen kanssa. WHI-tutkimus kuitenkin lopetettiin ennenaikaisesti, ja tämän sekä saatujen tutkimustulosten seurauksena myös WISDOM-tutkimus keskeytettiin. Julkaistujen WHI-tulosten johdosta myös Viron EPHT-tutkimuksen lääkehoito lopetettiin ennenaikaisesti.

Tavoitteet: Ehkäisevän satunnaistetun hormonihoitokokeen tavoitteena oli selvittää yhdistelmävalmisteen vaikutus terveiden naisten sepelvaltimotaudin, aivoverenkierron häiriöiden, syöpien ja luunmurtumien ilmaantuvuuteen pitkällä aikavälillä. Lisäksi pyrittiin selvittämään hormonihoidon vaikutuksia elämänlaatuun ja oireiden raportoimiseen, terveyspalveluiden käyttöön ja terveydenhuollon kustannuksiin sekä vertaamaan reseptilääkkeiden käyttöä hormonihoitoa saavien ja hormonihoitoa käyttämättömien naisten välillä.

Aineisto ja menetelmät: Vuosina 1999–2001 Virossa rekrytoitiin ehkäisevään satunnaistettuun kokeeseen 1 823 otantahetkellä iältään 50–64-vuotiasta vaihdevuodet ohittanutta naista. Sokkotutkimuksen rinnalla toteutettiin avoin tutkimus, jolloin voitiin selvittää vaihdevuosien jälkeisen hormonihoidon vaikutuksia terveyspalveluiden käyttöön ja terveydenhuollon kustannuksiin. Sokkotutkimukseen osallistui yhteensä 796 naista ja avoimeen tutkimukseen 1 027 naista. Sokkoryhmä

jaettiin kahteen haaraan, joista toinen sai hormonilääkettä ja toinen lumelääkettä. Avoimessa tutkimusryhmässä toinen haara sai hormonilääkettä, kun taas toinen haara ei saanut mitään lääkettä tai hoitoa.

Osallistujat ottivat päivittäin suun kautta lääkettä, joka sisälsi 0,625 mg konjugoitua estrogeenia ja 2,5 mg medroksiprogesteroniasetaattia, tai lumelääkettä. Avoimen tutkimuksen kontrolliryhmä ei saanut mitään hoitoa. Jos vaihdevuosista oli alle kolme vuotta, suun kautta otettu hormonilääke sisälsi 0,625 mg konjugoitua estrogeenia ja 5,0 mg medroksiprogesteroniasetaattia, tai oli lumelääkettä. Ensimmäisen vuoden aikana yli 80 prosenttia annetuista lääkkeistä käyttäneiden naisten osuus laski noin puoleen. Määrä pysyi lähes muuttumattomana tutkimuksen ajan. Alle 10 prosenttia avoimen haaran kontrolliryhmän naisista alkoi käyttää lääkärin määräämiä hormonilääkkeitä. Lääkehoidon pituudeksi oli suunniteltu viittä vuotta, mutta WHI-tutkimuksen tulosten julkaisemisen seurauksena tutkimuksen puolueeton seurantaryhmä suositteli lääkehoidon lopettamista, ja se päätettiin lopettaa ennenaikaisesti toukokuussa 2004.

Lyhyin seuranta-aika oli 2,00 vuotta ja pisin 4,97 vuotta. Kliinisten vaikutusten ja terveyspalveluiden käytön osalta seuranta-ajan keskimääräinen pituus oli 3,43 vuotta. Hormonihoidon vaikutusta elämänlaatuun ja vaihdevuosioireisiin analysoitiin keskimäärin 3,60 vuoden seuranta-ajan jälkeen. Kokeen aikana käytettyjen reseptilääkkeiden määrän analysoinnissa keskimääräinen seuranta-aika oli 4,40 vuotta. Tietoja naisten voinnista kerättiin vuosittain sekä naisille lähetetyllä kyselyllä että selvittämällä tiedot Viron syöpärekisteristä, sairausvakuutusrahastosta ja kuolinsyytilastoista. Osallistujista 75 prosenttia vastasi ensimmäiseen kyselyyn, 69 prosenttia seuraavan vuoden kyselyyn, kolmannen vuoden kyselyyn vastasi 68 prosenttia ja viimeiseen kyselyyn, joka postitettiin tutkimuksen lopussa, vastasi 81 prosenttia. Vuosikyselyihin vastanneiden osuuksissa ei ollut eroja tutkimuksen eri haarojen välillä. Rekistereiden kautta tapahtuneen seurannan oletettiin olleen 100-prosenttinen.

Tulokset: Kun sokkouttaminen, osallistumisikä ja aikaisempi ehkäisypillerien käyttö oli vakioitu, hormonihoitohaarojen yhdistetty sepelvaltimotaudin suhteellinen vaara (HR) oli 1,12 (95 %:n luottamusväli 0,90–1,40). Hormonihoitohaarojen aivoverenkierron häiriöiden vakioitu suhteellinen vaara (HR) oli 1,24 (95 %:n luottamusväli 0,85–1,82) ja syöpien vakioitu suhteellinen vaara (HR) 1,36 (95 %: n luottamusväli 0,73–2,52). Hormonihoitohaarojen luunmurtumien vakioitu suhteellinen vaara (HR) oli 0,61 (95 %:n luottamusväli 0,42–0,89).

Tutkimuksen päättyessä hormonihoitohaaroissa raportoitiin vähemmän kuumia aaltoja (Oddin luku [OR] 0,54; 95 %:n luottamusväli 0,41–0,71) ja hikoilua (Oddin luku 0,74; 95 %:n luottamusväli 0,58–0,93), mutta enemmän vuotoja (Oddin luku 8,40; 95 %:n luottamusväli 3,27–27,43). Hormonihoito helpotti nukkumisvaikeuksia, mutta vaikutti negatiivisesti selkäsärkyihin. Tutkimushaarojen välillä ei todettu eroa muiden oireiden esiintymisessä tai elämänlaadussa.

Avoimessa osatutkimuksessa hormonihoitoa saavien naisten kaikkien terveydenhuoltokäyntien määrä oli 10 prosenttia suurempi ja perhelääkärin vastaanotolla käyntien määrä 16 prosenttia suurempi henkilövuotta. Avoimen tutkimuksen hormonihoitoa saavien naisten haarassa emättimen ultraäänitutkimuksia oli 14 prosenttia ja sydänfilmejä 19 prosenttia enemmän henkilövuotta kohden kuin kontrollihaarassa. Avohoidon kustannukset ja lääkekulut olivat suuremmat avoimen tutkimuksen hormonihoitoa saavien naisten haarassa. Sokkotutkimuksessa gynekologisia leikkauksia ja kohdun ultraäänitutkimuksia tehtiin enemmän ja terveydenhuollon kokonaiskustannukset olivat suuremmat hormonihoitoa saavien naisten kuin lumelääkettä saavien haarassa.

Hormonihoidon lisäksi muita reseptilääkkeitä käyttävien naisten osuudessa ei ollut eroja tutkimuksen eri haarojen välillä. Reseptilääkkeiden tyypit vaihtelivat eri haaroissa. Kun tiedot molemmista hormonihoitoa saavista tutkimushaaroista yhdistettiin, yhteenlaskettu kalsiumkanavan salpaajien käytön suhteellinen vaara (HR) oli 1,26 (95 %:n luottamusväli 1,05–1,53), paikallisten emätinlääkkeiden käytön suhteellinen vaara oli 1,48 (95 %:n luottamusväli 1,10–1,99), uni- ja rauhoittavien lääkkeiden käytön suhteellinen vaara 0,70 (95 %:n luottamusväli 0,50–0,99) ja serotoniinin takaisinoton estäjien käytön suhteellinen vaara oli 0,77 (95 %:n luottamusväli 0,60–0,99).

Pohdinta: EPHT-kokeesta saatujen tulosten mukaan yhdistelmähormonihoito vähensi terveiden naisten luunmurtumia. Tutkimustulokset eivät anna aihetta olettaa, että yhdistelmähormonihoito ehkäisisi sepelvaltimotautia, aivoverenkierron häiriöitä tai syöpiä. Tutkimuksen tulokset vastaavat WHI-tutkimuksen löydöksiä.

Yhdistelmähormonihoito lievitti vasomotorisia oireita ja nukkumisvaikeuksia, mutta lisäsi vuotoja ja selkäsärkyä vaihdevuodet ohittaneilla naisilla. Hormonihoito ei vaikuttanut EPHT-kokeeseen osallistuneiden naisten elämänlaatuun.

Vaihdevuosien jälkeinen hormonihoito kasvatti lääkekuluja ja avohoidon kustannuksia. Avohoidon kustannusten kasvu johtui hormonihoitoa saavien naisten lisääntyneestä terveydenhoitokäyntien ja lääkinnällisten toimenpiteiden määrästä. Itse hormonivalmisteita lukuun ottamatta hormonihoito ei lisännyt reseptilääkkeiden käytön määrää. Hormonihoitoa saavien naisten tutkimushaaroissa ja ilman hoitoa olevien naisten tutkimushaaroissa oli eroavaisuuksia käytettyjen lääkkeiden tyypeissä: Hormonihoitoa saavien naisten tutkimushaaroissa verenpainetaudin hoidossa käytettiin kalsiumkanavan salpaajia ja emättimen hiivatulehduksesta johtuvia paikallishoitoja enemmän kuin tutkimushaaroissa, joissa ei käytetty hormonihoitoa. Sen sijaan unilääkkeiden, rauhoittavien lääkkeiden ja serotoniinin takaisinoton estäjien käyttö oli vähäisempää.

Avainsanat: vaihdevuosien jälkeinen hormonihoito, ehkäisevä satunnaistettu koe, terveysvaikutukset, terveyspalveluiden käyttö, reseptilääkkeiden käyttö, terveydenhuollon kustannukset, elämänlaatu, vaihdevuosioireet, Viro

Summary in Swedish

Piret Veerus. The Impact of Postmenopausal Hormone Therapy on Health and Use of Health Services: Experience from the Estonian Postmenopausal Hormone Therapy (EPHT) Trial [Inverkan av postmenopausal hormonterapi på hälsan och användningen av hälsotjänster: erfarenheter från en studie av postmenopausal hormonterapi i Estland (EPHT)]. STAKES, Research Report 168. Helsinki 2007.
ISBN 978-951-33-2024-9

Inledning: När studien inleddes baserade sig kunskaperna om de långvariga effekterna av hormonterapi (HT) på icke-experimentella studier, men användningen av HT höll på att öka i snabb takt. De huvudsakliga långtidsfördelarna med HT förväntades vara förebyggande avseende osteoporos och till denna relaterade frakturer, samt eventuellt avseende kardiovaskulära sjukdomar. Utöver att HT:s långtidseffekter på hälsan skulle undersökas var avsikten med EPHT-studien att säkerställa HT:s effekt på den hälsorelaterade livskvaliteten, de menopausala symtomen, användningen av hälso- och sjukvårdstjänster och kostnaderna för hälso- och sjukvården.

Från 1993 till 1998 rekryterades i Förenta Staterna, i studien Women's Health Initiative (WHI), deltagare till en randomiserad HT-studie, som var planerad att vara i 8,5 år. År 1999 inleddes studien European Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) i Storbritannien. Enligt planerna skulle EPHT-studien genomföras i samarbete med WISDOM-studien och vara i fem år. WISDOM-studien avslutades emellertid på ett tidigt stadium på grund av att WHI-studien avbröts i förtid och på grund av resultaten i den. Behandlingen i EPHT-studien avbröts också i förtid, vilket berodde på de resultat som publicerats från WHI-studien.

Mål: Avsikterna med denna studie var att använda strukturen för randomiserad preventiv studie för att undersöka effekterna av kontinuerlig kombinerad HT bland friska kvinnor på incidensen för kranskärlssjukdomar, cerebrovaskulära sjukdomar, totala antalet cancerfall och frakturer över tid. Vidare för att studera effekten av HT på livskvaliteten och symtom som rapporteras, och för att studera användningen av hälso- och sjukvårdstjänster och kostnaderna för hälso- och sjukvård relaterad till HT samt för att studera användningen av ordinerade mediciner hos dem som använder HT jämfört med dem som inte använder HT.

Material och metoder: 1 823 postmenopausala kvinnor, som var i åldern 50 till 64 år när samplingen utfördes, rekryterades till en randomiserad preventiv studie i Estland mellan åren 1999 och 2001. För att studera användningen av hälso- och sjukvårdstjänster och utreda hälso- och sjukvårdskostnaderna för postmenopausal

hormonterapi användes en icke-blind delstudie parallellt med den blinda. Sammanlagt 796 kvinnor rekryterades till den blinda delstudien och allokerades antingen till hormonbehandling eller placebo, och 1 027 kvinnor rekryterades till den icke-blinda delstudien och allokerades antingen till öppen hormonterapi eller till ingen behandling.

Läkemedlet i oralt dagligt bruk i behandlingsarmarna innehöll 0,625 mg konjugerat östrogen och 2,5 mg medroxiprogesteronacetat eller matchat placebo. I den icke-blinda kontrollarmen använde kvinnorna ingen behandling. Kvinnor som hade varit i menopausen i mindre än tre år fick dagligen oralt 0,625 mg konjugerat östrogen och 5,0 mg medroxiprogesteronacetat eller placebo i behandlingsarmarna. Andelen kvinnor som använde mer än 80 % av den i studien allokerade behandlingen sjönk med ungefär 50 % under studiens första år, och förblev ungefär på denna nivå under hela studien. Mindre än 10 % av kvinnorna började ta ordinerad HT i den icke-blinda kontrollarmen. Behandlingen i studien planerades vara i fem år, men efter att resultaten i WHI-studien offentliggjordes rekommenderade den oberoende övervakningskommittén (Data Monitoring Committee) att behandlingen avbryts, vilket gjordes före utsatt slutdatum i maj 2004.

Uppföljningstiden varierade från 2,00 år till 4,97 år. Medelvärdet för uppföljningstiden var 3,43 år för fastställandet av kliniska resultat och användningen av hälsotjänster, 3,6 år för analys av HT:s effekt på den hälsorelaterade livskvaliteten och de menopausala symtomen och 4,40 för analys av användningen av de läkemedel som ordinerades under studien. Kvinnorna följdes upp med årliga frågeformulär och årliga kopplingar till Estlands cancerregister, hälsoförsäkringsfond och mortalitetsdatabas. Svarsfrekvensen var 75 % i den första årliga enkäten, 69 % i den andra årliga enkäten, 68 % i den tredje årliga enkäten och 81 % i den avslutande enkäten som postades i slutet av studien. Det fanns ingen skillnad i de årliga svarsfrekvenserna mellan behandlingsarmarna. Uppföljningen via registren antas ha varit fullständig.

Resultat: Den kombinerade riskkvoten (hazard ratio) för kranskärlssjukdomar efter justering med blindning, ålder vid rekryteringen och tidigare oral användning av preventivmedel i HT-armarna var 1,12 (95 % CI:0,90–1,40). Den justerade riskkvoten (hazard ratio) i HT-armarna för cerebrovaskulära sjukdomar var 1,24 (95 % CI: 0,85–1,82) och för total cancer 1,36 (95 % CI: 0,73–2,52). Den justerade riskkvoten (hazard ratio) för frakturer i HT-armarna var 0,61 (95 % CI: 0,85–0,89).

I HT-armarna var det färre kvinnor som rapporterade blodvallningar (OR 0,54; 95 % CI: 0,41–0,71) och svettning (OR 0,74; 95 % CI: 0,58–0,93), men fler kvinnor som rapporterade vaginal blödning (OR 8,40; 95 % CI: 3,27–27,43) i slutet av studien. HT lindrade också sömnproblemen men hade en negativ effekt på ryggsmärta. Det fanns ingen skillnad över tid i förekomsten av andra symtom eller i resultatet i fråga om livskvaliteten mellan behandlingsarmarna.

I den icke-blinda delstudien var antalet av alla hälsovårdsbesök 10 % högre och antalet besök hos familjeläkare 16 % högre per personår i HT-armen. Antalet vaginala ultraljudsundersökningar var 14 % och antalet elektrokardiogram 19 % högre per personår i HT-armen i den icke-blinda delstudien. Kostnaderna för poliklinikvård och läkemedel var högre i den icke-blinda HT-armen. I den blinda delstudien var antalet gynekologiska operationer och vaginala ultraljudsundersökningar samt de totala hälso- och sjukvårdskostnaderna högre i HT-armen än i placeboarmen.

Andelen kvinnor som använde någon annan ordinerad medicinering än HT skiljde sig inte mellan armarna. Typerna av ordinerade läkemedel varierade mellan armarna. Efter kombinering av data från de båda HT-armarna var den kombinerade riskkvoten (hazard ratio) 1,26 (95 % CI: 1,05–1,53) för användning av kalciumkanalblockerare, 1,48 (95 % CI: 1,10–1,99) för lokal vaginalbehandling, 0,70 (95 % CI: 0,50–0,99) för sömnmedel och lugnande medel och 0,77 (95 % CI: 0,60–0,99) för selektiva serotoninåterupptagshämmare (SSRI-preparat).

Slutsatser: Enligt resultaten i EPHT-studien reducerade kombinerad HT frakturerna hos friska kvinnor. Studien gav inga bevis för nyttan av kombinerad HT för kranskärlssjukdomar, cerebrovaskulära sjukdomar eller totala antalet cancerfall. Resultaten är överensstämmande med resultaten i WHI-studien.

Kombinerad HT lindrade de vasomotoriska symtomen och sömnproblemen men ökade antalet blödningar och ryggsmärtorna bland postmenopausala kvinnor och hade ingen effekt på livskvaliteten bland deltagarna i EPHT-studien.

Postmenopausal HT ökade utgifterna för läkemedel och öppen hälso- och sjukvård. Kostnadsökningen för den öppna hälso- och sjukvården berodde på ett ökat antal hälso- och sjukvårdsbesök och medicinska åtgärder i HT-armarna. HT ökade inte den totala användningen av andra ordinerade mediciner än de som användes vid hormonterapin, men typerna av läkemedel som användes i hormonterapiarmarna skiljde sig från dem som användes i icke-terapi-armarna. I HT-armarna användes i större utsträckning kalciumkanalblockerare för hypertoni och lokala vaginalbehandlingar för vaginal candidiasis och i mindre utsträckning sömnmedel, lugnande medel och selektiva serotoninåterupptagshämmare.

Nyckelord: postmenopausal hormonterapi; randomiserad preventiv studie; hälsoeffekter; användning av hälso- och sjukvårdstjänster, användning av ordinerade läkemedel; hälso- och sjukvårdskostnader; livskvalitet; menopausala symtom

Contents

List of original publications

The present thesis is based on the following articles, which are referred to in the text by their Roman numerals:

I Veerus P, Hovi SL, Fischer K, Rahu M, Hakama M, Hemminki E. Results from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]. Maturitas 2006;55:162–73.

II Veerus P, Fischer K, Hovi SL, Karro H, Rahu M, Hemminki E. Symptom reporting and quality of life in the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757] (submitted).

III Veerus P, Fischer K, Hovi SL, Hakama M, Rahu M, Hemminki E. Postmenopausal hormone therapy increases use of health services: experience from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]. Am J Obstet Gynecol 2006;195:62–71.

IV Veerus P, Fischer K, Hovi SL, Karro H, Hemminki E. Does hormone replacement therapy affect the use of prescription medicines in postmenopausal women: experience from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]. BJOG 2007;114:548–54.

List of abbreviations

BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
CVD	cerebrovascular disease
ET	oestrogen therapy
EVTET	Estrogen in Venous Thromboembolism trial
EMEA	European Agency for the Evaluation of Medicinal Products
EPHT	Estonian Postmenopausal Hormone Therapy trial
EQ-5D	European Quality of Life questionnaire
FDA	Food and Drug Administration
HERS	Heart and Estrogen/Progestin Study
HR	hazard ratio
HT	hormone therapy
ICD-10	the 10th International Classification of Diseases
MWS	Million Women Study
RH	relative hazard
RR	relative risk
WHI	Women's Health Initiative trial
WHO	World Health Organization
WISDOM	Women's International Study of Long Duration Oestrogen after Menopause

1 Introduction

Approximately 10% of the global female population is currently either going through menopause or have already gone through it, and at least another 2% will reach this stage of life in the next decade (Skouby 2004). Several hormonal changes take place during the menopausal transition, which may cause dysfunctional uterine bleeding, hot flushes, and atrophic endothelial changes in the vagina (Sowers 2000).

Menopause is immediately followed by a period of rapid bone loss (Sowers 2000). The average woman who reaches menopause in western society has a remaining life expectancy of nearly 30 years, and her probability to develop coronary heart disease is 46%, while for stroke it is 20% (Skouby 2004). Whether the increased incidence of cardiovascular disease and diseases like diabetes, hypertension, cancer, osteoarthritis, or dementia is associated with the menopause is a matter of speculation (Sowers 2000).

Oestrogen therapy (ET) was first developed and marketed for the prevention of short-term menopausal symptoms, particularly vasomotor symptoms and urogenital tract atrophy (MacLennan et al, 2004). The first known negative effect of ET was an increase in endometrial hyperplasia sometimes leading to endometrial cancer (Cramer et al, 1979). Progestogen counters this proliferative effect, and combined progestogen and oestrogen hormone therapy is still used to relieve short-term menopausal symptoms (MacLennan et al, 2004), but may have other effects which alter its overall risk-benefit profile.

This thesis analyses the impact of hormone therapy (HT) on women's health, symptoms of menopause, health-related quality of life, use of health services, and health care costs. The data were collected prospectively between 1999 and 2004 within the randomised controlled Estonian Postmenopausal Hormone Therapy (EPHT) trial with 1823 participants.

The objective of the EPHT trial was to study:

1) the long-term health effects of HT on the risk of cardiovascular diseases, bone fractures, and cancer,
2) the immediate effect of HT on well-being and symptoms of menopause,
3) the effect of HT on the experience of climacteric, ageing and partner relationship,
4) the effect of HT on the use of health services,
5) the placebo effect and the trial effect as well as by their effect on recruitment and adherence.

At the time of starting the trial, knowledge of the long-term effects of HT was based on non-experimental studies (Hemminki 1988; McKinlay et al, 1989), but the use of hormone therapy was rapidly increasing (Barlow et al, 1989; Topo et al, 1991; Mansfield et al, 1994; Banks et al, 1996). The main anticipated long-term benefits of HT were to be prevention of osteoporosis and related fractures (Kiel et al, 1987; Gallagher et al, 1991; Felson et al, 1993) and a possible prevention of cardiovascular disease (Stampfer et al, 1991; Writing Group for the PEPI Trial, 1995). Although non-experimental studies demonstrated that HT had a favourable effect on blood lipids (Writing Group for the PEPI Trial, 1995), pooled data from small clinical trials did not show a preventive effect of HT on cardiovascular events (Hemminki and McPherson 1997).

The results from observational studies suggested that postmenopausal hormone therapy may have a beneficial effect on stroke incidence and mortality (Paganini-Hill et al, 1988; Hunt et al, 1990; Falkeborn et al, 1993; Finucane et al, 1993). An increase in the risk of deep vein thrombosis and pulmonary embolism was reported in many observational studies (Daly et al, 1996b; Daly et al, 1996c; Grodstein et al, 1996; Jick et al, 1996; Gutthann et al, 1997).

Non-experimental studies showed that combined HT did not increase incidence or mortality of uterine cancer (Persson et al, 1989; Schairer et al, 1997), but the effect of HT on breast cancer remained unclear (Yuen et al, 1993; Colditz et al, 1995; Stanford et al, 1995). There was weak evidence of a small increased risk of ovarian cancer (Risch 1996) and inconsistent evidence of decreased colorectal cancer (Risch et al, 1995; Fernandez et al, 1996; Grodstein et al, 1998; Grodstein et al, 1999) in women taking HT.

Growing interest centred on whether HT would help preserve cognitive function and confer protection against dementia (Tang et al, 1996; Kawas et al, 1997). The impact of HT use on health services utilization and health care costs was not considered important, with most cost-effectiveness analyses assuming that the effect of HT on cardiovascular diseases would be favourable (Cheung et al, 1992; Whittington et al, 2004; Samsioe 1995; Daly et al, 1996; Armstrong et al, 2001).

Estonia was chosen as a suitable site for carrying out the trial because the sales of hormone therapy as daily defined doses (DDDs) in 1995 were only 1.96 per 1000 inhabitants (Riigi Ravimiamet, 1996), and neither the women nor the physicians were expected to have strong preferences about HT. In 1994, 145 women were recruited to participate in a HT trial in the city of Tampere, Finland, organised by the same research, but contamination in the control arm was unacceptably high (Hokkanen et al, 1997).

It was planned to carry out the EPHT trial in co-operation with a European project, the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM), which was co-ordinated from the UK (Vickers et al, 2002). Drugs were donated to the EPHT trial by the Wyeth Ayerst Company via WISDOM

and the outcomes of the Estonian trial were meant to contribute to WISDOM. The trial design and follow-up of patients were partly different in the two trials because the EPHT trial aimed to study not just clinical effects but also the non-clinical effects of HT. Another contemporary long-term trial for hormone therapy was the Women's Health Initiative (WHI) trial, which recruited participants in the United States between 1993 and 1998 (Writing Group for the Women's Health Initiative Investigators, 2002). Agreement had been reached with the WISDOM and WHI researchers to combine data from the two trials to enable the detection of smaller effects and/or earlier results.

In June 2002, the combined therapy arm of the WHI trial was stopped after an average 5.2 years of treatment because the overall health risks exceeded the benefits. The WISDOM trial used the same medication as the WHI trial and was stopped in October 2002 while still recruiting participants. The decision was based on financial evaluations, assuming that ten more study years would have been needed for additional results (Vickers et al, 2002). As the collaboration between the EPHT trial and the WISDOM trial was not contract-based, the stopping of WISDOM did not have an immediate impact on the trial in Estonia. However, based on the publications from the WHI trial, the Data Monitoring Committee of the EPHT trial recommended stopping trial treatment in December 2003, and the closure visits were scheduled from January 2004 to May 2004 so as to give a thorough medical check-up to the participants, as decided by the Trial Steering Committee and requested by the trial protocol. In February 2004, the oestrogen-only arm of the WHI trial was also stopped pre-term.

The course of the EPHT trial has been described and analysed thoroughly in the doctoral dissertation of Hovi in 2006 (Hovi, 2006). Estonian women's views of the climacteric (Hovi et al, 2005a) and the comparison of women either willing and not willing to participate in the trial (Hovi et al, 2005b) have been described separately, as well as the effect of blinding on recruitment (Hemminki et al, 2004) and adherence (Vorobjov et al, 2005).

2 Review of literature

Knowledge about the different health effects of HT is more complete now than before the start of the EPHT trial. Studies with English-language abstracts identified in Medline (up to April 19, 2007) and articles listed in reference lists of key articles were searched to present the outcomes of HT on several diseases, symptoms of menopause, survival, and use of health services. Double-blind, randomised, placebo-controlled trials of oral HT with adequate sample size and for at least 12 months of duration were included (Table 1, Appendix 14). For the symptoms of menopause, also shorter trials were included. Results from observational studies were included if they have been of determined importance.

2.1 HT and health outcomes

2.1.1 HT and bone fractures

The Framingham Heart Study showed that oestrogen therapy taken at any time reduced the risk of hip fractures (RH in the publication, hereafter RR 0.65; 95% CI: 0.44-0.98) in that cohort (Kiel et al, 1987), but the changes in bone mineral density were strongly influenced by body weight change (Felson et al, 1993). Also the Million Women Study (MWS) showed a significant reduction in the incidence of bone fractures (RR 0.62; 95% CI: 0.50–0.66) among hormone therapy users, not depending on the types of hormones used (Banks et al, 2004).

The HERS study showed no significant decrease (RH in the publication, hereafter RR 0.95; 95% CI: 0.75–1.21) in bone fractures among HT users with coronary disease after 4.1 years (Hulley et al, 1998) or 6.8 years of follow-up (RR 1.04; 95% CI: 0.87–1.25) (Hulley et al, 2002). The Esprit trial showed no significant effect among women with prior myocardial infarction (The Esprit team, 2001).

The beneficial effect of combined HT on bone fractures among healthy women was proved first by some smaller studies (Heikkinen et al, 1997; Komulainen et al, 1998), and later by the WHI trial showing that both combined hormone therapy (HR 0.76, 95% CI: 0.69–0.85) and oestrogen therapy (HR 0.70, 95% CI: 0.63–0.79) reduced the risk of bone fractures (Writing Group for the Women's Health Initiative Trial, 2002; The Women's Health Initiative Steering Committee, 2004) and increased bone mineral density (Cauley et al, 2003).

Women who discontinued HT during or after the PEPI trial had similar loss in bone mineral density as women who did not undergo HT, and the loss did not depend on the duration of use (Greendale et al, 2002). Another study showed that

postmenopausal women who had earlier been treated with HT in a randomised trial had higher bone mineral density values even many years after stopping HT (Bagger et al, 2004).

2.1.2 HT and coronary heart disease

Hormone therapy was anticipated to reduce the risk of atherosclerosis (Sullivan et al, 1990; Stampfer et al, 1991; Grady et al, 1992; Writing Group for the PEPI Trial, 1995; O'Brien et al, 1996; O'Keefe et al, 1997; Sullivan et al, 1997). The data from the Nurses' Health Study showed that in the cohort of 48,470 women aged from 30 to 63, oestrogen therapy reduced the risk of coronary disease (RR 0.89; 95% CI: 0.78–1.00) (Stampfer et al, 1991). Literature reviews showed that hormone therapy should be recommended for women with coronary heart disease or at high risk for it (Grady et al, 1992), and cohort studies suggested that oestrogen therapy might be associated with prolonged survival in a population-based cohort (Persson et la, 2003), among women undergoing coronary angiography (Sullivan et al, 1990), bypass grafting (Sullivan et al, 1997), or coronary angioplasty (O'Keefe et al, 1997).

Thus, it was unexpected when the HERS I trial showed no overall effect (RR 0.99; 95% CI: 0.81–1.22) for secondary prevention of coronary heart disease (CHD) after 4.1 years of combined hormone therapy (Hulley et al, 1998). An additional 2.7 years of follow-up in the HERS II did not produce evidence of later risk reduction for CHD events (RR 1.00; 95% CI: 0.77–1.29), and the risk was not altered by statin use (Grady et al, 2002).

Since then, numerous small trials have been completed that confirm the overall null effects of HT both on primary and secondary prevention of CHD (de Kleijn et al, 1999; Herrington et al, 2000; Clarke et al, 2002; Angerer et al, 2001; Viscoli et al, 2001; Waters et al, 2002; the Esprit team, 2002; Hodis et al, 2003). Still the publication of the results from the large WHI trial (Writing Group for the WHI Initiative, 2002) showing that after a mean 5.2 years of follow-up, combined hormone therapy increased the risk of coronary heart disease among healthy users (HR 1.29, 95% CI: 1.02-1.63) was a shock for the public audience. The results from the WHI oestrogen-only arm confirmed also that oestrogens did not provide any protection against myocardial infarction or coronary death (HR 0.91; 95% CI: 0.75–1.12) (Hsia et al, 2006).

For women who initiated HT within 10 years of menopause in the WHI trial, the risk of CHD was non-significantly reduced (HR 0.76; 95% CI: 0.50–1.16) (Rossouw et al, 2007).

2.1.3 HT and stroke

Cohort studies suggested that postmenopausal hormone therapy may reduce the incidence of stroke (Falkeborn et al, 1993; Finucane et al, 1993) and the risk of dying from stroke (Paganini-Hill et al, 1988; Hunt et al, 1990).

The WEST trial showed that the risk of fatal stroke was higher among oestrogen therapy users with prior ischemic stroke or transient ischemic attack (RR 2.9; 95% CI: 0.9–9.0), and their non-fatal strokes were associated with worse functional deficits (Viscoli et al, 2001). The Esprit trial showed an increased risk of stroke (RR 1.64; 95% CI: 0.60–4.47) among women with prior myocardial infarction (The Esprit team, 2001).

The WHI trial showed that combined hormone therapy increased the risk of ischemic stroke (HR 1.44; 95% CI: 1.09–1.90), but not the risk of hemorrhagic stroke (HR 0.82; 95% CI: 0.43–1.56) among healthy women (Wassertheil-Smoller et al, 2003) and that oestrogen therapy also increased the risk of stroke (HR 1.39; 95% CI: 1.10–1.77)(Women's Health Initiative Steering Committee, 2004). The WHI trial data showed that the increased risk of stroke among HT users did not vary by age or time since menopause (Rossouw et al, 2007).

2.1.4 HT and deep vein thrombosis

A two- to three-fold increase in the risk of deep vein thrombosis and pulmonary embolism was reported in four case-control studies (Daly et al, 1996b; Jick et al, 1996; Daly et al, 1996c; Gutthann et al, 1997) and one cohort study (Grodstein et al, 1996), the effect not being modified by progestogen. A recent case-control study suggested that oral but not transdermal HT is associated with an increased risk of venous thromboembolism (Canonico et al, 2007).

The HERS I trial reported an increased risk for venous thromboembolism (RR 2.66; 95% CI: 1.41–5.04) in combined hormone therapy users with coronary heart disease after 4.1 years of use (Hulley at el, 1998; Grady et al, 2000). The risk was decreased with aspirin or statin use (Grady et al, 2000) and declined by time during HERS II (RR 1.40; 95% CI: 0.64–3.05) after 6.8 years of use (Hulley et al, 2002). The oestrogen in the venous thromboembolism trial (EVTET) showed an increased risk of recurrent venous thromboembolism during hormone therapy (Hoibraaten et al, 2000). The Esprit trial showed an increase of deep vein thrombosis (RR 1.96; 95% CI: 0.18–21.6) and pulmonary embolism events (RR 0.98; 95% CI: 0.25–3.91) among women with prior myocardial infarction (The Esprit team, 2001). The WHI trial observed a significant increase in pulmonary embolism (HR 2.13, 95% CI: 1.39–3.25) among healthy users of combined HT (Writing Group for the WHI Initiative, 2002), and a non-significant increase (HR 1.34; 95% CI: 0.87–2.06) among healthy users of oestrogen therapy (Women's Health Initiative Steering

Committee, 2004). The risk associated with combined hormone therapy increased with age, obesity, and factor V Leiden (Cushman et al, 2004).

2.1.5 HT and atherosclerosis

Cohort studies showed that HT may prevent carotid atherosclerosis, as assessed by ultrasound (Jonas et al, 1996; Le Gal et al, 2003). A 2-year trial did not demonstrate any benefit from HT on carotid intima-media thickness (de Kleijn et al, 1999). In a 1-year trial among healthy women, HT did not inhibit progression of carotid atherosclerosis (Angerer et al, 2001) or femoral artery atherosclerosis (Angerer et al, 2002). After 3 years of follow-up, no difference in the percentage of coronary stenosis was detected in a randomized HT trial of women with coronary artery lesions (Hodis et al, 2003).

In the HERS trial, combined HT had no effect on the progression of carotid atherosclerosis (Byington et al, 2002) and did not reduce peripheral arterial events (RR 0.87; 96% CI: 0.66–1.14) in women with pre-existing CHD (Hsia et al, 2000). The incidence of peripheral arterial events (carotid disease, lower extremity disease, and abdominal aneurysm) was non-significantly higher among adherent participants in the combined hormone therapy arm of the WHI trial (HR 1.23; 95% CI: 0.79–1.91) over the 5.6 years of follow-up (Hsia et al, 2004) and also in the oestrogen alone arm (HR 1.32; 95 % CI: 0.99–1.77) after a mean follow-up of 7.1 years (Hsia et al, 2006).

2.1.6 HT and breast cancer

The data from observational studies about the effect of HT on breast cancer was controversial. In a case-control study in the USA, HT did not appear to be associated with an increased risk of breast cancer (Stanford et al, 1995). In a cohort of 23 000 Swedish women, HT did not change breast cancer mortality despite increased incidence (Yen et al, 1993). The Nurses' Health Study showed both an increased risk of breast cancer and death due to breast cancer (Colditz et al, 1995). A register-based study from Finland showed that oestradiol either orally or transdermally for 5 years or more resulted in 2–3 extra cases of breast cancer per 1 000 women followed for 10 years (Lyytinen et al, 2006). A review of 51 studies in 21 countries showed an excess risk of breast cancer of 1.023 (95% CI: 1.011–1.036) for each year of use (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). The MWS demonstrated an increase of breast cancer rates both in current users of oestrogen (RR 1.30; 95% CI: 1.21–1.40) and combined hormone therapy (RR 2.00; 95% CI: 1.88–2.12) (Million Women Study Collaborators, 2003), but also a

difference in the tumour histology between current and never users (Reeves et al, 2006).

The PEPI trial demonstrated that HT was already within the first year of use associated with an increase in mammographic density, a predictor of breast cancer (Greendale et al, 1999). In the Esprit trial, breast cancer was not more frequent among the HT users (RR 0.98; 95% CI: 0.25–3.91) (The Esprit team, 2001). The WHI trial demonstrated an increase of breast cancer rates (HR 1.26; 95% CI: 1.00–1.59) among users of combined hormone therapy (Writing Group for the Women's Health Initiative investigators, 2002) and in the number of women with abnormal mammograms among them (Chlebowski et al, 2003). The breast cancers diagnosed in the WHI combined HT group were similar in histology and grade but were larger and at a more advanced stage (Chlebowski et al, 2003). No increase in breast cancer rates among users of unopposed oestrogens was observed in the WHI trial (HR 0.77; 95% CI: 0.59–1.01) (The Women's Health Initiative Steering Committee, 2004).

2.1.7 HT and gynaecologic cancers

Observational studies suggested that oestrogen therapy increased the risk of endometrial cancer (Smith et al, 1975; Ziel et al, 1975; Mack et al, 1976; Hulka et al, 1980; Shapiro et al, 1985; Henderson, 1989). The PEPI trial confirmed the hypothesis (Writing Group for the PEPI trial, 1996). Two case-control (Risch, 1996; Moorman et al, 2005) and one cohort study (Lacey et al, 2002) showed an increase in ovarian cancer rates in women using oestrogen therapy.

The MWS demonstrated an increase in the risk of endometrial cancer among oestrogen therapy users, but not in users of cyclic combined preparations, and the risk was decreased among users of continuous preparations (Beral et al, 2005). The MWS showed that current users of HT have an increased risk for ovarian cancer and death from ovarian cancer, and the risk increases with increasing duration of use. Past users were not found at increased risk (Million Women Study Collaborators, 2007).

The WHI results showed that combined HT may increase the risk of invasive ovarian cancer (HR 1.58; 95% CI: 0.77–3.24), but not the risk of endometrial cancer (HR 0.81; 95% CI: 0.48-1.36) (Anderson et al, 2003).

2.1.8 HT and colorectal cancer

Before the WHI trial, a record linkage study showed a non-significant elevated risk of colon cancer in women who took oestrogens (RR 1.29; 95 % CI: 0.86–1.93) (Risch et al, 1995), but a case-control study demonstrated a decrease in the

risk of colorectal cancer for women ever using HT (OR 0.40; 95% CI: 0.25–0.66) (Fernandez et al, 1996). The Nurses' Health Study showed a decreased risk for colorectal cancer among HT users (RR 0.65; 95% CI: 0.50–0.83) (Grodstein et al, 1998). In a meta-analysis of 18 epidemiologic studies of HT and colorectal cancer, a 20% risk reduction was found (RR 0.80; 95 % CI: 0.74–0.86) (Grodstein et al, 1999).

According to the WHI trial, combined HT decreased the risk of colon cancer (HR 0.54; 95% CI: 0.36–0.82), but not the risk of rectal cancer (HR 0.66; 95% CI: 0.26–1.64). However, colorectal cancers in women who used HT were diagnosed at a more advanced stage (Chlebowski et al, 2004). Among women using only oestrogen therapy in the WHI, the risk of colorectal cancer remained unchanged (HR 1.08; 95% CI: 0.75–1.55) (Women's Health Initiative Steering Committee, 2004).

2.1.9 HT and dementia

The relative risk of Alzheimer's disease was earlier reported to be reduced by oestrogen use in cohort studies (Paganini-Hill et la, 1994; Tang et al, 1996; Kawas et al, 1997; Carlson et al, 2001). Also, a meta-analysis of studies of HT for preventing cognitive decline and dementia found a decreased risk of dementia in HT users (LeBlanc et al, 2001).

The Women's Health Initiative Memory Study (WHIMS), nested in the WHI trial, showed that for women over 65 years of age combined hormone therapy did not improve cognitive function (Rapp et al, 2003), and increased the risk for probable dementia (HR 2.05; 95% CI: 1.21–3.48) (Shumaker et al 2003). Oestrogen only therapy showed a similar adverse effect on cognition (HR 1.38; 95% CI: 1.01–1.89) (Shumaker 2004). Pooling data for oestrogen alone and combined therapy showed an increased risk of probable dementia (HR 1.76; 95% CI: 1.19–2.60) (Espeland et al 2004). Detailed analysis of the WHIMS data showed that combined therapy had a negative impact on verbal memory and a trend to a positive impact on figural memory with other cognitive domains not affected after long-term therapy (Resnick et al, 2006).

2.1.10 HT and diabetes

Observational studies have given conflicting results about the incidence of diabetes among users of HT (Manson et al, 1992; Gabal et al, 1997). The PEPI trial showed that HT may decrease fasting levels of insulin and glycose (Espeland et al, 1998). In the HERS trial, hormone therapy reduced the incidence of diabetes by 35% in women with coronary disease (RR 0.65; 95% CI: 0.48–0.89) (Kanaya et al, 2003).

The WHI trial confirmed that combined hormone therapy reduced the incidence of diabetes also in healthy women (HR 0.79; 95% CI: 0.67-0.93) (Margolis et al, 2004).

2.1.11 HT, urinary incontinence, and urinary infections

In the Nurses' Health Study, postmenopausal HT appeared to increase the risk of developing urinary incontinence (Grodstein et al, 2004). In the HERS trial, urinary tract infection frequency was higher in the HT group, although the difference was not statistically significant (OR 1.16; 95% CI: 0.99–1.37) (Brown et al, 2001). In the WHI trial, conjugated equine oestrogen with progestin (RR 1.18; 95% CI: 1.06–1.32) or without it (RR 1.29; 95% CI: 1.15–1.45) increased the risk of urinary incontinence among continent women at year one. Both combined hormone therapy (RR 1.38; 95% CI: 1.06–1.32) and oestrogen alone therapy (RR 1.47; 95% CI: 1.15–1.45) worsened the characteristics of urinary incontinence among symptomatic women (Hendrix 2005).

2.1.12 HT and biliary tract disease

The HERS trial showed an increased risk (RR 1.38; 95 % CI: 1.00–1.92) of gallbladder disease after 4.1 years of follow-up (Hulley et al, 1998) and for biliary tract surgery (RR 1.48; 95 % CI: 1.12–1.95) after 6.8 years of follow-up among women assigned to hormone therapy (Hulley et al, 2002). The WHI trial confirmed that HT increases the risk of gallbladder disease (HR 1.67; 95% 1.35–2.06 for ET; HR 1.59; 95% CI: 1.28–1.97 for combined therapy) and cholecystectomy (HR 1.93; 95% CI: 1.52–2.44 for ET; HR 1.67; 95% CI: 1.32–2.11 for combined HT) (Cirillo et al, 2005).

2.1.13 HT and osteoarthritis

Observational studies suggested that osteoarthritis might be less common in HT users than in those not taking HT (Felson et al, 1995; Nevitt at al, 1996). The data of women who underwent hip or knee replacement in Germany showed that both bilateral osteoarthritis and generalized osteoarthritis were more common among HT users than non-users (Erb et al, 2000). The HERS trial found no effect of combined HT on knee pain and related disability (Nevitt et al, 2001).

2.2 HT, symptom reporting, and quality of life

Randomised trials of HT have found a substantial placebo effect, with approximately 25 per cent of women in placebo groups reporting improvements in health-related quality of life (Girdler et al, 1999). Therefore, only results from randomised trials were included in this literature review.

A meta-analysis of randomised trials showed that oestrogen therapy reduced depressed mood among menopausal women, and combined with progesterone was associated with smaller reductions in depressed mood (Zweifel et al, 1997). The Cochrane Database of Systematic Reviews examined data from 24 trials to compare the effect of oral HT to placebo on hot flushes and night sweats as well as on side effects (Cochrane Database 2004). HT reduced hot flushes by 75% (95% CI: 64.3–82.3) and placebo by 58% (95% CI: 45.1–67.7), but increased the risk of adverse events like breast tenderness, water retention, joint pain and psychological symptoms (OR 1.25, 95% CI: 0.83–1.90).

The PEPI trial showed a marked effect of postmenopausal hormone therapy on vasomotor symptoms (Greendale et al, 1998). In the HERS trial, the effect of HT on woman's quality of life depended on the presence or absence of flushing: women with hot flushes had improved mental health and had fewer depressive symptoms, while women without flushes had greater declines in physical measures and energy over the follow-up period in the HT arms (Hlatky et al, 2002). In the WHI trial, combined hormone therapy relieved hot flushes (OR 4.40; 95% CI: 3.40–5.71), night sweats (OR 2.58; 95% CI: 2.04–3.26), vaginal or genital dryness (OR 2.40; 95% CI: 1.90–3.02), joint pain or stiffness (OR 1.43; 95% CI: 1.24–1.64) and general aches or pains (OR 1.25; 95% CI: 1.08–1.44), but contributed to side effects like breast tenderness (OR 4.26; 95% CI: 3.59–5.04), vaginal or genital discharge (OR 4.47; 95% CI: 3.44–5.81), vaginal or genital irritation (OR 1.52; 95% CI: 1.27–1.81) and headaches (OR 1.26; OR 1.08–1.46) (Barnabei et al, 2005). No clinically meaningful effect on health-related quality of life was found either in the combined therapy (Hays et al, 2003) or in the oestrogen only arm (Brunner et al, 2005).

2.3 HT and survival

The Nurses' Health Study reported a lower risk of death for current hormone users, users with coronary risk factors having the largest reduction in mortality, but the benefit decreased with long-term use (Grodstein et al, 1997). A cohort study from Sweden showed a slightly higher survival rate than in the general population among HT users (Persson et al, 1990), with a reduced risk of death from coronary heart disease and cerebrovascular disease (Schairer et al, 1997).

No statistically significant reduction in all-cause mortality (RR 0.79; 95% CI: 0.50–1.27) or cardiac death (RR 0.61; 95% CI: 0.35–1.09) among women with prior myocardial infarction was found in the Esprit trial (The Esprit team, 2001). The HERS trial found no difference in total mortality among women with coronary heart disease using HT after 4.1 years (RR 1.08; 95% CI: 0.84–1.38) (Hulley et al, 1998) or 6.8 years (RR 1.10; 95% CI: 0.92–1.31) of follow-up (Hulley et al, 2002). The WHI trial showed that neither combined HT (HR 0.98; 95% CI: 0.82–1.18) (Writing Group for the Women's Health Initiative Investigators, 2002) nor oestrogen-only therapy (HR 1.04; 95% CI: 0.88–1.22) (The Women's Health Initiative Steering Committee, 2004) had an effect on total mortality among healthy women. The effect on mortality was more favourable in younger than older women in the WHI trial (Rossouw et al, 2007).

2.4 HT and the use of health services

Estimations of health care utilization and health care costs in observational studies were contradictory. A retrospective cohort study among women who had self-initiated HT showed that high compliers had higher costs for obstetric and gynaecologic care and prescriptions, and lower compliers for emergency visits during 18 months of follow-up (Hurley et al, 1998). Survey and discharge data in the USA showed that HT might be cost-effective for preventive purposes (Hoerger et al, 1999), whereas according to Canadian register-based data, new users of HT had more visits to physicians and gynaecologists, and slightly more endometrial procedures (Thorp et al, 2001). Retrospective analysis of Canadian register-based data about HT users and demographically matched non-users over a seven year period showed that HT resulted in excess costs due to uterine- and breast-related diagnostic and treatment procedures (Ohsfeldt et al, 2004).

Before the publication of the WHI trial results, HT was found to be cost effective by some authors (Cheung et al, 1992; Whittington et al, 2004; Samsioe 1995; Daly et al, 1996a; Armstrong et al, 2001) while others pointed to the need for clarification on the potential risks and benefits (Tosteson et al, 1991; Townsend 1998; Zethraeus et al, 1999). A later modelling study showed that HT results in net harm (Mullins et al, 2003). A model studying cost-effectiveness of a one-year treatment for women with moderate-to-sever symptoms showed HT to be cost-effective (Botteman et al, 2004). Another modelling study comparing the cost-utility of one year's treatment with a low-dose and a higher-dose HT preparation among symptomatic women showed a greater health gain with the low dose (Swift et al, 2005).

A randomised controlled trial studied the cost-effectiveness of combined continuous HT for nine consecutive years with data accrued for cardiac and vascular events, cancers and fractures, but not for gynaecologic and breast procedures. The

appraisal found HT to be cost-effective for the relief of symptoms of menopause (Ylikangas et al, 2007).

Prior to the current trial, the impact of HT on health care use and health care costs for preventive purposes had not been previously reported for randomised trials.

2.5 HT and the use of other prescription drugs

Based on data from administrative database and surveys, prescription drug use has been reported to be higher in current and former hormone therapy users in the United States (Small et al, 2001), the United Kingdom (Jacobs et al, 2003) and Sweden (Khatibi et al, 2004). Hormone therapy has been reported to increase the use of thyroid hormone preparations and antimigraine preparations (Small et al, 2001), antacids and antihistaminic drugs (Khatibi et al, 2004), and antihypertensive medication (Thorp et al, 2001). No difference in the use of cardiac drugs or bisphosphonates has been observed (Thorp et al, 2001). The use of antidepressants and sedatives is reported to be higher among hormone therapy non-users (Thorp et al, 2001; McIntyre et al, 2005).

Details of concomitant medication use have not previously been reported from clinical trials. Only baseline medication use has been reported in the Heart and Estrogen/Progestin Study (Furberg et al, 2002) and the Women's Health Initiative trial (Hays et al, 2003).

TABLE 1. Long-term (over 12 months) randomised clinical trials of hormone therapy*

Author, publication year	Name of the trial (acronym); recruitment period	Participants (N; mean age)	Treatment	Follow-up
The Writing Group for the PEPI Trial; 1996	Postmenopausal Estrogen/Progestin Interventions Trial (PEPI); 1989–1991	875 (596 with uterus); 56 yrs	CEE alone; three CEE + P regimens; placebo	3 yrs
Hulley et al; 1998	Heart and Estrogen/ Progestin Study (HERS I); 1993–1994	2 763 with CHD; 67 yrs	CEE + MPA	4.1 yrs
Grady et al; 2002	HERS II; 1993–1994	2 763 with CHD; 67 yrs	CEE + MPA	6.8 yrs
De Kleijn et al; 1999	Name not reported; duration 1992–1995	121 healthy women; 47 yrs	Estradiol + cyclic desogestrel; CEE + cyclic norgestrel; placebo	2 yrs
Herrington et al; 2000	Estrogen Replacement and Atherosclerosis (ERA); 1995–1996	309 with CHD; 66 yrs	CEE +- MPA; placebo	3.2 yrs

Table 1 continues

Table 1 continues

Author, publication year	Name of the trial (acronym); recruitment period	Participants (N; mean age)	Treatment	Follow-up
Hoibraaten et al; 2000	Estrogen in venous thromboembolism trial (EVTET); 1996–1998	140 women with previous VTE	Estradiol + NETA; placebo	
Viscoli et al; 2001	Women's Estrogen for Stroke Trial (WEST); 1993–1998	664 with ischemic stroke or transient ischemic attack; 71 yrs	Estradiol; placebo	3 yrs
Hodis et al; 2001	Estrogen and Prevention of Atherosclerosis Trial (EPAT)	222 healthy women; 62 yrs	Estradiol; placebo; LLMs if indicated	2 yrs
The Esprit team; 2001	ESPRIT; 1996–2000	1 017 women with MI; 63 yrs	Estradiol; placebo	2 yrs
Waters et al; 2002	The Women's Angiographic Vitamin and Estrogen Trial (WAVE); 1997–1999	423 with CHD; 65 yrs	CEE + -MPA or placebo; Vit E + Vit C or placebo; factorial design	2.8 yrs
Clarke et al; 2002	Papworth HRT Atherosclerosis Enquiry (PHASE)	255 with coronary heart disease; 67 yrs	Estradiol +-norethisterone; no treatment	3 yrs
WHI team; 2002	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16 608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs
WHI team; 2004	Estrogen arm of the Women's Health Initiative (WHI) Trial; 1993–1998	10 739 healthy hysterec-tomised women; 64 yrs	CEE; placebo	6.8 yrs
Hodis et al; 2003	Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART); 1995–2000	226 women with coronary artery lesion; 64 yrs	Estradiol; Estradiol + cyclic MPA; placebo	3.3 yrs

* By publication year of outcomes, except HERS I and II and oestrogen plus progestin and the oestrogen arm of WHI trial, which are presented subsequently.

CEE = conjugated equine oestrogen; CHD = coronary heart disease; IMT = intima-media thickness; LLMs = lipid-lowering medications; MI = myocardial infarction; MLD = minimal lumen diameter; MPA = medroxyprogesterone acetate; NETA = noretisterone acetate; VTE = venous thromboembolism

2.6 Summary of the current knowledge about HT

Data from cohort studies and randomised trials show that both oestrogen-only and combined hormone therapy reduce the risk of bone fractures among healthy women, but not in women with coronary heart disease. The data about bone loss after discontinuation is controversial.

Observational studies show a positive effect of hormone therapy on the progression of atherosclerosis. The effect is not confirmed by data from randomised trials, showing no effect of HT on atherosclerosis among women with coronary disease, and a negative effect of HT on atherosclerosis among healthy women.

Although data from observational studies suggest a favourable effect of HT on blood lipids and coronary disease, results from randomised trials show a negative effect of oestrogen therapy and combined therapy for both primary and secondary prevention of coronary heart disease.

Contrary to earlier data from observational studies, the data from randomised trials show that oestrogen therapy and combined therapy increase the risk of stroke in women with prior stroke and coronary heart disease as well as in healthy women.

Similar to non-experimental studies, the results from randomised trials demonstrate an increased risk of deep vein thrombosis among healthy hormone therapy users and users with prior coronary heart disease or thromboembolism. The risk may be higher during the first years of use.

Data from observational studies and randomised trials show an increased risk of breast cancer among women using combined hormone therapy, while data on the risk of breast cancer among users of oestrogen therapy are controversial. The risk of endometrial cancer is increased by oestrogen therapy, but not by combined therapy. The risk of ovarian cancer is increased by both oestrogen therapy and combined therapy. The risk of colorectal cancer is smaller among women using combined hormone therapy, whereas oestrogen therapy does not affect the risk of colorectal cancer.

Data from randomised trials demonstrate a reduced risk of diabetes among healthy women and women with coronary heart disease using either oestrogen therapy or combined therapy. The positive effect of HT on cognition and dementia observed in cohort studies was not confirmed in the WHI sub-trial among older women.

Hormone therapy increases the quality of life among women with hot flushes, but increases the risk of side effects (vaginal bleeding, breast tenderness, migraine headaches, mood alterations, abdominal bloating) as well. For asymptomatic women, hormone therapy has no effect on quality of life. Both oestrogen therapy and combined therapy increase the risk of incontinence, and possibly the risk of

urinary infections as well. Unlike data from observational studies, results from clinical trials do not show any effect of hormone therapy on survival.

There are no discrepancies between the results from observational studies and randomised trials regarding the effect of HT on the incidence of bone fractures, deep vein thrombosis, breast cancer, ovarian cancer, and colorectal cancer, but the effect of HT on coronary heart disease, stroke, atherosclerosis, dementia, and survival is not consistent. The differences in outcomes are probably influenced by lifestyle factors, due to the fact that randomisation controls for confounding. The comparison of results from different trials does not support the hypothesis that the results can be attached to the regimens used (Appendix 14). There is insufficient evidence of the effects being age-specific (Rossouw et al, 2007). Sub-group analyses in the HERS and WHI trial have not shown a susceptible cohort (Furberg et al, 2002; Denes et al, 2007).

3 Aims of the study

The overall aims of the EPHT trial were to study the long-term effect of HT on the incidence of diseases, the short-term effect of HT on well-being, experience of ageing, and partner relationship, the impact of HT use on the utilization of health services, and the effect of blinding on trial recruitment and treatment adherence.

The specific objectives of this study undertaken within the framework of a randomised preventive trial were:

1) to evaluate the effects of continuous combined hormone therapy on the incidence of coronary heart disease, cerebrovascular disease, total cancer and bone fractures among healthy postmenopausal women (Article I);
2) to find out the effect of postmenopausal hormone therapy on quality of life and symptom reporting (Article II);
3) to determine the use of health services by hormone therapy users in comparison with non-users and to estimate the health care costs linked with hormone therapy (Article III);
4) to follow the use of prescription medication by hormone therapy users versus non-users (Article IV).

4 Material and methods

4.1 Screening

The names, personal identification numbers and addresses of all 39 713 women living in two Estonian counties of Tartumaa and Harjumaa – including Tallinn, the capital of Estonia – and aged 50 to 64 years in March 1999 were obtained from the Estonian Population Registry. These women were mailed information about the trial (Appendix 2) and a questionnaire (Appendix 9). The questionnaire included questions about their willingness to join a randomised trial and health status, including possible contraindications for joining the study and the date of their last period. Of the 14 743 women who returned the questionnaire, 6606 respondents were interested in participating (Figure 1). Among these, 2 311 women were found to be ineligible (38% were still menstruating, 26% had reported a condition defined by the study group as a medical contraindication for hormone therapy, 22% were already using hormone therapy, 7% had no health insurance, 6% asked for open-label hormone therapy or for no treatment, and 1% had moved to a new location).

4.2 Randomisation and recruitment

Randomisation was carried out before recruitment in permuted blocks, each with 16 persons, at the National Research and Development Centre for Welfare and Health (STAKES) in Finland. There were four study arms: 1) blind drug arm; 2) placebo arm; 3) non-blind drug arm and 4) non-blind control arm. The treatment allocation was enclosed in a non-transparent sealed envelope with a woman's study number and name on it, and sent to whichever clinic in Estonia the woman had stated as her preference in the recruitment questionnaire. The randomly assigned women were mailed a doctor's appointment. The invitation letters were different in the blind (Appendix 3) and non-blind sub-trials (Appendix 4). The randomisation envelope was opened only after checking the woman's eligibility criteria and after signing the informed consent during the recruitment visit to the trial physician. Unopened randomisation envelopes were collected from the clinics by the research team in order to detect deviations from the trial protocol.

Eight gynaecologists at three clinical centres (two in Tallinn, one in Tartu) were trained to participate in the trial (Appendix 1). They conducted a thorough medical examination during the recruitment visits, including questioning about reproductive and health history, risk factors for coronary heart disease, and

medication use, as well as measurement of blood pressure, examination of breasts, pelvic examination, a Pap-smear for all women, and transvaginal sonography for women in the treatment arms. The inclusion criteria for joining the trial were an age of 50 to 64 at the time of sampling from the Estonian Population Registry, valid health insurance and an elapsed time of 12 months or more since the last period at the randomisation stage. The exclusion criteria were as follows: use of hormone therapy during the past 6 months; untreated endometrial adenomatosis or atypical hyperplasia of the endometrium; a history of breast cancer, endometrial cancer or ovarian cancer; any other cancer treated less than 5 years ago; a history of meningioma; myocardial infarction within the last 6 months; a history of hepatitis or functional liver disorders in the last 3 months; a history of deep vein thrombosis, pulmonary embolism, or cerebral infarction; porphyria; hypertension of more than 170/110 mm Hg despite medication; laparoscopically or histologically confirmed endometriosis.

Of the 4 171 (4 295 together with the pilot study) randomly assigned women, 2 323 (2 383 including the pilot study) actually responded by visiting the doctor. Of these, 1 778 (1 823 including the pilot study) proved to be eligible, and their randomisation envelope was opened. Recruitment lasted from January 1999 to December 2001. All participants gave written informed consent. The study protocol was approved by the Tallinn Medical Research Ethics Committee, Estonia, and by the Ethical Committee of Pirkanmaa Hospital District, Tampere, Finland. The trial has been registered in the International Standard Randomised Controlled Trial (ISRCT) Register and was assigned the number ISRCTN35338757 on October 15, 2004. The trial was co-ordinated by the Trial Steering Committee and the interim safety follow-up was carried out by the Data Monitoring Committee (Appendix 1).

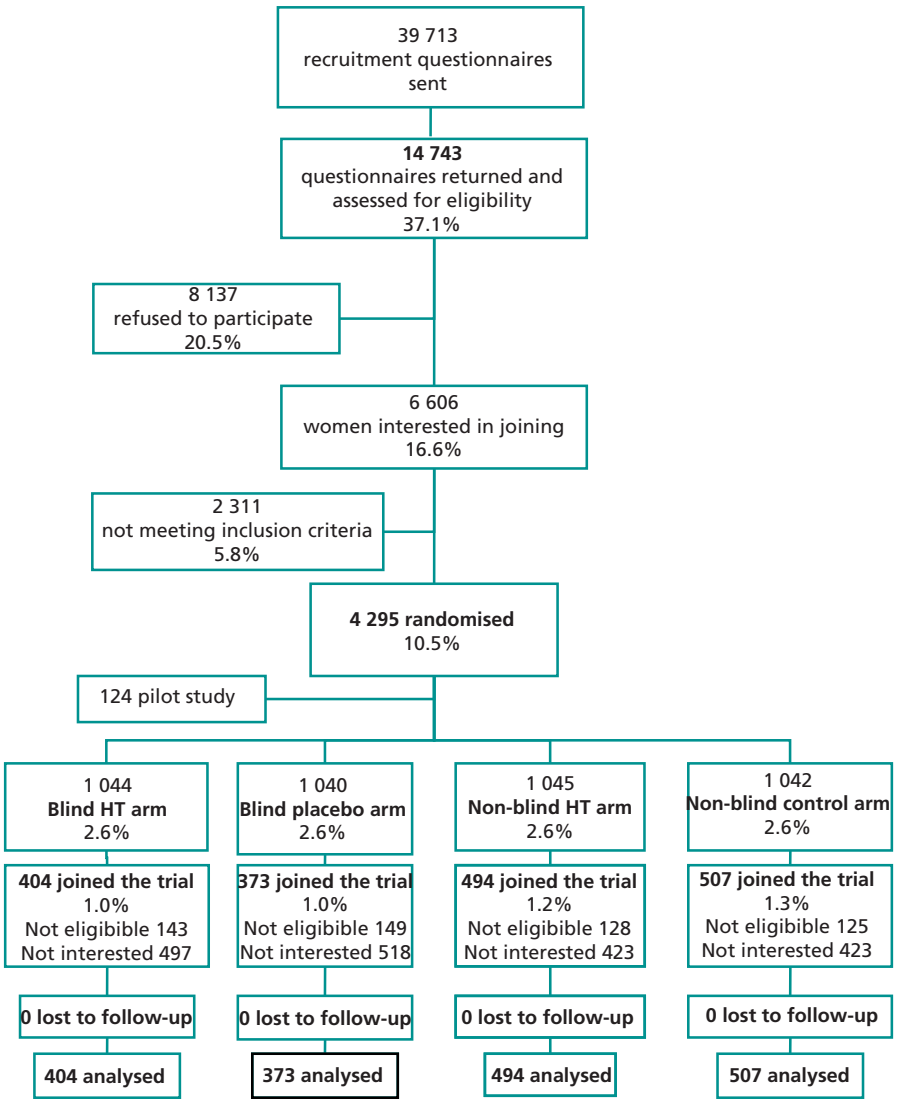


FIGURE 1. Flow chart of the main trial

4.3 Sample size

The Estonian Postmenopausal Hormone Therapy (EPHT) trial was originally planned to be part of the international arm of the WISDOM trial in the United Kingdom which would take the overall sample size in WISDOM together with other international collaborators from 18 000 to 34 000 (Vickers et al, 2002). No sample size calculations were made for health outcomes in the Estonian trial. Recruiting 2000 women was assumed to give enough power to study the effect of HT on quality of life and the use of health services.

4.4 Pilot study

The feasibility of the study design was tested during the pilot study, which took place before the main trial in the same clinical centres. The 45 women participating in the pilot study proceeded to the main trial. The women randomly selected for the pilot study had the same inclusion and exclusion criteria as women in the main trial, except that their age was 45 to 59 at the time of sampling in February 1998 (there were 4 women under the age of 50 at recruitment), the time since the cessation of periods was 6 months, and 7 hysterectomised women were randomly allotted either to treatment with 0.625 mg of oral conjugated oestrogens daily or to non-treatment.

4.5 Intervention and clinical follow-up

After the woman's health status had been checked and the form for informed consent (Appendix 8) had been signed, the sealed non-transparent randomisation envelope was opened. The drug sheet in the envelope indicated the number of the drug bottle in the blind sub-trial and in the hormone treatment arm of the non-blind sub-trial. In the non-blind control arm the drug sheet was empty. In the blind sub-trial, the women were told by the trial physician that they would be using either hormone therapy or a placebo; in the non-blind sub-trial, they were told that they would be receiving hormone therapy or non-treatment. In addition, the women received a written explanatory letter, different for the blind sub-trial (Appendix 5), for the control arm (Appendix 6) and hormone therapy arm of the non-blind sub-trial (Appendix 7).

During the final recruitment visits, women in treatment arms received their first drug bottle. Drugs were manufactured by the Wyeth Ayerst Company in the United States and donated via the WISDOM trial in the United Kingdom. The drug in oral daily use in the treatment arms contained 625 μg of conjugated oestrogens

and 2.5 mg of medroxyprogesterone acetate (or matched placebo in the placebo arm). Altogether 251 women within 3 years of their last period received daily 625 μg of oral conjugated oestrogens and 5.0 mg of oral medroxyprogesterone acetate in the treatment arms (or matched placebo in the placebo arm, or non-treatment in the control arm) to reduce the risk of uterine bleeding. The drug bottles had a unique bottle number; in the non-blind sub-trial the label contained information about the composition of the drug.

Study participants were asked to fetch their drug bottles every 7 months after recruitment (in the pilot study, the second drug bottle was fetched 3 months after recruitment), and were invited to annual clinical examinations by means of mailed letters. The annual medical examination included measurement of weight and arterial blood pressure, pelvic examination and breast examination. A Pap-smear was taken every second year. Other examinations (endometrial biopsy, blood sample) were made only on clinical indications. Vaginal bleeding was managed by an algorithm that accounted for time and severity of bleeding, and sonographically determined endometrial thickness. All women were trained to palpate their breasts monthly. Women were advised to use screening mammography every second year, and starting in 2003, mammograms for those trial women who were not eligible for the national screening program were paid for. The trial midwives had fixed calling hours in order to answer any questions by the trial women.

Permanent discontinuation of trial medication was required by protocol for women who developed breast cancer, invasive cancer at any other site, meningioma, deep vein thrombosis, pulmonary embolism, retinal vein occlusion, porphyria, stroke or brain haemorrhage, hypertension over 170/110 mm Hg despite medication, renal failure, or for whom any other hormone therapy regimen was prescribed. Medication was temporarily discontinued in patients who experienced sudden loss of vision, proptosis or diplopia, liver functional disorders, active hepatitis or active gall bladder disease, angina pectoris, myocardial infarction, hospitalisation for other cardiovascular conditions, heart failure, cerebrovascular accident, subarachnoid haemorrhage, transient ischaemic attacks, pancreatitis, or long-term immobilization.

Grouping into low (1–9%), medium (20–79%) and high adherence (80–100%) groups was used to calculate adherence rates in different trial years. Adherence was assessed by the number of collected and returned drugs and by the information from annual questionnaires and weekly reports from the clinics. Collected drugs were regarded as taken if woman had not stated otherwise. The use of prescribed HT in the non-treatment arms was ascertained by annual linkages to the Estonian Health Insurance Fund. Women taking more than 80% of the allocated drugs were considered to be adherent, whilst women in the control arm were considered to be adherent if they were not taking hormone therapy for 80% of the time.

The intervention was originally planned to last 5 years, but in May 2003 the Study Group decided to shorten trial treatment to 4 years for women who had not

completed their 4th year by that time. On December 2, 2003 the Data Monitoring Committee recommended stopping trial treatment, which was implemented gradually by informing the participants individually and was completed on May 31, 2004. Both decisions were based respectively upon the published reports of the Women's Health Initiative trial and the Million Women Study, which showed that the health risks from hormone therapy exceeded the benefits (Writing Group for the Women's Health Initiative Investigators, 2002; Anderson et al, 2003; Cauley et al, 2003; Chlebowski et al, 2003; Hays et al, 2003; Manson et al, 2003; Million Women Study Collaborators 2003; Rapp et al, 2003; Shumaker et al, 2003; Wassertheil-Smoller et al, 2003). As the Trial Steering Committee wanted to offer a thorough medical check-up at the closure visit to all trial participants, in keeping with the study protocol, it took six months to schedule the final clinic visits.

Participants in the blind sub-trial received a letter containing information on their treatment allocation within one month of their final visit. The trial staff remained blinded until the end of the trial as regards the drug allocation in the blind sub-trial.

4.6 Data collection

4.6.1 Register-based data

The trial cohort was monitored by means of annual linkages to the Estonian Health Insurance Fund database, the Estonian Cancer Registry database, and the Estonian Mortality Database (latter via the Estonian Cancer Registry). Assessments of trial outcomes were done blindly; the persons doing linkages in the Health Insurance Fund database, in the Estonian Cancer Registry and in the Estonian Mortality Database were unaware of the treatment allocation. All the linkages were made using personal identification numbers. No technical problems occurred while doing the linkages.

To analyse the hazard ratios for cardiovascular diseases and bone fractures in the different trial arms, the diagnosis according to the 10th revision of the International Classification of Diseases (ICD-10) (WHO, 1982) and the start and end date of the episode were obtained from the Estonian Health Insurance Fund. Coronary heart disease was defined as diagnoses I20 to I25 (angina pectoris, acute myocardial infarction, subsequent myocardial infarction, current complications following acute myocardial infarction, other acute ischaemic heart disease, chronic ischaemic heart disease) according to the 10th revision of the International Classification of Diseases (ICD-10) (WHO, 1992). Cerebrovascular disease was defined as diagnoses I60 to I69 according to ICD-10 (subarachnoid haemorrhage, intracerebral haemorrhage, other nontraumatic intracranial haemorrhage, cerebral infarction, stroke, occlusion and stenosis of precerebral arteries, occlusion

and stenosis of cerebral arteries, other cerebrovascular diseases, cerebrovascular disorders, sequelae of cerebrovascular disease). Bone fractures defined as diagnoses S12, S22, S32, S42, S52, S62, S72, S82, S92 according to ICD-10 (fracture of neck, fractures of ribs, sternum and thoracic spine, fracture of lumbar spine and pelvis, fracture of shoulder and upper arm, fracture of forearm, fracture at wrist and hand level, fracture of femur, fracture of lower leg, including ankle).

To analyse the hazard ratios for cancer, the diagnosis according to ICD-10 and the date of diagnosis were obtained from the Estonian Cancer Registry together with the extent, laterality, and stage of the disease and the basis of the diagnosis. Total cancer was defined as diagnoses C00–C97 according to ICD-10 (all malignant neoplasms).

To analyse the use of health services and health care costs in the different trial arms, selected medical procedures and dates, visits to different medical specialist and dates, hospitalisations and their first and final dates, and sickness leaves were obtained from the Estonian Health Insurance Fund. In addition, purchased costs of outpatient and inpatient visits and procedures with dates, purchased costs of sickness leaves with the first and final date, and purchased costs of prescription drugs with the prescribing date were obtained from the Health Insurance Fund. To analyse the use of prescription medication in the different trial arms, the date of the prescription, the name and type of prescription medication according to the anatomical therapeutic chemical (ATC) classification of drugs (WHO, 2005), the purchased cost of the drug and the reason for the prescription as a diagnosis according to ICD-10 were retrieved. The Estonian Mortality Database was used to ascertain the date and underlying cause of death.

Estonian health insurance covers 92% of the population; all participants in the trial were insured. The Health Insurance Fund covers the costs of health services required by an individual in the case of illness, regardless of the amount of social tax paid for the person concerned. Health insurance has been in force since 1992 (Estonian Health Insurance Fund, 2004). Health services are equally available in all regions. The Health Insurance Fund stores information about all health care contacts, using an individual's personal identification code. In the data file, the unit is one disease episode, covering all health care services resulting from a particular case. For each disease episode, the following data is recorded in a centralised, computerised database: dates of the start and end of the episode, number of visits to the doctor or number of inpatient days in hospital, diagnostic examinations, treatment procedures, surgical interventions, medical diagnoses of insured persons as the cause for care according to ICD-10 (WHO, 1982), and the date of death if relevant. Up to three diagnoses and one external cause of morbidity or death can be coded by the physician who offers a medical service; the first two diagnoses are also recorded in writing. The diagnosis is certified during the final visit of the disease episode. The data is transferred electronically to the database of the Estonian Health Insurance Fund. For prescribed drugs, the following information is recorded: data

about the physician and the patient, name and ATC-code (WHO, 2006) of the drug, diagnosis according to ICD-10, and the date of writing the prescription.

4.6.2 Questionnaire-based data

Assessments on prevalence of symptoms and of health-related quality-of-life were made through the annual questionnaires (Appendix 10-13). The participating women were mailed a questionnaire at the end of each trial year asking about their health status and drug use over the past 12 months. All questionnaires included questions about the prevalence of 17 symptoms in the previous two weeks (dizzy spells, lack of energy, diarrhoea or constipation, irritability, persistent cough, feeling down or depressed, backaches, upset stomach, headaches, cold sweats, aches/stiffness in the joints, shortness of breath, hot flashes, sore throat, trouble sleeping, loss of appetite, water retention), and questions about number, duration and severity of bleeding episodes in the previous 12 months. The same questions were asked from all participants before recruitment. The first and the final annual questionnaire included questions about painful intercourse in the previous 12 months.

Health-related quality of life was assessed with the help of the European Quality of Life questionnaire (EQ-5D) (EuroQoL, 2006). EQ-5D is a standardized instrument for measuring health outcomes. It contains five questions asking whether the respondent has problems with mobility, self-care, usual activities, pain/discomfort and anxiety/depression with three possible responses available (no problems, moderate problems, severe problems). EQ-5D is designed for self-completion and provides a single index score for health status. The second annual and the final questionnaires contained EQ-5D questions.

All participants filled in the recruitment questionnaire. The response rate was 75% for the first annual survey, 69% for the second annual survey, and 81% for the final survey mailed at the end of the trial and followed by one reminder. On average, the final survey was filled in 3.6 years after recruitment. There was no difference in the annual response rates between the trial arms.

4.7 Statistical analysis

All baseline characteristics were compared using χ^2-tests (categorical variables) or analysis of variance (continuous variables). Comparing the baseline characteristics in the four arms showed a difference in the former use of oral contraceptives, while comparing the hormone therapy and no hormone therapy arms showed a difference in the age at recruitment. The women participating in the pilot study

were not included in the analysis except for analysing the effect of HT on symptom reporting and quality of life.

All the main analyses were based on the intention-to-treat principle. To calculate the hazard ratios of coronary heart disease, cerebrovascular disease, total cancer, and also bone fractures, the time of the first event in each disease group was defined as the number of days from recruitment to the first diagnosis in this disease group, as registered in the Health Insurance Fund database or in the Estonian Cancer Registry database.

Hazard ratios with 95% confidence intervals for main outcomes were calculated within the blind and the non-blind sub-trial using Cox proportional hazards modelling, adjusted on the basis of stratification by age group at recruitment and former oral contraceptive use. To statistically analysis the main outcomes, the hormone therapy arms were then combined, as well as the placebo arm and non-blind control arm. This analysis was based on Cox proportional hazards modelling, using stratification by blinding, and adjustment by age group at recruitment and former oral contraceptive use. Interaction between treatment arm and blinding was tested but not included in the model. The assumption of proportionality was tested and met. A sub-group analysis for women within three years of menopause was performed. An additional analysis that censored a woman's event history six months after stopping trial treatment was performed within the blind sub-trial. The software used was R for Windows, version 1.9. (The R Project for the Statistical Computing).

To analyse the effect of HT on symptom reporting and health-related quality of life, we used Stata version 9.2 (StataCorp, Texas, USA) and R version 2.3.1 and 2.4.0 (The R Project for Statistical Computing) to analyse the data on an intention-to-treat basis. Numbers of women reporting menopausal symptoms and vaginal bleeding as well as quality of life scores according to EQ-5D were compared for the different trial arms. The EQ-5D score was calculated using the simple formula (Prieto et al, 2004). Linear regression was used to analyse the influence of treatment allocation, age, and socioeconomic factors (living-place, education, marital status, employment status, smoking status, parity) on quality of life according to the EQ-5D at the end of the trial. The model was adjusted for interactions between age and smoking status, age and employment status, and education and living place, as these were statistically significant. General linear mixed modelling (Diggle et al, 1994) using penalised quasi-likelihood (and assuming a first-order autoregressive correlation structure for the error term) was performed to analyse if the prevalence of different symptoms over time depended on the prevalence of these symptoms at baseline, on hormone treatment, on time, on participant's age or being randomized to a blind sub-trial.

To analyse the impact of HT on the use of health services and health care costs, log-linear Poisson regression was used for a statistical comparison of the number of health care visits and instances of health services utilized within the non-blind

and blind sub-trial according to the intention-to-treat principle. The total number of visits in each six-month time period in each of the five-year-interval age groups at recruitment was used as a dependent variable, using the total number of person-years observed in this interval as the denominator. The model was adjusted for time period since recruitment and age group at recruitment. Interactions between age and treatment, age and time, time and treatment were tested for. No interactions were detected. In order to adjust for over-dispersion in cases where repeated health care visits or repeated procedures like heart electrocardiograms for each disease instance per woman are likely to occur, the iterative algorithm proposed by Breslow was used (Breslow, 1984). The software used was R for Windows, version 2.0.0 with the add-on package *dispmod* to adjust for over-dispersion in the log-linear models (The R Project for Statistical Computing).

Cox proportional hazards modelling was used to compare the use of 21 classes of selected drugs according to the anatomical therapeutic chemical (ATC) (WHO, 2005) in different trial arms throughout the trial. The data were analysed according to the intention-to-treat principle. The software used was R for Windows, version 2.1.1 (The R Project for Statistical Computing).

4.8 Funding of the EPHT trial

The trial was funded by the Academy of Finland (grants 69 838 and 201 490), Finland, and the National Research and Development Centre for Welfare and Health (STAKES), Finland, the Estonian Science Foundation (grants 5 203 and 6 570), and the Estonian Ministry of Education and Research (target funding 0192112s02), Estonia. Piret Veerus received a fellowship from the Finnish Ministry of Education (Doctoral Programs in Public Health) from 2000 to 2004. Drugs were donated by the Wyeth Ayerst Company via the WISDOM trial in the United Kingdom. The funding bodies had no role in the study design, data collection, data analysis, data interpretation, writing the papers or in the decision to submit the papers for publication.

5 Results and comments

5.1 Recruitment, follow-up time, and adherence

The number of women attending the recruitment visit was higher in the non-blind sub-trial (60.1% versus 51.3%), and more women attending the recruitment visit were recruited into the non-blind sub-trial by trial physicians (79.8% versus 72.7%). The impact of blinding on recruitment has been described elsewhere (Hemminki et al, 2004). Besides being randomised to a blind sub-trial, various other factors influenced the probability for joining the trial at different stages. Women with a higher education, being married and non-smokers had a higher probability to attend the recruitment visit (unpublished data). Women being previously diagnosed with cancer and having a body weight over 110 kg were less eager to attend the recruitment visit (unpublished data).

In addition to the exclusion criteria, women being previously diagnosed with cancer, with high blood pressure or a concomitant disease, with an abnormal pap-smear, vaginal sonography or palpatory finding of the breasts were more often excluded from the trial during the recruitment visits. Some of the trial physicians preferred to recruit women to the non-blind sub-trial, while the behaviour of other physicians was not influenced by blinding. If the woman had high blood pressure or a concomitant disease, her probability to be recruited to the blind sub-trial was smaller than to the non-blind one (unpublished data).

Comparing the baseline characteristics in the four arms showed a difference in the former use of oral contraceptives, comparing the hormone therapy and no hormone therapy arms showed a difference in the age at recruitment (Table 2). There were no baseline differences in the prevalence of symptoms in different arms except for sweating, which was reported more often in recruitment questionnaires by women in the hormone therapy arm than in the non-treatment arm of the non-blind sub-trial (OR 1.29, 95% CI 1.00–1.67). No differences between the arms were found in the use of prescription medication three months prior to enrolment.

TABLE 2. Number and percentage distribution of women by trial arms and baseline characteristics* in the EPHT trial

Characteristics	Open HT (n = 503)	Control (n = 524)	Blind HT (n = 415)	Placebo (n = 381)
Age, mean (SD), yrs	58.0 (4.1)	58.4 (4.0)	58.0 (3.9)	58.5 (4.0)
Age at recruitment, yrs				
50–54	130 (25.8)	115 (22.0)	100 (24.1)	77 (20.2)
55-59	182 (36.2)	183 (34.9)	161 (38.8)	130 (34.1)
60–64	165 (32.8)	204 (38.9)	141 (34.0)	157 (41.2)
65–70	26 (5.2)	22 (4.2)	13 (3.1)	17 (4.5)
Age at menopause, mean (SD) *	50.1 (3.7)	50.4 (3.8)	50.1 (4.4)	50.3 (3.9)
Prior OC use *	40 (10.8)	26 (6.6)	46 (14.7)	32 (11.6)
BMI, mean (SD), kg/m2 *	27.0 (4.5)	26.9 (4.6)	26.9 (4.4)	27.2 (4.4)
BMI, kg/m2				
< 25	189 (37.6)	179 (34.2)	152 (36.6)	135 (35.4)
25…29.9	189 (37.6)	226 (43.1)	167 (40.2)	143 (37.5)
> = 30	125 (24.9)	119 (22.7)	96 (23.1)	103 (27.0)
Parity *				
No term pregnancy	44 (9.4)	49 (9.9)	34 (8.9)	29 (8.1)
> = 1 term pregnancy	424 (90.6)	448 (90.1)	350 (91.1)	329 (91.9)
Education *				
< 4 y	13 (2.6)	21 (4.0)	17 (4.1)	13 (3.4)
4–7 y (basic)	34 (6.8)	42 (8.0)	29 (7.0)	28 (7.4)
8–11 y (secondary)	281 (55.9)	291 (55.5)	232 (56.2)	221 (58.2)
University	175 (34.8)	170 (32.4)	135 (32.7)	118 (31.1)
Hysterectomy (self-reported) *	68 (13.7)	71 (13.9)	46 (11.4)	48 (12.9)
Current smoking *	68 (13.5)	88 (16.8)	67 (16.2)	52 (13.6)
Treated for hypertension	75 (15.2)	63 (12.4)	53 (13.1)	45 (12.1)
History of angina	10 (2.7)	16 (4.0)	9 (2.9)	10 (3.6)
History of MI	4 (0.8)	7 (1.4)	7 (1.7)	5 (1.3)
Systolic BP, mean (SD), mm Hg	136.7 (17.6)	137.1 (16.6)	136.7 (17.3)	137.0 (16.0)
Diastolic BP, mean (SD), mm Hg	86.8 (11.2)	86.2 (11.0)	85.8 (11.0)	86.2 (10.2)
Female relative with breast cancer	25 (5.1)	27 (5.4)	22 (5.5)	24 (6.5)

Percentage totals may not equal 100 because of rounding.
For selected variables also mean and standard deviation (SD) are indicated.
HT = hormone therapy, OC = oral contraceptives, BMI = body mass index, MI = myocardial infarction, BP = blood pressure

* Among women for whom data was available

The mean follow-up time from recruitment was 3.43 years for the ascertainment of clinical outcomes and the use of health services, 3.60 years for analysing the effect of HT on health-related quality of life and menopausal symptoms and 4.40 for the analysis of prescription medication usage during the trial. The potential follow-up time was from 2.00 years to 4.97 years. Until December 31, 2003, there were seven deaths among participating women – one in the blind hormone therapy arm, one

in the blind placebo arm, two in the non-blind hormone therapy arm, and three in the non-blind control arm. The number of women in different trial arms over time is presented in Table 3.

TABLE 3. Number of women by follow-up time and trial arm for analysis of clinical outcomes and health care utilization in the EPHT trial

	Follow-up time (years)									
Arm	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**2.5**	**3.0**	**3.5**	**4.0**	**4.5**
Non-blind hormone therapy	494	494	493	493	492	434	355	254	83	21
Blind hormone therapy	404	404	403	403	403	360	295	203	60	22
Non-blind control	507	507	507	506	506	447	382	264	93	26
Blind placebo	373	373	373	372	370	332	274	195	60	19
Total	1 778	1 778	1 776	1 774	1 771	1 573	1 306	916	296	88

The rate of women in the group of high adherence taking more than 80% of allocated treatment declined approximately 50% during the first trial year in all treatment arms and stayed about the same until trial treatment was stopped. Women were not persuaded by the research team to use trial treatment which explains the loss to adherence. The dramatic fall in adherence coincides with the time when the women had to fetch their second drug bottle. The rates of highly adherent women in different trial arms have been reported in paper I.

The proportions of women in the medium adherence group taking more than 20% of allocated treatment were much higher. At the end of the first trial year, 83% of the participants took over 20% of their assigned trial medication in treatment arms. At the end of the third trial year, there were on average 61% of participants in therapy arms using more than 20% of allocated trial treatment. For the whole trial period, there were on average 62% of participants in the medium adherence group in treatment arms.

Adherence was lower in the placebo arm than in the HT arms of the trial. The rates of adherent women did not differ in the blind and in the non-blind HT arm. Contamination was higher in the non-blind than in the blind sub-trial. Throughout the trial, there were about 90% of women in the control arm who did not start hormone therapy. In the placebo arm, 5% of women started prescribed hormone therapy.

Reasons for non-adherence have been reported separately (Vorobjov et al, 2005). In hormone therapy arms, the most common reasons for stopping trial treatment were side effects (for 40% of women who stopped treatment in the non-blind HT arm and for 32% of women who stopped treatment in the blind HT arm) or no wish to continue trial treatment. The most often reported side effects were vaginal bleeding, mastodynia, weight gain, headache, and fluid retention. From the women who started HT in non-treatment arms, 77% did so due to menopausal symptoms and 50% on doctor's recommendation (more than one reason could be indicated).

5.2 Coronary heart disease, cerebrovascular disease, total cancer, and bone fractures (Paper I)

During the mean follow-up period of 3.4 years, there were 171 coronary heart disease events among 898 women in the hormone therapy arms and 159 events among 880 women in the non-therapy arms within the main trial. The women participating in the pilot study were excluded from the present analysis as their background data were slightly different. The number of women experiencing coronary heart disease events after adjustment by blinding, age at recruitment and former oral contraceptive use was higher in the hormone therapy arms (HR 1.12; 95% CI: 0.90–1.40). The increase in the adjusted cerebrovascular disease rates in hormone therapy arms (HR 1.28; 95% CI: 0.85–1.82) resulted from 58 events in the hormone therapy arms and 48 in the non-therapy arms. The total cancer rates after adjustment were higher in the hormone therapy arms (HR 1.36; 95% CI: 0.73–2.52) with 23 cases in the hormone therapy and 18 in the non-therapy arms. None of these differences were statistically significant. There were two cases of colorectal cancer in the non-blind hormone therapy arm. No pulmonary embolism or deep vein thrombosis events occurred. The incidence of bone fractures was reduced in the hormone treatment arms (HR 1.39; 95% CI: 0.42–0.89). The number of bone fractures diagnosed in the hormone therapy arms was 44 versus 69 in the non-therapy arms. There were no hip fractures among the trial participants.

For all diseases, there were more events in the non-blind sub-trial. No significant interactions were detected between treatment arm and blinding except on risk for cerebrovascular disease (p=0.05). Among 39 women diagnosed with cerebrovascular disease in the non-blind control arm, ten had been using hormone therapy.

An additional analysis that censored a woman's event six months after becoming non-adherent in the blind sub-trial showed a hazard ratio of 1.07 (95% CI: 0.67–

1.70) for coronary heart disease, 6.06 (95% CI: 1.37–26.8) for cerebrovascular disease, 2.35 (95% CI: 0.43–12.8) for total cancer, and 0.49 (95% CI: 0.22–1.09) for bone fractures after adjustment by age group and former oral contraceptive use.

The percentage of women diagnosed with coronary heart disease and bone fractures was lower in the sub-group of women who were within three years of menopause, with the percentage of women diagnosed with cerebrovascular disease and cancer in this group being about the same as in the main trial. The number of total events in this sub-group was small, but the outcomes did not differ from those in the main trial (Table 4).

TABLE 4. The main trial outcomes and hazard ratios with 95% confidence intervals by trial arm for all women and for women within 3 years of menopause at recruitment in the EPHT trial

	Blind		Non-blind		Blind and non-blind	
Outcome	**HT*** **N[1] = 404** **N[2] = 67**	**Placebo*** **N[1] = 373** **N[2] = 41**	**HT*** **N1 = 494** **N[2] = 72**	**Control*** **N[1] = 507** **N[2] = 71**	**Hazard ratio, crude (95% CI) †**	**Hazard ratio, adjusted (95% CI) ‡**
CHD:						
All women	66 (16.3)	62 (16.6)	105 (21.3)	97 (19.1)	1.07 (0.87–1.33)	1.12 (0.90–1.40)
Within 3 yrs of menopause	10 (14.9)	5 (12.2)	5 (6.9)	7 (9.8)	0.96 (0.45–2.05)	1.09 (0.48–2.46)
CVD:						
All women	23 (5.7)	9 (2.4)	35 (7.1)	39 (7.7)	1.22 (0.83–1.78)	1.24 (0.85–1.82)
Within 3 yrs of menopause	4 (6.0)	0	3 (4.2)	1 (1.4)	5.74 (0.70–46.99)	NC
Total cancer:						
All women	6 (1.5)	4 (1.1)	17 (3.4)	14 (2.8)	1.31 (0.71–2.43)	1.36 (0.73–2.52)
Within 3 yrs of menopause	1 (1.5)	0	3 (4.2)	2 (2.8)	1.86 (0.34–10.23)	3.26 (0.35–29.95)
Bone fractures:						
All women	15 (3.7)	25 (6.7)	29 (5.9)	44 (8.7)	0.62 (0.43–0.91)	0.61 (0.42 – 0.89)
Within 3 yrs of menopause	1 (1.5)	2 (4.9)	3 (4.2)	5 (7.0)	0.49 (0.14–1.69)	0.44 (0.13–1.56)

HT = hormone therapy, CI = confidence interval, N1 = number all women, N2 = number of women within 3 yrs of menopause, CHD = coronary heart disease, CVD = cerebrovascular disease, NC = model did not converge

* Data is presented as number (percentage) of women.

† Combined hazard ratio, obtained by Cox proportional hazards modelling, adjusted on the basis of stratification by blinding.

‡ Combined hazard ratio, obtained by Cox proportional hazards modelling, adjusted on the basis of stratification by blinding, age group and prior oral contraceptive use.

5.3 Quality of life and symptoms reporting (Paper II)

Data from annual questionnaires were used to study the effect of HT on quality of life and symptoms of menopause. Symptoms reported most often by all participants in the annual questionnaires during the trial were chronic fatigue, stiffness or aches in joints, and backache. During the trial, women in the hormone therapy arms reported vaginal bleeding more often than women in non-therapy arms (OR 3.54; 95% CI: 1.85–7.26 at the end of the second year, OR 8.40; 95% CI: 3.27–27.43 at the end of the trial). The number and the severity of bleeding episodes in the previous 12 months per woman were also higher in the hormone therapy arms.

Hot flushes (OR 0.34; 95% CI: 0.25–0.48 at the end of the second year, OR 0.54; 95% CI: 0.41–0.71 at the end of the trial) and sweating episodes (OR 0.63; 95% CI: 0.49–0.82 at the end of the second year, OR 0.74; 95% CI: 0.58–0.93 at the end of the trial) were reported less often by women in the hormone therapy arms. After combining data from both sub-trials, there were fewer women in the hormone therapy arms reporting painful intercourse at the end of the first trial year (OR 0.59; 95% CI: 0.37–0.94), but more at the end of the trial (OR 3.12; 95% CI: 1.65–6.25). The proportion of women having had no intercourse was similar in all arms over time.

At the end of the second trial year, women randomised to hormone therapy reported stiffness and aches in joints less often than women not randomized to hormone therapy (OR 0.77; 95% CI: 0.61–0.97), but the difference disappeared at the end of the trial (OR 0.98; 95% CI: 0.80–1.21). At the end of the trial, women in the hormone therapy arms reported backache more often than women in non-therapy arms (OR 1.12; 95% CI: 1.05–1.61). Sleeping problems were reported less often by women in the hormone therapy arms at the end of the second trial year, but there was no significant difference at the end of the trial. There was no difference in the reporting of depression, fatigue, dizzy spells or any other of the 17 symptoms asked of participants in the different trial arms in annual surveys.

Despite the differences in the prevalence of symptoms, there was no difference in the distribution of women with different EuroQoL scores in the different trial arms. At the end of the second trial year, half of the trial participants had a quality of life score of 0.90 (95% CI: 0.88–0.92) and at the end of the trial, half of the women participating in the trial had a score of 0.80 (95% CI: 0.78–0.82). Women with hot flushes had lower quality of life, the effect of sweating episodes on quality of life was inconsistent, and bleeding had no effect on the quality of life.

There was no difference between the arms in reporting problems with self-care, everyday activities, pain or discomfort, anxiety or depression, but problems with mobility were reported more often by women in the blind hormone therapy

arm at the end of the trial (OR 1.43, 95% CI 1.01–2.05). This may be explained by more women reporting backache in hormone therapy arms at the end of the trial.

Women being employed had better quality of life (OR 1.64; 95% CI: 1.16–2.31) and former smokers worse (OR 0.68; 95% CI: 0.49–0.94) in comparison with the others. Women with a higher parity tended to have a better quality of life after menopause (OR 1.01; 95% CI: 1.00–1.02). Being randomised to hormone therapy or not, marital status and living-place had no effect on the quality of life.

The prevalence of hot flushes at the end of the trial was higher ($p<0.05$) among women with hot flushes before recruitment, decreased with time and age, and was less frequent among women in hormone therapy arms. Sweating episodes at the end of the trial were more frequent among women having them at baseline, decreased with time, and were less frequent in hormone therapy arms, but did not depend on participant's age. Stiffness or aches in joints at the end of the trial was more frequent among women with these complaints at baseline and increased with age, but did not depend on hormone treatment or time. Backache at the end of the trial was more frequent among women with backache at baseline and in hormone therapy arms, increased with age, but there was no effect of time. Depression at the end of the trial was associated with depression at baseline, and decreased with age, but did not depend on hormone treatment or time. Sleep problems at the end of the trial were reported more often by women reporting sleep problems before recruitment, increased with time and were less frequent in hormone therapy arms, not depending on age. Blinding had no effect on the prevalence of any symptoms over time.

5.4 Health care utilization (Paper III)

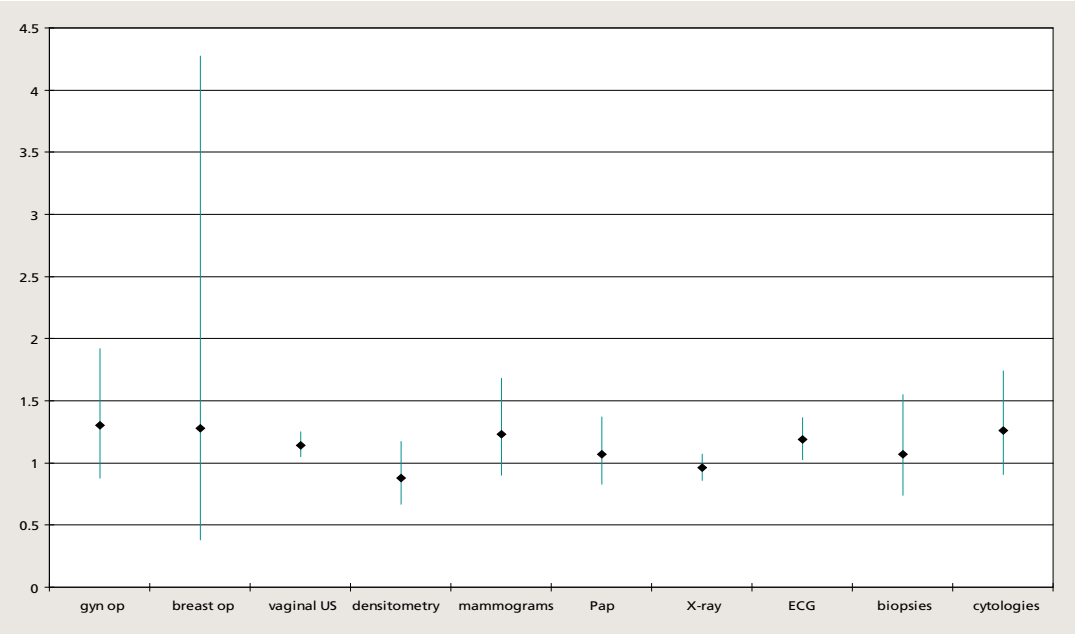
The main outcome measures were number of health care visits, number of visits to family practitioners, to all medical specialists and separately to gynaecologists, number of hospitalizations and hospital days, number of sick-leave days, and number of women who used selected medical procedures, each calculated in four trial arms per person-year. Based on previous literature (Thorp et al, 2001; Writing Group for the Women's Health Initiative Investigators, 2002) we selected from the list of medical procedures vaginal ultrasonography, biopsies, gynaecological operations, mammography, breast operations, bone densitometry, Pap-smears, cytological investigations, X-ray investigations and electrocardiograms of the heart. A comparison of the 20 most often-used medical services in trial arms did not provide any additional information. Follow-up was done by annual linkages to the database of the Estonian Health Insurance Fund. The last follow-up date was December 31, 2003. The mean follow-up time in the trial was 3.4 years. The women participating in the pilot study were excluded from the present analysis.

Recruitment visits and clinical investigations before enrolment were not included in the present analysis. Women were invited to see the trial physician once a year. Annual visits to trial physicians were included in the analysis. We assume that these visits would normally appear in everyday practice as well. In the non-blind sub-trial, the percentage of women attending the first annual examination was higher in the hormone therapy arm, but was not significantly different in the two trial arms of the non-blind sub-trial in subsequent years. In the blind sub-trial, the proportion of women attending annual visits did not differ in the two trial arms.

Half of the women in the non-blind HT arm had up to 5.9 health care visits per person-year, while in the control arm the corresponding figure was 5.5 (OR 1.10; 95% CI: 1.02–1.18). Half of the women in the non-blind HT arm had up to 2.5 visits to the family practitioner per person-year, the corresponding figure in the control arm being 2.2 (OR 1.16; 95% CI: 1.06–1.26). In the blind sub-trial, the number of visits to family practitioners, to all medical specialists or separately to gynaecologists did not differ significantly between the arms. There were no significant differences in the numbers of hospitalisations, hospital care days or sick-leave days between the four trial arms.

Women in HT arms had more vaginal sonograms per trial year (RR 1.14; 95% CI: 1.05–1.25). They had also more electrocardiograms per trial year (RR 1.19; 95% CI: 1.03–1.36). There was no significant difference in the number of gynaecological (RR 1.30; 95% CI: 0.88–1.92) or breast operations (RR 1.28; 95% CI: 0.38–4.27), in the numbers of bone densitometry scans, mammograms, Pap-smears, cytological investigations, X-ray investigations or biopsies between the two arms of the non-blind sub-trial (Figure 2). In the blind sub-trial, the number of vaginal sonograms per trial year was higher in the HT arm as well (RR 1.38; 95% CI: 1.06–1.81). In the blind sub-trial, women in the HT arm had more gynaecological operations for each year in the trial (RR 2.54; 95% CI: 1.54–4.37). There were no differences in the use of other medical procedures between the arms of the blind sub-trial. The number of electrocardiograms per trial year was not significantly higher in the blind HT arm (RR 1.02; 95% CI: 0.88–1.17).

The number of health care visits was different between the trial arms only within the non-blind and not the blind sub-trial, suggesting that health care visits in the placebo arm could have been influenced by the trial effect. In the non-blind HT arm, the number of vaginal sonograms and electrocardiograms was higher than in the control arm. In the blind HT arm, the number of sonograms and gynaecological investigations was higher than in the placebo arm. The use of medical procedures seems to be related to the biological effects of hormone therapy, and not to the number of medical visits or the trial effect. The use of health services was less influenced by the trial effect in the non-blind than in the blind sub-trial. The biological effect of HT was not influenced by blinding.



gyn op – gynaecologic operations; breast op – breast operations; vaginal US – vaginal sonograms; densitometry – bone densitometry scan; Pap – Pap-smears; ECG – electrocardiograms of the heart

FIGURE 2. Rate ratios and 95% CI for the use of selected medical procedures by women in the non-blind EPHT sub-trial

5.5 Health care costs (Paper III)

Inpatient and outpatient health care costs, costs of prescribed drugs and sick-leave days were calculated in the four trial arms per person-year according to the data in the database of the Estonian Health Insurance Fund. Dental care was not included in the present analysis. Costs of drugs and sick leave were analyzed as costs purchased by the Health Insurance Fund. The cost of trial treatment based on adherence rates in the hormone therapy arm was calculated separately from the costs of prescribed drugs. Costs of prescribed drugs include hormone therapy prescribed in the control arm. The rate of currency conversion was 15.65 Estonian kroon per 1 euro (EUR). The average rise in the costs to the Estonian Health Insurance Fund from 1999 to 2004 was about 15% (unpublished data). The mean follow-up time was 3.4 years. Women participating in the pilot study were not included in the analysis.

The distribution of health care costs was skewed in all trial arms. In the non-blind sub-trial, outpatient health care costs were higher in the HT arm (Figure 3). Half of the women in this arm used outpatient health care costing up to 45 EUR per person-year, while the corresponding figure in the control arm was 41 EUR per person-year. Inpatient health care costs did not differ in the two non-blind arms. Half of the women in both arms did not use inpatient care per person-year at all.

For 75% of women, inpatient health care costs were up to 53 EUR per person-year in the non-blind HT and up to 50 EUR per person-year in the control arm. There were no significant differences between inpatient and outpatient health care costs in the two arms of the blind sub-trial.

Total cost of prescribed drugs per person-year became significantly higher in the hormone therapy arms after including the cost of trial treatment in the calculations, reaching 59 EUR for half of the women in the non-blind HT arm, and 17 EUR in the control arm, the corresponding figures being 58 EUR in the blind HT arm and 15 EUR per person-year in the placebo arm. Reimbursements paid for temporary incapacity from work were similar in all arms.

Because of increased expenses on drugs and added costs on outpatient health care in the non-blind HT arm, total health care costs were higher in the hormone therapy arms. For half of the women in the non-blind HT arm, total health care costs were up to 130 EUR per person-year (113 EUR in the blind HT arm), the corresponding figure in the control arm was 98 EUR (90 EUR in the placebo arm).

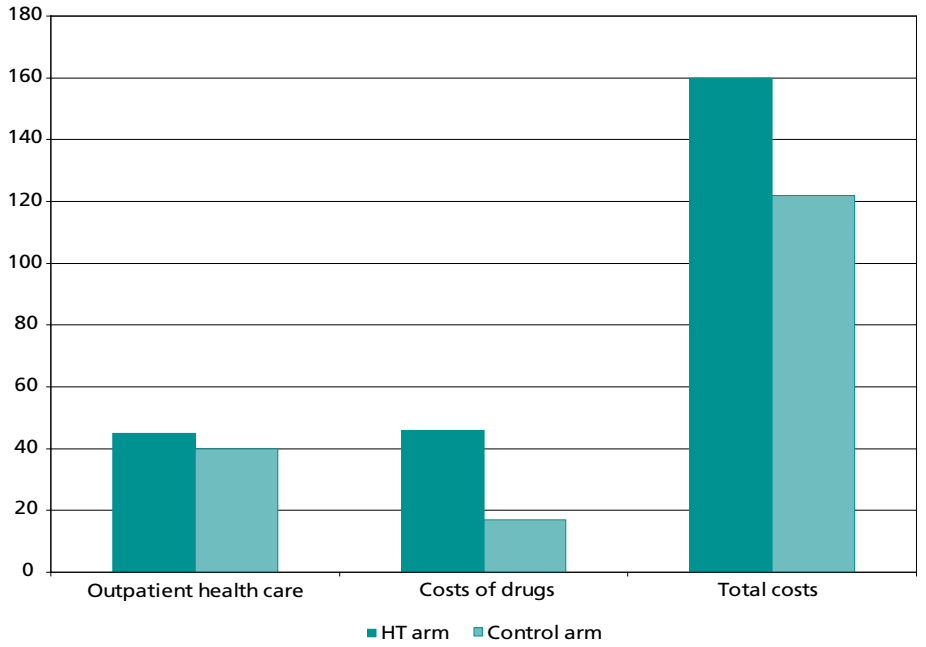


FIGURE 3. Median health care costs in the non-blind EPHT sub-trial in euro per person-year

5.6 Use of prescription medication (Paper IV)

Using the centralised electronic database of the Estonian Health Insurance Fund, prescription medication was analysed in the hormone therapy arms and non-treatment arms during a mean follow-up time of 4.4 (SD 0.7) years. As we had no data about the use of over-the-counter drugs, vitamin D and calcium supplements among them, we were not able to analyse the use of these.

Based on previous literature (Small et al, 2001; Thorp et al, 2001; Jacobs et al, 2003; Khatibi et al, 2004; McIntyre et al, 2005) and on the outcomes of hormone therapy trials (Writing Group for the Women's Health Initiative Investigators, 2002), 21 types of prescription medication according to the anatomical therapeutic chemical (ATC) (WHO, 2006) classification of drugs were selected to calculate the drug usage in hormone therapy versus non-therapy arms throughout the trial. In addition, drug usage was compared between the arms within the blind and non-blind sub-trial. The numbers of women using no prescription drugs, one, two, three, and four or more prescription drugs were compared in four trial arms during the first three trial years. The background characteristics of participating women were analysed to check their influence on the intensity of concomitant drug use during the first two trial years.

In the non-blind sub-trial, women in the HT arm used antihypertensive treatment more frequently than women in the placebo arm. There was no difference between the arms in the use of most classes of anti-hypertensive treatment (antihypertensives, diuretics, beta-blocking agents or agents acting on the renning-angiotensin system), except that the use of calcium channel blockers was higher in both hormone therapy arms (combined HR 1.26; 95% CI: 1.05–1.53). For the majority of prescriptions, hypertensive diseases were the reason for the use of calcium channel blockers. There were no significant differences in the use of drugs for coronary heart disease or drugs lowering serum cholesterol.

There was no difference in the overall use of antidepressants between the trial arms, but the use of selective serotonin reuptake inhibitors was lower in the hormone therapy arms (HR 0.77; 95% CI: 0.60–0.99). After combining data from both sub-trials, the use of hypnotics and sedatives was lower in hormone therapy arms (HR 0.70; 95% CI: 0.50–0.99). The use of anxiolytics did not differ significantly between the trial arms.

There was no difference between the arms in the use of non-steroid anti-inflammatory drugs, antacids, anti-allergic drugs, thyroid replacement therapy, painkillers, bisphosphonates, anti-diabetic drugs, anti-thrombotic agents, or anti-migraine preparations during the trial. The use of local gynaecological anti-inflammatory drugs was higher among women randomised to the hormone therapy arms of both sub-trials (HR 1.48; 95% CI: 1.10–1.99). The reasons for the increased use of local vaginal treatment in the HT arms were more frequent vaginal candidiasis and acute vulvitis or vaginitis.

During the trial, the proportion of women using prescription drugs increased in all trial arms. The proportion of women using prescribed drugs in different trial years did not differ between the four trial arms. Women who used four or more prescription drugs during the first two trial years were older, had a higher body mass index (BMI) and lived outside the capital. Being randomised to the hormone therapy arm or not did not have an impact on the intensity of the prescription drug usage in either sub-trials. Blinding had no effect on the overall use of prescribed drugs.

6 Discussion

6.1 Key findings from the EPHT trial

The EPHT trial was carried out among healthy and relatively young women in Estonia. The main outcomes were ascertained with the help of routinely collected clinical data with a complete follow-up. The results of the EPHT trial show a statistically significant reduction in bone fractures. The risk of coronary heart disease, cerebrovascular disease and cancer was not significantly affected, probably due to the small number of subjects. The results of the EPHT trial adds to evidence that hormone therapy reduces bone fractures in healthy women, and provides no evidence of benefits for coronary heart disease, cerebrovascular disease, or total cancer.

As it was originally planned to pool the results from the EPHT trial with the WISDOM trial data (the trial was prematurely stopped), the study power in the EPHT trial alone was not enough to detect the effect of HT on the risk of breast, colorectal, ovarian or endometrial cancer, or the risk of venous thrombosis. The effect of HT on gallbladder disease, diabetes, and dementia was not studied in the EPHT trial.

Timing of the initiation of HT relative to menopause with regard to cardiovascular and other outcomes has been stated as a need for future research. A sub-group analysis of 251 women within three years of menopause in the EPHT trial did not give different results to the main analysis (Table 4).

Despite being a preventive trial, a substantial proportion of women among the participants of the EPHT trial were symptomatic. The EPHT trial proved HT to be effective for alleviating vasomotor symptoms and sleep problems. The positive effect of HT on sexual functioning was not confirmed in the EPHT trial. The local administration of oestrogens may be more effective than systemic administration in reducing vaginal and genital dryness. For the participants of the EPHT trial, HT was associated with bleeding episodes and backache. The effect of HT on backache has not been reported on previously from randomised trials. The positive effect of HT on depression, stiffness or aches in joints, or physical functioning described in some earlier studies was not confirmed. No effect on any other symptoms was observed. HT did not influence overall health-related quality of life.

The EPHT trial was the first to evaluate the effects of HT on the use of health services and prescription medication and on health care costs in the framework of a randomised trial. The results from the EPHT trial show that hormone therapy users created additional health care expenses. The increase in health care costs was caused by the additional costs of outpatient health services and drugs. Hormone therapy added to the number of outpatient health care visits, vaginal sonograms, and

electrocardiograms. HT users also tended to have more gynaecological operations. Hormone therapy did not increase the overall use of prescription medication other than hormone therapy, but the types of drugs used in hormone therapy and non-therapy arms varied. HT increased the use of calcium channel blockers for hypertension and the use of local vaginal treatments for vaginal candidiasis and decreased the use of hypnotics, sedatives and selective serotonin reuptake inhibitors in the HT arms. The increased use of selective serotonin reuptake inhibitors and sedatives in the non-treatment arms may be due to their effectiveness in treating menopausal symptoms.

Conjugated oestrogens are not in clinical use in some countries, including Finland. Data from different trials show that the health effects differ for ET and combined HT, but do not depend on the regimen used. Thus the results of the EPHT trial on the clinical effects of combined HT can be generalized to similar patients in any other country. The results concerning health-related quality of life may have been influenced by cultural and socio-economic factors. The results concerning health care utilization cannot be directly transferred to any other country, but they can be calibrated to other health care systems and health behaviour.

6.2 Strengths and limitations

6.2.1 Losses before recruitment of the EPHT trial

Altogether 39 713 recruitment questionnaires were mailed to a group of 44 664 women residing in the areas around the three trial clinics. As the recruitment questionnaires were in Estonian, Russian speaking women were not approached, hence the discrepancy between the population and the number of questionnaires sent out. Of the mailed questionnaires, 14 743 (37%) were returned. Of the approached women, 6606 (17%) were interested in joining the trial. Women with less education, retired, not married or widowed, moved to a new location, and in a higher age group were less interested in participation (unpublished data). Current and former smokers were more interested in participation in comparison with non-smokers (unpublished data).

The 4 295 women willing and eligible for participation formed 10.5% of the original cohort and were randomised into four trial arms (Figure 1). At the moment of mailing the invitations to the recruitment visit, the number of women in all four trial arms was balanced. More than half of the randomly assigned women were lost before recruitment, some did not attend the recruitment visit, and some did not join the trial during the recruitment visit. The number of women attending the recruitment visit was bigger in the non-blind sub-trial (1241 in the

non- blind versus 1069 in the blind sub-trial). The number of women who signed the informed consent during the recruitment visit was also higher in the non-blind sub-trial (79.6% of women attending the visit in the non-blind sub-trial versus 72.7% in the blind sub-trial). It resulted in 2.5% of the original population being included in the non-blind sub-trial and 2.0% being included in the blind trial arm (Hemminki et al, 2004).

The loss of more than half of the randomly assigned women before recruitment happened without the woman or the trial staff knowing to which arm the woman belonged. Thus, this loss did not endanger comparability between the trial arms. All trial outcomes have been presented separately for all four trial arms, and the data analysis has been done within the blind and non-blind sub-trial in addition to the combined analysis for the treatment versus non-treatment arms.

6.2.2 The blind and the non-blind sub-trial

Randomisation was, unconventionally, carried out before recruitment in order to study the impact of blinding on the recruitment process, adherence, and health care costs, and for logistic reasons (Figure 1). Blinding resulted in less women being recruited in the blind sub-trial. The impact of blinding on recruitment has been described elsewhere (Hemminki et al, 2004). Despite the differences in the numbers of women recruited in the blind and in the non-blind sub-trial, the baseline characteristics of women did not differ between the four trial arms except for small differences in age and history of contraceptive use. The possible bias was corrected for by using an adjustment for former oral contraceptive use and age group in the analysis.

Adherence was similar in the hormone therapy arms, and lower in the placebo arm. Contamination was higher in the control arm than in the placebo arm. The impact of blinding on adherence has been analysed in detail elsewhere (Vorobjov et al, 2005).

For all outcomes, there were more events in the non-blind sub-trial. This may have been a chance finding, but may also have resulted from women with poor health being accepted more eagerly by some trial physicians in the non-blind sub-trial. It may also have resulted from less care-seeking in the blind sub-trial, perhaps due to the placebo effect. The difference in the cerebrovascular endpoints in different sub-trials may have resulted from HT use in the non-blind control arm. Surprisingly, blinding had no effect on the prevalence of symptoms over time, and did not influence the quality of life.

The number of health care visits was different only between the arms of the non-blind trial but not in the arms of the blind sub-trial, suggesting that health care visits in the placebo arm could have been influenced by the trial effect. Trial costs were higher in the blind sub-trial. The use of prescription drugs and selected

medical procedures seemed to be related to the biological effects of hormone therapy only.

Utilization of health services and health care costs could not have been studied within a blind setting. Health outcomes can be studied both in blind and non-blind settings. Blinding adds to trial costs. The effect of blinding on trial outcomes will be analysed systematically later.

6.2.3 Validity and quality of data

The adherence rate in treatment arms was not very high, but it was about the same as can be expected in real life circumstances (Thorp et al, 2001). This may have caused dilution of the differences between the treatment and non-treatment arms as regards trial results. For health outcomes, the results of the analysis censoring women six months after becoming non-adherent did not differ from the uncensored results. There was no difference between adherent and non-adherent women in regard to the use of calcium channel blockers, selective serotonin reuptake inhibitors and anxiolytics or the time of starting such treatment.

We assume that follow-up of the participants in regard to health outcomes, use of health services and prescription medication was complete, as the probability of missing data in the Health Insurance Fund database is small. Compensation to clinics and drug stores does not depend on the diagnosis but on the services that have been provided. As the compensation depends on the transmission of data to the central database, the process is quick, and the probability of there being missing data in the database is small. However, the quality of the diagnoses in the Health Insurance Fund database has not been validated. The Estonian Cancer Registry database has been validated for overall completeness of registration, being 90.8% in 1998 without linkages to the databases of the major hospitals (Lang et al, 2003).

The last follow-up date for the Estonian Mortality Database was 12 months earlier than the last follow-up date for the Estonian Health Insurance Fund database and Estonian Cancer Registry database. We assume that it does not have any practical effect on the estimation of outcomes.

The subjects and investigators were not blinded in the non-blind sub-trial, only persons doing linkages in the registries were blinded. The data processing in the registries had no information on women's participation in the trial. Blind assessment of the trial outcome is more important than blinding the treatment (Day and Altman, 2000).

No data for EuroQoL scores was collected at baseline. We assume that the EuroQoL scores at baseline were similar in all trial arms. As the response rate to the annual questionnaires varied, and the final questionnaire was filled in at a different time, longitudinal data analysis was used to estimate the impact of HT on the prevalence of symptoms over time.

6.3 Comparison of the results with the WHI trial

Before the EPHT trial, the WHI trial in the United States was the only long-term randomised trial to report the outcomes of HT among healthy postmenopausal women. Most of the participants in the EPHT trial used the same regimen as those in the WHI trial. The WHI trial has been criticised for having partly been a secondary preventive trial because of participants' age and other background characteristics (MacLennan et al, 2002; McDonough, 2002).

In comparison with women participating in the WHI trial, women in the Estonian trial were younger and healthier (Table 5). On average they were 5 years younger on entering the trial, and the average time since menopause was 8 years in the EPHT trial compared to 13 years in the WHI trial. All women in the EPHT trial were white. The mean BMI of the Estonian participants at screening was lower. There were more current smokers among the participants in the EPHT trial. About the same proportion of women had a college degree or higher in both studies (Stefanick et al, 2003). The proportion of nulliparous women was about the same in both trials. Fewer women in the Estonian trial had been treated for hypertension before recruitment, but their baseline mean systolic and diastolic blood pressure was slightly higher. Fewer women in the Estonian trial had a history of myocardial infarction, a history of diabetes, and a female relative with breast cancer. Women with a history of stroke or deep venous thrombosis were excluded from the EPHT trial. In the Women's Health Initiative trial, prior hormone therapy use was nearly 26%. Data from the EPHT pilot study showed a lower proportion of women having used prior HT (Hovi et al, 2004). According to the State Agency of Medicine, oestrogen use in Estonia was low between 1999 and 2001 (Hovi et al, 2004). Prior use of oral contraceptives was 43% in the Women's Health Initiative and 7% in the Estonian trial. Some 13% of women who had had a hysterectomy before entering the trial also used combined hormone therapy in the Estonian trial. There are no data as to whether the hysterectomies were done with or without oophorectomy. The proportion of women with baseline vasomotor symptoms was higher in the EPHT trial.

The main outcome results in the EPHT trial concerning coronary heart disease, cerebrovascular disease, and bone fractures are consistent with the results of the WHI trial. For total cancer, the hazard ratio was higher than in the WHI trial. The number of participants in the EPHT trial was not sufficient to guarantee the statistical significance of the findings except for bone fractures.

Quality of life among healthy women using HT for preventive purposes was assessed for three years in the WHI trial. The follow-up period for menopausal symptoms and quality of life in the EPHT trial was longer than in the WHI trial. According to the WHI trial data, combined hormone therapy improved vasomotor symptoms, vaginal or genital dryness, and all pain symptoms, but increased the rates of breast tenderness during the first year of use and vaginal bleeding persistently

(Barnabei et al, 2005). In the EPHT trial, HT alleviated vasomotor symptoms and sleeping problems, but added bleeding episodes and backache. The effect of HT on painful intercourse and stiffness or aches in joints was not consistent in the EPHT trial. The difference in outcomes can be explained with differences in the baseline prevalence of symptoms, in the participants' health indicators and age, in the difference of measurement tools, and cross-cultural differences (Avis et al, 2006). No clinically meaningful effect of combined HT on health-related quality of life among women without vasomotor symptoms was detected either in the EPHT or in the WHI trial (Hays et al, 2003).

The impact of HT on the use of health care services and health care costs has not been studied previously in randomised controlled trials. Only baseline medication use has been reported in the WHI trial (Furberg et al, 2002). The use of health services and health care costs has not been reported from the WHI trial.

TABLE 5. Comparison of the baseline characteristics of participants in the Estonian Postmenopausal Hormone Therapy (EPHT) and the Women's Health Initiative (WHI) trial

Characteristics	EPHT N = 1 823	WHI (E+P) N = 16 608
Age, mean (SD), yrs	58.2 (4.0)	63.2 (7.1)
Time since menopause, yrs	8.0	13.4
Age groups at screening, yrs		
50–59	58.6%	33.3%
60–69	41.4%	45.2%
70–79	-	21.5%
BMI, mean (SD), kg/m2	27.0 (4.5)	28.5 (5.9)
BMI groups, kg/m2		
< 25	36.0%	30.6%
25–29	39.6%	35.3%
> = 30	24.4%	34.1%
Education		
College degree or higher	34.6%	34.9%
Systolic BP, mean (SD), mm Hg	136.9 (16.9)	127.7 (17.6)
Diastolic BP, mean (SD), mm Hg	86.3 (10.9)	75.7 (9.1)
Smoking*		
Never	70.3%	49.8%
Past	15.1%	39.7%
Present	14.6%	10.5%
Parity*		
> = 1 term pregnancy	90.9%	89.8%
Treated for diabetes	3.5%	4.4%
Treated for hypertension	13.2%	36.1%
History of angina	3.3%	2.8%
History of myocardial infarction	1.3%	1.7%
Female relative with breast cancer	5.6%	15.7%
Prevalence of vasomotor symptoms	44.9%	12.5%

For selected variables also mean and standard deviation (SD) are indicated.
BMI = body mass index, BP = blood pressure.

* Among women for whom data was available.

7 Conclusions

7.1 Implications for clinical practice

In 2003, the European Agency for the Evaluation of Medicinal Products (EMEA) recommended HT only for the treatment of climacteric complaints, using the minimal effective dose and shortest duration of treatment (EMEA, 2003). In the same year, the US Food and Drug Administration (FDA) requested that manufacturers update labelling for hormone therapy products, stating that HT products are approved for use in treating moderate to severe hot flushes and night sweats, moderate to severe vaginal dryness, and for preventing osteoporosis associated with menopause in women at significant risk where non-oestrogen regimens are inappropriate. Solely for vaginal symptoms, topical products were advised to be considered (FDA, 2003).

Several countries modified the guidelines for HT use accordingly. The latest conclusion by the British Menopause Society states that the results from the WHI trial and the MWS show that HT should not be prescribed solely for possible prevention of cardiovascular disease and dementia (British Menopause Society, 2006). The North American Menopause Society's latest position statement, published in March 2007, recommends HT for hot flushes and vaginal atrophy, and for preventing osteoporosis (North American Menopause Society, 2007). However, both societies raise a timing hypothesis that HT may not increase the risk of coronary heart disease if used during or shortly after menopause.

The results from the EPHT trial confirm the positive effect of HT on bone fractures and vasomotor symptoms, and provide no evidence of benefits for cardiovascular disease or total cancer in any age group. HT added episodes of vaginal bleeding and backache, and had no effect on health-related quality of life among women without vasomotor symptoms.

7.2 Implications for policy makers

The EPHT trial was the first trial to study the impact of HT on the use of health services and evaluate health care costs related to HT. The results of the trial show that HT increases health care expenses. Adjudication of the endpoints was based on routinely collected data in the Estonian Health Insurance Fund.

Clinical and political decisions in health care should be based on clear evidence, and gaps between evidence and practice should be avoided. Innovative health interventions and new indications for the use of drugs that have been already

marketed should be first studied in randomised clinical trials. Insufficient use of evidence in clinical guidelines and recommendations reveals a need for a culture change to improve public health through evidence-based policy. In addition to the risk-benefit profile of medical interventions, decision-makers need information about their impact on health care utilization and related costs.

Post-marketing research is needed to assess the long-term effects and costs of interventions already in wide use. Routinely collected data about adverse events of drugs and interactions between them is not enough to evaluate long-term risks and benefits of different interventions, and more powerful surveillance tools are needed to guarantee the safety of patients. In addition to data from clinical trials, data from various health registries could be combined into a pan-European or regional (Nordic, Central European, Mediterranean, etc) database, forming a basis for monitoring the outcomes of therapies, vaccination strategies, and other interventions as well as costs related to them. Such information should be used for the public interest and would be valuable for policy-makers, health professionals and patients.

Evidence-based public health actions often face a mismatch between the importance of the public health problem and the adequacy of evidence on potential interventions to address the problem. Therefore, research topics and research funding should be prioritized in correspondence with the needs of the society.

7.3 Implications for future research

The effect of HT on coronary heart disease, dementia and cognition among younger women and the effect of oestrogen therapy on the risk of breast cancer have recently been debated. It is unlikely that any future randomised trials would be large enough to evaluate these risks in younger postmenopausal women or the risk of oestrogen therapy on breast cancer, which has also been debated. The low absolute rate of these diseases would require many thousands of women to be recruited in randomised trials.

Routinely collected data in hospital discharge registries, pharmacy registries, cancer registries and other databases can be used to support data from randomised trials quickly and at a relatively low cost (Williams et al, 2003). Thus, register-based data from different countries could be used to study the effect of HT among younger women, the effect of ET on breast cancer, and the health outcomes for HT over long-term use. It would also give an answer to the questions of whether lower doses and different regimens, or the route of administration would impact the effect of HT, or if sequential combined therapy or the progestin-releasing intrauterine system has a different effect than combined continuous HT, or whether HT will affect morbidity or mortality from premature menopause and premature ovarian failure, and many others.

Biomedical research can be harnessed to determine the role of biomarkers on health outcomes, to understand the pathophysiology of the outcomes, and to study if genetic variants might affect response to HT. Still, further research is not likely to change the overall estimate of the effect of HT. Health-related quality of life should be incorporated in the composite risk-benefit ratio for HT, although it is difficult to evaluate it because of the different measurement tools used, variations in menopausal symptomatology across cultures, a large placebo effect, and extrinsic factors that alter women's responses. More evidence is required of possible health changes after discontinuation of HT. Besides medical interventions, the role of lifestyle on health in ageing populations deserves more attention in health research.

References

Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. The Women's Health Initiative randomized trial. JAMA 2003;290:1739–48.

Angerer P, Stork S, Kothny W, Schmitt P, von Schacky C. Effect of oral postmenopausal hormone replacement on progression of atherosclerosis. A randomized, controlled trial. Arterioscler Thromb Vasc Biol 2001;21:262–8.

Angerer P, Stork S, Kothny W, von Schacky C. Effect of postmenopausal hormone replacement on atherosclerosis in femoral arteries. Maturitas 2002;41:51–60.

Armstrong K, Cheng TM, Albert D, Randall TC, Schwartz JS. Cost-effectiveness of raloxifene and hormone replacement therapy in postmenopausal women: impact of breast cancer risk. Obstet Gynecol 2001;98:996–1003.

Avis NE, Brockwell S, Colvin A. A universal menopausal syndrome? Am J Med 2006;118:37-46.

Bagger YZ, Tanko LB, Alexandersen P, Hansen HB, Mollgaard A, Ravn P, Qvist P, Kanis JA, Christiansen C. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. Bone 2004;34:728–35.

Banks E, Beral V, Reeves G, Balkwill A, Barnes I. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. JAMA 2004: 291:2212–20.

Banks E, Hunskaar S, Skolbekken JA. High prevalence of use is not confined to doctors. BMJ 1996;312:638.

Barlow DH, Grossett KA, Hart H, Hart DM. A study of the experience of Glasgow women in the climacteric years. BJOG 1989;96:1192–7.

Barnabei VM, Cochrane BB, Aragaki AK, Nygaard I, Williams RS, McGovern PG, et al. Menopausal symptoms and treatment-related effects of estrogen plus progestin in the Women's Health Initiative. Obstet Gynecol 2005;105:1063–73.

Botteman MF, Shah NP, Lian J, Pashos CL, Simon JA. A cost-effectiveness evaluation of two continuous-combined hormone therapies for the management of moderate-to-severe vasomotor symptoms. Menopause 2004;11:343–55.

Breslow NE. Extra-Poisson variation in log-linear models. Applied Statistics 1984; 33:38–44.

British Menopause Society Council Consensus Statement on Hormone Replacement Therapy. Available at: http://www.thebms.org.uk/statementcontent.php?id=1 (accessed May 14, 2007).

Brown JS, Vittinghoff E, Kanaya AM, Agarwal SK, Hulley S, Foxman B; Heart and Estrogen/Progestin Replacement Study Research Group. Urinary tract infections in postmenopausal women: effect of hormone therapy and risk factors. Obstet Gynecol 2001;98:1045–52.

Brunner RL, Gass M, Aragaki A, Hays J, Granek I, Woods N, et al. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy. Arch Intern Med 2005;165:1976–86.

Byington RP, Furberg CD, Herrington DM, Herd JA, Hunninghake D, Lowery M, et al. Effect of estroegn plus progestin on progression of carotid atherosclerosis in postmenopausal women with heart disease: HERS B-mode substudy. Arterioscler Thromb Vasc Biol 2001;22:1692–7.

Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Levesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation 2007;115:840–5.

Carlson MC, Zandi PP, Plassman BL, Tschanz JT, Welsh-Bohmer KA, Steffens DC et al. Hormone replacement therapy and reduced cognitive decline in older women: the Cache County Study. Neurology 2001;57:2210–6.

Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density. The Women's Health Initiative Randomized Trial. JAMA 2003;290:1729–38.

Cheung AP, Wren BG. A cost-effectiveness analysis of hormone replacement therapy in the menopause. Med J Aust 1992;156:312–6.

Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The Women's Health Initiative Randomized Trial. JAMA 2003;289:3243–53.

Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao C, Rodabough RJ, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004;350:991–1004.

Cirillo DJ, Wallace RB, Rodabough RJ, Greenalnd P, LaCroix AZ, Limacher MC, Larson JC. Effect of estrogen therapy on gallbladder disease. JAMA 2005;293:330–9.

Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofield PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT Atherosclerosis Study. BJOG 2002;109:1056–62.

Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332:1589–93.

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350:1047–59.

Cramer DW, Knapp RC. Review of epidemiologic studies of endometrial cancer and exogenous estrogen. Obstet Gynecol 1979;54:521–7.

Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al. Estrogen plus progestin and risk of venous thrombosis. JAMA 2004; 292:1573–80.

Daly E, Vessey MP, Barlow D, Gray A, McPherson K, Roche M. Hormone replacement therapy in a risk-benefit perspective. Maturitas 1996a;23:247–59.

Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. Lancet 1996b;348:977–980.

Daly E, Vessey MP, Painter R, Hawkins MM. Case control study of venous thromboembolism risk in users of hormone replacement therapy. Lancet 1996c;348:1027.

Day SJ, Altman DG. Blinding in clinical trials and other studies. BMJ 2000;321:504.

de Kleijn MJJ, Bots ML, Bak AAA, Westendorp ICD, PLanellas J, Coelingh Bennink HJT, et al. Hormone replacement therapy in perimenopausal women and 2-year change of carotid intima-media thickness. Maturitas 1999;32:195–204.

Denes P, Larson JC, Lloyd-Jones DM, Prineas RJ, Greenland P. Major and minor ECG abnormalities in asymptomatic women and risk of cardiovascular events and mortality. JAMA 2007;297:978–85.

Diggle PJ, Liang KY, Zeger SL. Analysis of Longitudinal Data. Oxford University Press; 1994.

EMEA Public Statement on recent publications regarding hormone replacement therapy. Available at: http://www.emea.europa.eu/pdfs/human/press/pus/3306503en.pdf (accessed May 2, 2007).

Erb A, Brenner H, Günther KP, Stürmer T. Hormone replacement therapy and patterns of osteoarthritis: baseline data from the Ulm Osteoarthritis Study. Ann Rheum Dis 2000;105–9.

Espeland MA, Hogan PE, Fineberg SE, Howard G, Schrott H, Waclawiw MA, Bush TL. Effect of postmenopausal hormone therapy on glucose and insulin concentrations. PEPI Investigators. Postmenopausal Estrogen/Progestin Interventions. Diabetes Care 1998;21: 1589–95.

Espeland MA, Rapp SR, Shumkaer SA, Brunner R, Manson JE, Sherwin BB, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women. Women's Health Initiative Memory Study. JAMA 2004;291:2959–68.

Estonian Health Insurance Fund. Available at: http://www.haigekassa.ee/HK/in_english.htm. (accessed 14 October, 2004).

Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of the North American Menopause Society. Menopause 2007;14:168–82.

Falkeborn M, Persoon I, Terent A, Adami HO, Lithell H, Bergstrom R. Hormone replacement therapy and the risk of

stroke. Follow-up of a population-based cohort in Sweden. Arch Intern Med 1993;153:1201–9.

FDA Approves New Labeling and Provides New Advice to Postmenopausal Women Who Use or Who Are Considering Using Estrogen and Estrogen With Progestin. Available at: http://www.fda.gov/oc/factsheets/WHI.html (accessed May 14, 2007).

Felson DT, Zhang Y, Hannan MT, Kiel DO, Wilson PW, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. N Eng J Med 1993;329:1141–6.

Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, Levy D. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1995;38:1500–5.

Fernandez E, La Vecchia C, D´Avanzo B, Franceschi S, Negri E, Parazzini F. Oral contraceptives, hormone replacement therapy and risk of colorectal cancer. Brit J Cancer 1996;73:1431–5.

Finucane FF, Madans JH, Bush TL, Wolf PH, Kleinman JC. Decreased risk of stroke among postmenopausal hormone users. Results from a national cohort. Arch Intern Med 1993;153:73–9.

Furberg CD, Vittinghoff E, Davidson M, Herrington DM, Simon JA, Wenger NK, Hulley S. Subgroup interactions in the Heart and Estrogen /Progestin Replacement Study. Lessons Learned. Circulation 2002;105:917–22.

Gabal LL, Goodman-Gruen D, Barrett-Connor E. The effect of postmenopausal estrogen therapy on the risk of non-insulin-dependent diabetes mellitus. Am J Public Health 1997;87:443–5.

Gallagher JC, Kable WT, Goldgar D. Effect of progestin therapy on cortical and trabecular bone: comparison with estrogen. Am J Med 1991;90:171–8.

Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. JAMA 2002;288:49–57.

Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992; 117:1016–37.

Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. Ann Int Med 2000;132:689–96.

Greendale GA, Espeland M, Slone S, Marcus R, Barrett-Connor E, for the PEPI Safety Follow-up Study (PFES) Investigators. Arch Intern Med 2002;162:665–72.

Greendale GA, Reboussin BA, Sie A, Singh HR, Olson LK, Gatewood O, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Ann Intern Med 1999;130:262–9.

Grendale GA, Reboussin BA, Hogan P, Barnabei VM, Shumkaer S, Johnson S, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions trial. Obstet Gynecol 1998;92:982–8.

Grodstein F, Lifford K, Resnick NM, Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. Obstet Gynecol 2004;103:254–60.

Grodstein F, Martinez ME, Platz EA, Giovannucci E, Colditz GA, Kautzky M, et al. Postmenopausal hormone use and risk for colorectal cancer and adenoma. Ann Intern Med 1998;128:705–12.

Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 1999;106:574–82.

Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, Joffe M, et al. Postmenopausal hormone therapy and mortality. N Engl J Med 1997;336:1769–75.

Grodstein F, Stampfer MJ, Goldhaber SZ, Manson JE, Colditz GA, Speizer FE, et al. Prospective study of exogenous hormones and risk of pulmonary embolism in women. Lancet 1996;348:983–7.

Gutthann SP, Rodriguez LAG, Castellsague S, Oliart AD. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. BMJ 1997;314:796–800.

Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, Rossouw JE. The Women's Health Initiative Recruitment Methods and Results. Ann Epidemiol 2003;13:S18–S77.

Hays J, Ockene JK, Brunner RL, Kotchen JM, Manson JE, Patterson RE, et al. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med 2003;348:1839–54.

Heikkinen J, Kyllönen E, Kurttila-Matero E, Wilèn-Rosenqvist G, Lankinen KS, et al. HRT and exercise: effects on bone density, muscle strength and lipid metabolism. A placebo controlled 2-year prospective trial on two estrogen-progestin regimens in healthy postmenopausal women. Maturitas 1997;26:139–49.

Hemminki E. Use of combined estrogen-progestin replacement therapy – an example of the dissemination of new indicators for an old technology. Int J Technol Assess Health Care 1988;4:511–9.

Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. BMJ 1997;315:149–53.

Hemminki E, Hovi SL, Veerus P, Tuimala R, Rahu M, Hakama M. Impact of blinding on recruitment – The Estonian Postmenopausal Hormone Therapy Trial. J Clin Epidemiol 2004;57:1237–43.

Henderson BE. The Cancer question: an overview of recent epidemiologic and retrospective data. Am J Obstet Gynecol 1989;161:1859–64.

Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA 2005; 293:935–48.

Herrington DM, Reboussin DR, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, et al. Effects of estrogen replacement therapy on the progression of coronary-artery atherosclerosis. N Engl J Med 2000;343:522–9.

Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy. Results form the Hearts and Estrogen/progestin Replacement (HERS) Study. JAMA 2002;287:591–7.

Hodis HN, Mack WJ, Azen SP, Lobo RA, Shoupe D, Mahrer P, et al. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med 2003;349:535–45.

Hoerger TJ, Downs KE, Lakshmanan MC, Lindrooth RC, Plouffe L Jr, Wendling B, West SL, Ohsfeldt RL. Healthcare use among U.S. women aged 45 and older: total costs and costs for selected postmenopausal health risks. J Womens Health Gend Based Med 1999;8:1077–89.

Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy – results of the double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost 2000;84:961–7.

Hokkanen T, Hemminki E, Aalto P, Hakama M, Huhtala H, Jylhä M, et al. Patient Managed Clinical trial. Contr Clin Trials 1997;18:140–50.

Hovi SL, Hakama M, Veerus P, Rahu M, Hemminki E. Who wants to join preventive trials?--Experience from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]. BMC Med Res Methodol 2005a;5:12.

Hovi SL, Veerus P, Karro H, Topo P, Hemminki E. Women's views of the climacteric at the time of low menopausal hormone use, Estonia 1998. Maturitas 2005b;5:413–25.

Hovi SL. Preventive trial on postmenopausal hormone therapy in Estonia. University of Tampere dissertation, 2006. Available at: http://acta.uta.fi/english/teos.phtml?10842 (accessed April 9, 2007).

Hsia J, Criqui MH, Herrington DM, Manson JE, Wu LL, Heckbert SR, et al. Conjugated equine estrogens and peripheral arterial disease risk: The Women's Health Initiative. Am Heart J 2006;152:170–6.

Hsia J, Criqui MH, Rodabough RJ, Langer RD, Resnick HE, Phillips LS, et al. Estrogen plus progestin and the risk of peripheral arterial disease. The Women's Health Initiative. Circulation 2004;109:620–6.

Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, et al. Conjugated equine estrogens and coronary heart disease. Arch Intern Med 2006;166:357–65.

Hsia J, Simon JA, Lin F, Applegate WB, Vogt MT, Hunninghake D, Carr M. Peripheral arterial disease in a randomized trial of estrogen with progestin in women with coronary heart disease: the Heart and Estrogen/Progestin Replacement Study. Circulation 2000 31;102:2228–32.

Hulka BS, Fowler WC, Kaufman DG, Grimson RC, Greenberg BG, Hogue CJ, et al. Estrogen and endometrial cancer: cases and two control groups from North Carolina. Am J Obstet Gynecol 1980;137:92–101.

Hulley S, Furberg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II). JAMA 2002;288:58–66.

Hulley S, Grady D, Bush T, Furberg C, Herrington DM, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605–13.

Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. BJOG 1990;97:1080–6.

Hurley JS, Frost EJ, Trinkaus KM, Buatti MC, Emmett KE. Relationship of compliance with hormone replacement therapy to short-term healthcare utilization in a managed care population. Am J Manag Care 1998;4:1691–8.

International Statistical Classification of Diseases and Related Health Problems, 1989. Revision. Geneva: World Health Organization; 1992.

Jacobs PA, Hyland ME. An evaluation of the benefits of taking hormone replacement therapy with other prescription drugs. Maturitas 2003;46:273–81.

Jick H, Derby LE, Myers MW, Vasilakis C, Newton KM. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. Lancet 1996;348:981–3.

Jonas HA, Kronmal RA, Psaty BM, Manolio TA, Meilahn EN, Tell GS, et al. Current estrogen-progestin and estrogen replacement therapy in elderly women: association with carotid atherosclerosis. CHS Collaborative Research Group. Cardiovascular Health Study. Ann Epidemiol 1996;6:314–23.

Kanya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, et al. Glycemic effects of postmenopausal hormone therapy: The Hearts and Estrogen/progestin Replacement Study: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2003;138:1–9.

Khatibi EA, Samsioe G, Li C, Lidfeldbt J, Agardh CD, Nerbrand C. Does hormone replacement therapy increase allergic reactions and upper gastrointestinal problems? Results from a population-based study of Swedish women. The women's health in the Lund area (WHILA) study. Maturitas 2004;48:438–45.

Kiel DP, Felson DT, Andersen JJ, et al. Hip fracture and the use of estrogens in postmenopausal women. The Framingham Study. N Eng J Med 1987;317:1169–74.

Komulainen MH, Kröger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, Saarikoski S. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. Maturitas 1998;31:45–54.

Lacey JV, Mink PJ, Lubin JH, Sherman ME, Troisi R, Hartge P, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA 2002;288:334–41.

Lang K, Mägi M, Aareleid T. Study of completeness of registration at the Estonian cancer registry. Eur J Cancer Prev 2003;12:153–6.

LeBlanc ES, Janowsky J, Chan BKS, Nelson H. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001;285:1489–99.

Le Gal G, Gourlet V, Hogrel P, Plu-Bureau G, Touboul PJ, Scarabin PY. Hormone replacement therapy use is associated with a lower occurrence of carotid atherosclerotic plaques but not with intima-media thickness progression among postmenopausal women. The vascular aging (EVA) study. Atherosclerosis 2003;166:163–70.

Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. Obstet Gynecol 2006;108:1354–60.

Mack TM, Pike MC, Henderson BE, Pfeffer RI, Gerkins VR, Arthur M, Brown SE. Estrogens and endometrial cancer in a retirement community. N Engl J Med 1976;294:1262–7.

MacLennan A, Sturdee D. The end of WISDOM. Climacteric 2002;5:313–6.

MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev 2004;18:CD002978.

Mansfield PK, Voda A. Hormone use of among middle-aged women: results of a three-year study. Menopause 1994;1:99–108.

Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523–34.

Manson JE, Rimm EB, Colditz GA, Willett WC, Nathan DM, Arky RA, et al. A prospective study of postmenopausal estrogen therapy and subsequent incidence of non-insulin-dependent diabetes mellitus. Ann Epidemiol 1992;2:665–73.

Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia 2004;47:1175–87.

McDonough P. The randomized world is not without its imperfections: reflections on the Women's Health Initiative Study. Fertil Steril 2002;78:951–6.

McIntyre RS, Konarski JZ, Grigoriadis S, Fan NC, Mancini DA, Fulton KA, Stewart DE, Kennedy SH. Hormone replacement therapy and antidepressant prescription patterns: a reciprocal relationship. CMAJ 2005;172:57–9.

McKinlay SM, Mc Kinlay JB. The impact of menopause and social factors on health. In: Hammond CB et al (Ed): Menopause. Evaluation, Treatment, and Health Concerns. New York: AR Liss Inc.; 1989, 137–61.

Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.

Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet 2007;369:1703–10.

Moorman PG, Schildkraut JM, Calingaert B, Halabi S, Berchuck A. Menopausal hormones and risk of ovarian cancer. Am J Obstet Gynecol 2005;193:76–82.

Mullins CD, Ohsfeldt RL. Modeling the annual costs of postmenopausal prevention therapy: raloxifene, alendronate, or estrogen-progestin therapy. J Manag Care Pharm 2003;9:150–8.

Nevitt MC, Cummings SR, Lane NE, Hochberg MC, Scott JC, Pressman AR, et al. Association of estrogen replacement therapy with the risk of osteoarthritis of the hip in elderly white women. Study of Osteoporotic Fractures Research Group. Arch Int Med 1996;156:2073–80.

Nevitt M, Felson DT, Williams EN, Grady D for the Heart and Estrogen/Progestin Replacement Study Research Group. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2001; 44:811–8.

O'Brien JE, Peterson ED, Keeler GP, Berdan LG, Ohman EM, Faxon DP, et al. Relation between estrogen replacement therapy and restenosis after percutaneous coronary interventions. J Am Coll Cardiol 1996;28:1111–8.

O'Keefe JH, jr, Kim SC, Hall RR, Cochran VC, Lawhorn SL, McCallister BD. Estrogen replacement therapy after coronary angioplasty in women. J Am Coll Cardiol 1997;29:1–5.

Ohsfeldt RL, Gavin NI, Thorp JM. Medical care costs associated with postmenopausal estrogen plus progestogen therapy. Value Health 2004;7:544–53.

Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol 1994;140:256–61.

Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal oestrogen treatment and stroke: a prospective study. BMJ 1988;297:519–22.

Persson I, Adami HO, Bergstrom R, Krusemo R, Hoover R. Survival in women receiving hormone replacement therapy. A record-linkage study of a large population-based cohort. J Clin Epidemiol 1990;43:677–85.

Prieto L, Sacristan JA. What is the value of social values? The usefulness of assessing health-related quality of life through preference measures. BMC Med Res Methodol 2004;4:10.

Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2663–72.

Reeves GK, Beral V, Green J, Gathani T, Bull D; Million Women Study Collaborators. Hormonal therapy for menopause and

breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 2006;7:910–8.

Resnick SM, Maki PM, Rapp SR, Espeland MA, Brunner R, Coker LH, et al. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J Clin Endocrinol Metab 2006;91:1802–10.

Riigi Ravimiamet. Eesti ravimistatistika 1995. Tartu: Riigi Ravimiamet; 1996.

Risch HA, Howe GR. Menopausal hormone use and colorectal cancer in Saskatchewan: a record linkage cohort study. Cancer Epidemiol Biomarkers Prev 1995;4:21–8.

Risch HA. Estrogen therapy and risk of epithelial ovarian cancer. Gynecol Oncol 1996;63:254–75.

Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465–77.

Samsioe G. The menopause revisited. Int J Gynaecol Obstet 1995;51:1–13.

Schairer C, Adami HO, Hoover R, Persson I. Cause-specific mortality in women receiving hormone replacement therapy. Epidemiology 1997;8:59–65.

Shapiro S, Kelly JP, Rosenberg L, Kaufman DW, Helmrich SP, Rosenstein NB, et al. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. N Engl J Med 1985;313:969–72.

Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. Women's Health Initiative Memory Study. JAMA 2004;291:2947–58.

Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene J, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2651–62.

Skouby SO. Health in the menopause: advances in management. International Congress Series 2004; 1266:151–5.

Small R, Friedman GD, Ettinger B. Concomitant medication use in postmenopausal women using estrogen therapy. Menopause 2001;8:120–6.

Smith DC, Prentice R, Thompson DJ, Herrmann WL: Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 1975;293:1164–7.

Sowers MR. Menopause: Its Epidemiology. In Women and Health. Academic Press; 2000. p.1155–68.

Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: Ten year following the Nurses' Health Study. N Eng J Med 1991;325:756–62.

Stanford JL, Weiss NS, Voigt LF, Daling JR, Habel LA, Rossing MA. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA 1995;274:137–42.

Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR. The women's health initiative postmenopausal hormone therapy trials: overview and baseline characteristics of participants. Ann Epidemiol 2003;13:S78–S86.

Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. Am J Cardiol 1997;79:847–50.

Sullivan JM, Vander Zwaag R, Hughes JP, Maddock V, Kroetz FW, Ramanathan KB, et al. Estrogen replacement and coronary artery disease. Effect on survival in postmenopausal women. Arch Int Med 1990;150:2557–62.

Swift JA, Conway P, Purdie DW. A cost-utility analysis of low-dose hormone replacement therapy in postmenopausal women with an intact uterus. Curr Med Res Opin 2005;21:2051–61.

The Esprit team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. Lancet 2002;360:2001–8.

The EuroQoL website. Available at: http://www.euroqol.org/web/ (accessed October 30, 2006).

The R Project for Statistical Computing. Available at: http://www.r-project.org (accessed 19 October 2004).

The Women's Health Initiative Steering Committee. Effects of Conjugated Equine

Estrogen in Postmenopausal Women with Hysterectomy. JAMA 2004;291:1701–12.

The Writing Group for the PEPI trial. Effects of estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/ Progestin Interventions (PEPI) trial. JAMA 1995;273:199–208.

The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women: the Postmenopausal Estrogen/ Progestin Interventions (PEPI) Trial. JAMA 1996;275:370–5.

Thorp JM, Gavin NI, Ohsfeldt RL. Hormone replacement therapy in postmenopausal women: utilization of health care resources by new users. Am J Obstet Gynecol 2001;185:318–26.

Topo P, Klaukka T, Hemminki E, Uutela A. Use of hormone replacement therapy in 1976-1989 by 45-64 year old Finnish women. J Epidemiol Community Health 1991;45:277–80.

Tosteson AN, Weinstein MC. Cost-effectiveness of hormone replacement therapy after the menopause. Baillieres Clin Obstet Gynaecol 1991;5:943–59.

Townsend J. Hormone replacement therapy: assessment of present use, costs, and trends. Br J Gen Pract 1998;48:955–8.

Vickers M, Meade T, Darbyshire J. WISDOM: history and early demise – was it inevitable? Climacteric 2002:5:317–25.

Viscoli CM, Brass LM; Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 2001; 345:1243–9.

Vorobjov S, Hovi S-L, Veerus P, Pisarev H, Rahu M, Hemminki E. Treatment adherence in the Estonian postmenopausal hormone therapy (EPHT) trial [ISRCTN35338757]. Maturitas 2005;52:286–95.

Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. Effect of estrogen plus progestin on stroke in postmenopausal women. The Women's Health Initiative: A randomized trial. JAMA 2003;289:2673–84.

Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women. JAMA;2002:2432–40.

Whittington R, Faulds D. Hormone replacement therapy II. A pharmacoeconomic appraisal of its role in the prevention of postmenopausal osteoporosis and ischaemic heart disease. Pharmacoeconomics 1994;5:513–54.

WHO Collaborating Centre for Drugs Statistics Methodology. ATC/DDD Index 2005. Available at: http://www.whocc.no/atcddd/ (accessed September 12, 2005).

Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT. Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment. Health Technology Assessment 2003;7:1–117.

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2002;288:321–33.

Ylikangas S, Backstrom T, Heikkinen J. Cost-effectiveness of continuous combined hormone replacement therapy in long-term use: economic evaluation based on a 9-year study in Finland. Curr Med Res Opin 2007;23:57–64.

Yuen J, Persson I, Bergkvist L, Hoover R, Schairer C, Adami HO. Hormone replacement therapy and breast cancer mortality in Swedish women: results after adjustement for 'healthy drug-user' effect. Cancer Causes Control 1993;4:369–74.

Zethraeus N, Johannesson M, Jonsson B. A computer model to analyse the cost-effectiveness of hormone replacement therapy. Int J Technol Assess Health Care 1999;15:352–65.

Ziel HK, Hinkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 1975;293:1167–70.

Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology 1997;22:189–212.

Acknowledgements

First of all, I would like to thank all the women who participated in the trial for giving so many years of their time and energy to protect women's health in the future.

I thank my supervisors, prof Elina Hemminki and prof Mati Rahu, for throwing me into the ocean of research and for the first swimming lessons.

I thank Sirpa-Liisa Hovi for not only being my right hand in co-ordinating the trial, but also for being the shoulder to lean on whenever feeling tired of swimming.

I thank prof Matti Hakama for more advanced swimming courses. I thank the other members of the Trial Steering Committee – Helle Karro, Risto Tuimala, Fred Kirss – for their help in drafting the questionnaires, planning and carrying out the trial. And I thank the members of the Data Monitoring Committee – Timo Hakulinen, Tiiu Aro, Kaja Rahu – for monitoring the health data of trial participants and for difficult decisions. I am grateful to the trial staff and to my colleagues Mare Tekkel, Tatjana Veideman, Lea Laaniste, Sigrid Vorobjov, and Tiiu Vahtramäe from the National Institute for Health Development (TAI) in Estonia and to Kati Tanninen, Hannamaria Kuusio, Tuula Väänänen and Tiina Sevon from the National Research and Development Centre for Welfare and Health (STAKES) in Finland for their input. I thank the director of TAI Toomas Veidebaum and the director of STAKES Vappu Taipale for their support.

I would like to thank Maie Thetloff for data linkages with the Estonian Health Insurance Fund database, and Tiiu Aareleid and Pille Härmaorg for data linkages with the Estonian Cancer Registry database. I sincerely thank and admire Krista Fischer for her help in the extremely complicated data analysis.

And most of all, I thank my parents and my children for everything that they mean to me and for giving me the courage and strength to fight through the storms.

Appendix 1. Trial organization of the EPHT trial

Trial Steering Committee

Krista Fischer, University of Tartu, Estonia; Matti Hakama, Tampere School of Public Health, Finland; Elina Hemminki, National Research and Development Centre for Welfare and Health, Finland; Sirpa-Liisa Hovi, National Research and Development Centre for Welfare and Health, Finland; Helle Karro, University of Tartu, Estonia; Fred Kirss, University of Tartu, Estonia; Mati Rahu, National Institute for Health Development, Estonia; Tiina Sevon, National Research and Development Centre for Welfare and Health, Finland; Risto Tuimala, Tampere University Women's Clinic, Finland; Piret Veerus, National Institute for Health Development, Estonia; Sigrid Vorobjov, National Institute for Health Development, Estonia; Tuula Väänänen, National Research and Development Centre for Welfare and Health, Finland.

Data Monitoring Committee

Tiiu Aro, Marja Jylhä, Timo Hakulinen (chair), Kaja Rahu.

Trial centres and clinical staff

West Tallinn Central Hospital: Dr. Anne-Mary Rumma, Dr. Reet Sokk, midwives Eevi Beldsinsky, Piia Reisman;
East-Tallinn Central Hospital: Dr. Zinaida Kuznetshikova, Dr. Reet Laasik, Dr. Tiiu Mäss, Dr. Reeli Saaron, midwives Made Bambus, Piia Heiman, Õie-Maret Leetberg, Riina Pajula;
Tartu University Clinic: Dr. Maret Ramm, Dr. Fred Kirss, Dr. Aira Peri, midwives Jelena Konoshina, Pille Joonas, Marge Mahla.

Appendix 2. Information leaflet sent with the recruitment questionnaire

Dear lady!

The Gynaecology Clinics of Tallinn and Tartu, the Institute of Experimental and Clinical Medicine and the Finnish Social and Health Research and Development Centre are jointly investigating the health problems of Estonian women in postmenopausal and older age, specifically the **long-term health effects of postmenopausal hormone replacement therapy.** Investigations performed in other countries have revealed that hormonal replacement therapy slows down the development of osteoporosis and may decrease the risk of certain cardiovascular diseases. Further, it is thought that hormonal replacement therapy may increase the risk of breast cancer, but the adequacy of proof is not clear-cut (you will find a more detailed overview of it on the reverse page).

Thousands of women aged between 50-64 and selected randomly from the population register are invited to take part in this study. In order to get reliable results, the participants will be randomly allocated to receive either hormonal medication, inert medicine (placebo) or no treatment at all (control arm). All the women wishing to participate in this study, and having no contraindications to hormone replacement therapy, will have an equal chance to be placed in any of these three treatment arms.

In the event that you **give your consent to participate, and you are found to be suitable to take part in the study, you will have a chance to visit very competent gynaecologists**, or receive advice from them via telephone. The clinical study will last for five years. If you wish, you can withdraw from using the study medicine or choose to start hormone replacement therapy even if you belong to the control arm. The study medicine is free of charge for women in the treatment arm. In the course of the trial we ask all the participants once a year to fill in a short questionnaire. The final health check will take place ten years after the beginning of the study. The results of the study will definitely help to solve the health problems of older women and increase their quality of life.

Data derived from the questionnaire and obtained at medical examination will be supplemented later and will be used for solving women's health problems and for scientific work. Your name and personal data will not be made public to anyone. Personal data will be separated from the research data before analyses. Only a few persons involved in the study can see your personal data.

We highly appreciate if you could answer all the questions in the questionnaire and send it back to us in the attached envelope. The postage is prepaid, you don't have to address a stamp to the envelope. **Further, we hope that you will participate in the study investigating the health effects of hormone therapy, given after the end of menstruations (at least 12 months should have elapsed from the last menstruation).** If – as established by the questionnaire - you are suitable to take part in the study we will shortly send you an invitation to a gynaecologist's reception.

If you have additional questions related to the questionnaire or participation in the study then you are welcome to telephone (22) 514-334 (Dr. Mare Tekkel) between 9.00-12.00 on working days.

We thank you in advance for a pleasant cooperation!

The aim of the study is to investigate the long-term health effects of hormone replacement therapy. We are trying to find out whether women receiving hormone replacement therapy have more or less certain diseases than women who do not receive this type of treatment. There is quite limited data available on whether combined hormone replacement therapy (oestrogens together with progestins) influence the

incidence of cardiovascular diseases and tumours. In order to prolong women's lifetime and improve their quality of life it's very important to get reliable data about the incidence or prevention of these diseases in connection with hormone replacement therapy,

During the so-called transitional age, the production of female sex hormones in the ovaries decreases, in order to maintain the prior hormone levels it is possible to use **hormone replacement therapy (usually a combination of oestrogens and progestins).** This type of treatment **is indicated for the alleviation of disturbances associated with transitional age and for prevention of certain diseases.**

Oestrogens are female sex hormones produced in the ovaries. In connection with the start of oestrogen production menstruations begin in teenage girls and they develop the characteristics typical to female sex. Cessation of menstruations in the middle age is also a sign of decreased oestrogen production.

Oestrogens play an important role in building up our bones. Due to a decrease in oestrogen production, loss of bone mineral density accelerates a few years after cessation of menstruations. **Hormone replacement therapy slows down the loss of bone mineral density and also helps to prevent osteoporotic fractures and changes in the vertebral column.**

Oestrogens are thought to have certain effects on blood coagulation and plasma lipid concentration - but their effect on cardiovascular diseases is still not clear. It is assumed that hormone replacement therapy decreases the risk of myocardial infarction, but may increase the risk of thrombosis for some women. Most conclusions are derived from studies in which the groups were formed by self-selection. Thus, it is not clear whether the risk of getting a disease would have been the same without hormone replacement therapy. Random allocation of women to receive either hormonal medicine, inert medicine (placebo) or no treatment at all (control arm), and long-term follow-up of these arms will ensure that the conclusions drawn from the results of the study will be reliable.

Women aged 50–64 have a higher risk for breast cancer than younger women. Long-term replacement treatment with estrogens may increase this risk in some women. **In order to detect possible alterations in an early stage the breasts of trial participants will be examined as part of each scheduled medical examination and participants are also taught how to examine their breasts themselves.**

Besides oestrogens the hormonal medicine also contains progestins (hormones of the corpus luteum), which have a protective action towards the endometrium. At the initial stage of treatment progestins can cause menstruation-like bleeding, but this is not dangerous, it doesn't require special treatment and usually disappears within a few months. The intensity of the bleeding can be reduced by increasing progestin's dose.

Based on available data it can be assumed that the positive effects of hormone replacement therapy are larger than its possible negative effects. Possible health problems of the women participating in the trial will be discovered early during regular medical examinations and therefore these are easy to treat.

Appendix 3. Invitation to the recruitment visit in the blind sub-trial

Dear participant!

Thank you for having shown interest in taking part in the study investigating the positive and negative effects of postmenopausal hormone replacement therapy. As you gave your consent to take part in the trial we kindly ask you to call the number …… within one week in order to arrange a suitable date for your medical examination. We thank you in advance for a pleasant cooperation!

Overview of the study course
When you come to the medical examination we kindly ask you to take along your Health Insurance Fund membership card, packages or prescriptions of the medicines that you are currently using and, if possible, any other documents related to your disease(s).

At the medical examination you will undergo a thorough gynaecological examination, your general health state will be evaluated and if necessary, additional investigations will be performed. In doing this we can be sure that you are not suffering from a disease that is a contraindication for hormone replacement therapy. The doctor will also examine your breasts and will teach you how to do this yourself at home.

You have been randomly allocated into a group, where some women will receive hormone medicine and some inert medicine (placebo). If – according to the doctor's judgement – you will be suitable to participate in the study and you are still willing to take part then we will ask you to sign a document called *Informed consent.* By signing this you will give your permission to us to collect over a 10 year period data about your health from various sources (ambulatory card, case report form, health databases). This data will be used only for solving women's health problems and for scientific work. Your name and personal data will not be made public to anyone. One copy of the signed *Informed consent* will be given to you. Only after signing the *Informed Consent* will you be finally regarded as a participant in the study and it will **appear whether you will receive hormone medicine or inert medicine (placebo)**. In order to get reliable data neither you nor your doctor will know which medicine you will actually receive, you will get to know it only after five years.

At first you will get medicines for a six-month treatment period. Three months after the initial visit we ask you to see your study physician again in order to discuss possible problems associated with the treatment. After six months you will receive medicines for the next half year. **In total you will take the study medicines for five years; the medicines are free of charge to you.**

During these five years we ask you to visit your study physician once a year. Every year we will also send you a short questionnaire and additionally ask you to fill in a card, where you should record all the health problems you had during the previous year. Filling of these papers is easy and will not take a long time.

In the course of the trial each participant will belong to the same treatment arm she was initially allocated. However, all the participants are free to withdraw from taking the study medicines at any time and to start taking it again. If you decide to stop taking the medicines we ask you to write down the date of stopping. You will still remain a participant in the study, therefore we ask you to fill in the questionnaire once in a year. The **last health check will take place ten years after the beginning of the study.**

We hope that you will take part in the study that deals with such an important women's health issue – the health effects of postmenopausal hormone replacement therapy.

Appendix 4. Invitation to the recruitment visit in the non-blind sub-trial

Dear participant!

Thank you for having shown interest in taking part in the study investigating the positive and negative effects of postmenopausal hormone replacement therapy. As you gave your consent to take part in the trial we kindly ask you to call the number …… within one week in order to arrange a suitable date for you for medical examination. We thank you in advance for a pleasant cooperation!

Overview of the study course
When you come to the medical examination we kindly ask you to take along your Health Insurance Fund membership card, packages or prescriptions of the medicines that you are currently using and, if possible, any other documents related to your disease(s).

At the medical examination you will undergo a thorough gynaecological examination, your general health state will be evaluated and if necessary, additional investigations will be performed. In doing this we can be sure that you are not suffering from a disease that is a contraindication for hormone replacement therapy. The doctor will also examine your breasts and will teach you how to do this yourself at home.

You have been randomly allocated into a group, where some women will receive hormone medicine and some will not. If – according to the doctor's judgement – you will be suitable to participate in the study and you are still willing to take part then we will ask you to sign a document called *Informed consent.* By signing this you will give your permission to us to collect over a period of 10 years data about your health from various sources (ambulatory card, case report form, health databases). This data will be used only for solving women's health problems and for scientific work. Your name and personal data will not be made public to anyone. One copy of the signed *Informed consent* will be given to you. Only after signing the *Informed Consent* you will be finally regarded as a participant in the study and it will **appear whether you will receive hormone medicine or remain in control arm and consequently will not receive treatment**.

In the event that you happen to be in a treatment arm you will initially receive medicines for a six-month treatment period. Three months after the initial visit we ask you to see your study physician again in order to discuss possible problems associated with the treatment. After six months you will receive medicines for the next half year. **In total you will take the study medicines for five years, the medicines are free of charge to you.**

If you are receiving hormone replacement therapy, then during these five years we ask you to visit your study physician once in a year. Women belonging to the control arm will visit the doctor when they feel a need for it. Every year we will also send you a short questionnaire and additionally we ask you to fill in a card, where you should record all the health problems you had during the last year. Filling of these papers is easy and will not take a long time.

In the course of the trial each participant will belong to the same treatment arm she was initially allocated. However, all the participants are free to withdraw from taking the study medicines at any time and to start taking it again or start the hormone replacement therapy when belonging to the control arm. If you decide to stop taking the medicines or when being in the control arm start with hormone replacement therapy, we ask you to write down the stopping or starting date. In both cases you will still remain a participant in the study, therefore we ask you to fill in the questionnaire once in a year. **The last health check will take place ten years after the beginning of the study.**

We hope that you will take part in the study that deals with so important women's health issue – health effects of postmenopausal hormone replacement therapy.

Appendix 5. Explanatory letter to the trial participants in the blind arm (after recruitment)

Dear study participant!

Thank you for deciding to take part in a study investigating the positive and negative effects of postmenopausal hormone replacement therapy. The study will last for ten years. During the first five years we ask you to take the study medicine, visit your study physician once a year and fill in the short questionnaire and health status card that will be sent to you.

You have been randomly allocated into a group where women will receive study medicine. In order to get reliable data neither you nor your doctor will know whether you receive hormone medicine or inert medicine (placebo). The presence of an inert medicine (placebo) arm is very important for drawing the right conclusions from the results of the study. You will get to know which medicine you actually received only after five years.

At first you will get medicines for a six-month treatment period. The medicine should be taken one tablet daily, preferably in the evening. If you forget to take the tablet, then on the next day still take one tablet. Three months after the initial visit we ask you to see your study physician again. After six months you will receive medicines for the next half year. During four consecutive years we ask you to visit your study physician and receive the study medicine once a year. The last health check will take place ten years after the beginning of the study. If you have additional questions during therapy then please call the study nurse at the number on the visit invitation. If you wish, you can always turn directly to the study physician also.

If the time from your last menstruation is less than three years, hormone replacement therapy may cause menstruation-like bleeding. To prevent this, the doctor will **prescribe for you progestin (corpus luteum hormone), which should also be taken in the form of one tablet daily.** If you still experience bleeding and it disturbs you or if it is heavy, then please contact your study physician. In certain cases, progestin may cause headache, tenderness of breasts, flatulence, nausea or cramps in legs, and oestrogens can cause retention of fluid in the body. These adverse effects usually diminish or disappear after some months of treatment.

Hormone replacement therapy is usually well tolerated and adverse events are rare. However, if you experience any unexpected health problem, then please inform your study physician. In case you develop persistent headache together with vision disturbances, swelling or pain in one hand or leg, breathing difficulty or any other serious health problem, then please seek instant medical aid. Later please always inform your study physician of it also.

As oestrogen therapy can slightly increase the risk of breast cancer, we suggest you to self-examine your breasts once a month during the treatment period and record the examination date on the *Breast Examination Card.* **If you notice any alterations in your breasts, then please immediately contact your study physician.** In order to evaluate your health status during the study more precisely, **we ask you to fill in the *Health Status Card.*** Please send the completed card back to us once a year together with the annual questionnaire.

If you decide to stop the treatment or you are forced to do it due to adverse effects, **we ask you to record the date when you took the last tablet and later write it down in the annual questionnaire.** If you start the therapy again, the date should also be recorded. For the success of the study it is important for us to know these dates. Nevertheless, whether you use the medicine or not, we still ask you to fill in annual questionnaires.

If during the therapy you are going to have medical investigations or receive some other treatment, then please **inform the doctor that you are participating in a hormone replacement therapy study and that you are receiving a medicine that might contain oestrogens.** Consult your study physician regarding the treatment continuation also before major elective surgery.

Your doctor is:

Dr. ..... telephone: .....

We hope that our pleasant cooperation will continue!

Appendix 6. Explanatory letter to trial participants in the control arm of the non-blind sub-trial (after recruitment)

Dear study participant!

Thank you for deciding to take part in a study investigating the positive and negative effects of postmenopausal hormone replacement therapy. The study will last for ten years.

You have been randomly allocated into a control arm where women will not receive treatment. The presence of the control arm is very important for drawing the right conclusions from the results of the study.

During the first five years we ask you to fill in a short annual questionnaire and health status card that will be sent to you. Every two years it is advisable to take analyses from the cervix of the uterus; women participating in the study can do it at their study physician. If needed, you can always turn to the study physician.

If you have additional questions during the study, then please call the study nurse at the number on the visit invitation. If you wish, you can always turn directly to the study physician also.

We suggest you to self-examine your breasts once a month during the study period and record the examination date on the *Breast Examination Card.* **If you notice any alterations in your breasts, then please immediately contact your study physician.** In order to evaluate your health status during the study more precisely, **we ask you to fill in the *Health Status Card*.** Please send the completed card back to us once a year together with the annual questionnaire.

If you decide to start hormone replacement therapy, **we ask you to record the start date and later write it down in the annual questionnaire.** If you stop the therapy, the date should also be recorded. For the success of the study it is important for us to know these dates. Irrespective of whether you use the medicine or not, we still ask you to fill in annual questionnaires and the Health Status Card.

Your doctor is:

Dr. ..... telephone: .....

We hope that our pleasant cooperation will continue!

Appendix 7. Explanatory letter to trial participants in the HT arm of the non-blind sub-trial (after recruitment)

Dear study participant!

Thank you for deciding to take part in a study investigating the positive and negative effects of postmenopausal hormone replacement therapy. The study will last for ten years. During the first five years we ask you to take the study medicine, visit your study physician once a year and fill in the short questionnaire and health status card that will be sent to you.

You have been randomly allocated into a group where women will receive hormone replacement therapy.

At first you will get medicines for a six-month treatment period. The medicine should be taken one tablet daily, preferably in the evening. If you forget to take the tablet, then the next day still take one tablet. Three months after the initial visit we ask you to see your study physician again. After six months you will receive medicines for the next half year. During the next four consecutive years we ask you to visit your study physician and receive the study medicine once a year. The last health check will take place ten years after the beginning of the study. **If you have additional questions during therapy then please call the study nurse at the number on the visit invitation. If you wish, you can always turn directly to the study physician also.**

If the time from your last menstruation is less than three years, hormone replacement therapy may cause menstruation-like bleeding. To prevent this, the doctor will **prescribe for you progestin (corpus luteum hormone), which should also be taken one tablet daily.** If you still experience bleeding and it disturbs you or if it is heavy, then please turn to your study physician. In certain cases progestin may cause headache, tenderness of breasts, flatulence, nausea or cramps in legs, estrogens can cause retention of fluid in the body. These adverse effects usually diminish or disappear after some months of treatment.

Hormone replacement therapy is usually well tolerated and adverse events are rare. However, if you experience any unexpected health problem, then please inform your study physician. In case you develop persistent headache together with vision disturbances, swelling or pain in one hand or leg, breathing difficulty or any other serious health problem, then please seek instant medical aid. Later please always inform your study physician of it also.

As oestrogen therapy can slightly increase the risk of breast cancer, then we suggest you self-examine your breasts once a month during the treatment period and record the examination date on the *Breast Examination Card.* **If you notice any alterations in your breasts, then please immediately contact your study physician.** In order to evaluate your health status during the study more precisely, **we ask you to fill in the *Health Status Card*.** Please send the completed card back to us once a year together with the annual questionnaire.

If you decide to stop the treatment or you are forced to do so due to adverse effects, **we ask you to record the date when you took the last tablet and later write it down in the annual questionnaire.** If you start the therapy again, the date should also be recorded. For the success of the study it is important for us to know these dates. Irrespective of whether you use the medicine or not, we still ask you to fill in annual questionnaires.

If during the therapy you are going to have medical investigations or receive some other treatment, then please **inform the doctor that you are participating in hormone replacement therapy**

study and that you are receiving a medicine that contains oestrogens. Also consult your study physician regarding the treatment continuation before major elective surgery.

Your doctor is:

Dr. ..... telephone: .....

We hope that our pleasant cooperation will continue!

Appendix 8. Informed consent

I hereby confirm that I am fully aware of the course of the clinical trial investigating the benefits and risks of postmenopausal hormone replacement treatment, and I agree to participate in this trial.

I have understood that I am allowed to stop taking the trial medication at any time. If I stop using the trial drugs, I will still visit the trial physician for annual medical check-ups.

I also hereby give my permission to the research team to use my personal health data through various sources (outpatient and inpatient records and health databases).

Tallinn date_____/month_____/year_____
Tartu

_____ _____

Woman's signature Doctor's signature

_____ _____

Name /capital letters/ Name /capital letters/

Woman's ID code _____

Appendix 9. Recruitment questionnaire in the EPHT trial (except the pilot study)

Climacteric and women's health – recruitment questionnaire

Study number_____

Please answer all questions. Encircle the number before the most suitable answer or after it or write your answer to the empty space provided.

1. Your place of residence
    1. Tallinn
    2. Harjumaa
    3. Tartu
    4. Tartumaa
    5. Other

2. Your education
    1. Preliminary
    2. Basic
    3. Secondary
    4. Vocational
    5. Higher
    6. Scientific degree

3. Do You work at the moment?
    1. No, I am retired
    2. No, I am a housewife
    3. No, I am unemployed
    4. Yes, I do

4. Your marital status
    1. Single
    2. Married, cohabiting
    3. Divorced
    4. Widow

5. Your birthdate: day/month/year
6. Your nationality:
7. Your height: cm
8. Your present weight: kg
9. Do You have health insurance?
    1. No
    2. Yes

10. Are Your menstrual periods over?
    1. No
    2. Yes, the last period was 6-12 months ago
    3. Yes, the last period was more than 12 months ago

11. When was Your last period? Year/month

12. Did You have any of the following symptoms in last two weeks?

	No		Yes	I do not know
dizzy spells (1)	12		3	
lack of energy (2)	1	2	3	
diarrhoea or constipation (3)	1	2	3	
irritability (4)	1	2	3	
persistent cough (5)	1	2	3	
feeling blue or depressed (6)	1	2	3	
backache (7)	1	2	3	
upset stomach (8)	1	2	3	
headache (9)	1	2	3	
cold sweats (10)	1	2	3	
aches/stiffness in the joints (11)	1	2	3	
shortness of breath (12)	1	2	3	
hot flashes (13)	1	2	3	
sore throat (14)	1	2	3	
trouble sleeping (15)	1	2	3	
loss of appetite (16)	1	2	3	
fluid (water) retention (17)	1	2	3	
menstrual disorders				

13. Which of these symptoms bother(ed) you (Write here the numbers of the symptoms above which bothered you) _

14. Did You use hormone therapy (oestrogens or oestrogens plus progestogens) in the last 6 months (excluding contraceptive pills)?
    1. No
    2. Yes
    3. I do not know

15. The name of the hormone therapy regimen You used in past 6 months (either pills, injections, transdermal patches or gel)?
    1. I have not used HT
    2. ……..
    3. I do not know

16. Have You ever been diagnosed as having had

	No	Yes	Year	Month	I do not know
Myocardial infarction					
Hepatitis or functional liver disorders					

17. Has Your doctor ever diagnosed You as having had

	No	Yes	I do not know
Brain infarction			
Pulmonary embolism			
Deep vein thrombosis			
Porphyria			
Endometriosis			

18. Have You ever had any of the following tumours?

	No	Yes	I do not know
Endometrial cancer			
Ovarian cancer			
Breast cancer			
Cancer at any other site			
Benign brain tumour			

19. Have You had a hysterectomy?

1. No
2. Yes
3. I do not know

20. Has Your mother, daughter or sister been diagnosed as having breast cancer?

	No	Yes	I do not have a sister	I do not have a daughter	I do not know
Mother	1	2			3
Daughter	1	2	4		3
Sister	1	2		4	3

21. Do/did You smoke?

1. No
2. Yes. I do
3. Yes, I did earlier

22. Do You wish to participate in the hormone therapy trial described in the leaflet that is attached to the questionnaire?

1. No
2. Yes, my contact data is the following

Name/address/phone at home, at work

If You have any questions related to the participation in the trial, please contact Dr Mare Tekkel by phone 514334 on workdays from 9 to 12 a.m.

23. If You wish to participate in the trial and live in Tallinn or Harju county, do You prefer to join the trial at
    1. East Tallinn Central Hospital
    2. West Tallinn Central Hospital
    3. I do not have any preferences

If You are eligible for participation, we will try to take your preference into consideration. Women from Tartu and Tartu County can join the trial at Tartu University Clinic.

Date of filling in the questionnaire: day/month/year

If You wish to add something important about climacteric or hormone therapy, You can do it here. Thank You for filling in the questionnaire!

Appendix 10. First year questionnaire in the EPHT trial

MENOPAUSE AND WOMEN'S HEALTH

Dear respondent. Typically circle only one option, the one which most closely corresponds to your view or situation. Those questions in which you may choose more than one alternative are indicated

1. Study number _ _ _ _ _ _

2. Your birthday _ _ _ _ _ _ _ _ _ _
dd mm yy

HEALTH

3. How do you assess your current health
1. very good
2. good
3. average
4. satisfactory
5. bad
6. very bad

4. In the **past 12 months** have you been found to have any of these diseases as diagnosed by a physician (if yes, circle the alternative, you may choose more than one alternative)

		No	Yes	Do not know
1.	myocardial infarction	1	2	3
2.	angina pectoris	1	2	3
3.	heart failure	1	2	3
4.	any type of stroke including TIA	1	2	3
5.	gall-bladder disease	1	2	3
6.	diabetes mellitus	1	2	3
7.	bone fracture(s)	1	2 which? _____	
	_____			
8.	other diseases	1	2 which?	
	_____			

5. In the **past 12 months** have you been found any of these symptoms

		No	Yes
1.	sudden loss of vision	1	2
2.	diplopia	1	2
3.	other symptoms	1	2 which ___
	_____		
4.	confinement to wheel chair	1	2

6. Have you within the **last 4 weeks** used any prescription medicines
   1. No,
   2. Yes, What are the names of the medicines?_____
      _____

7. Have you had any of the following operations within the **past 12 months?**
   You may choose more than one alternative.

   1. Oophorectomy one side,
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

   2. Oophorectomy both sides
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

   3. Hysterectomy,
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,
      Was the hysterectomy
      1. Total
      2 subtotal
      3 I do not know,

   4. Operation on breast
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

8. Have you had vaginal bleeding within **past 12 months**?
   1. No
   2. Yes, how many times?_____

8.A Was the bleeding bothersome?
   1. Yes
   2. No

9. During the **past 12 months** I have had pains during intercourse?
   1. No
   2. Yes
   3. I have had no intercourse

10. Have you ever used p-pills?
   1. No
   2. Yes
   3. I do not remember

11. How many times have you given birth: ____

12. Your current weight _____ kg

13. How much do you exercise during your free-time?
   1. Not at all
   2. A little
   3. Somewhat
   4. Rather a lot
   5. A lot

14. Have you within the **past 2 weeks** had the following symptoms or trouble ?

	No	Yes
dizzy spells (1)	1	2
lack of energy (2)	1	2
diarrhoea or constipation (3)	1	2
irritability (4)	1	2
persistent cough (5)	1	2
feeling of blue or depressed (6)	1	2
backaches (7)	1	2
upset stomach (8)	1	2
headaches (9)	1	2
cold sweats (10)	1	2
aches/stiffness in the joints (11)	1	2
shortness of breath (12)	1	2
hot flashes (13)	1	2
sore throat (14)	1	2
trouble sleeping (15)	1	2
loss of apetite (16)	1	2
fluid (water) retention (17)	1	2

15. Which of these symptoms bother(ed) you (Write here the numbers of the symptoms above which bothered you)
_____

HEALTH SERVICES USE

16. How many times have you seen the study physician in her/his office for the initial examinations to join the trial
____ times

17. In the **past 12 months**, how many times have you seen the study physician?

1. I visited his/ her office
    1. None
    2. _____times

2. I discussed with him/her over phone
    1. None
    2. ___ times

3 I consulted him/her somewhere else
    1. None
    2. ___ times, where? _____

18. What were the reasons for these contacts to the study physician mentioned in the question above

1. There were no extra contacts
2. Times_____

19. In the **past 12 months** how many times have you seen other physicians (excluding dentist)

1. I visited his/her office
    1. None
    2. _____times

2. A physician made a home visit
    1. None
    2. _____times

3. I discussed with him/her over phone
    1. None
    2. ___ times

20. What were the reasons for these visits or telephone contacts to a physician other than study physician?

_____

21. In the **past 12 months**, have you been in a hospital ward over night?

1. no
2. Yes _____ times, in total _____ days
   Hospital's name _____
   reason _____
   Hospital's name _____
   reason _____

22. In the **past 3 months** how many days have you been so sick that you could not go to work or do your normal duties at home?

1. Not at all
2. _____ days

TRIAL

23. Do you belong to the trial group which
1. Gets hormone treatment or placebo (blind arm)
2. Gets hormone treatment (non-blind arm)
3. Gets no treatment (non-blind arm)
4. I do not know

24. When you decided to join the trial which trial group did you wish to get
1. Hormone treatment
2. No treatment
3. I had no prior wish
4. I do not remember

The n**ext questions 25-32 are only for those women who have received trial drugs. Women in the control group, who have not received trial drugs, please leave these questions without answer and go straight to question 33.**

25. If you belong to the blind arm, do you think you get
    1. Hormone treatment
    2. Placebo
    3. It does not matter
    4. I do not know

26. If you belong to the blind arm, do you wish your drug to be
    1. Hormone treatment
    2. Placebo
    3. I do not know
    4. It does not matter

27. During the **past 12 months**, have you stopped taking trial drugs
    1. no
    2. yes
       what were you reasons for it_____
    3. I have not even started using them,
       what were your reasons for it_____

28. If you stopped the trial drugs have you started using them again?
    1. No
    2. Yes

29. Have you during the **past 4 weeks** taken trial drugs
    1. No
    2. Yes, (almost) every day
    3. Yes, every now and then

30. If you have within the **past 4 weeks** taken trial drugs less than advised what were the reasons?
    1. I did not get any trial drugs
    2. Pills were too few
    3. I did not consider them necessary
    4. I have forgotten
    5. I have got side effects
    6. something else _____
    7. I do not know

31. Have the trial drugs caused you side effects

1. no
2. yes, what _____

_____

32. Have the trial drugs had some positive consequences

1. No
2. Yes, what _____

_____

33. If you belong to the control group where women did not get trial drugs, have you used hormone replacement therapy?

1. No
2. Yes

34. Why did you want to join the trial (you may choose more than one alternative)

1. To facilitate research in Estonia
2. To help Estonian women in the future
3. To get drugs for free
4. To get better health care
5. To get better access to a gynaecologist
6. To get help with my menopausal symptoms
7. To get the annual physician's examination
8. Other, what _____

35. Which kind of views has your partner taken about your participation in this trial

1. I do not (currently) have a partner
2. He disagrees
3. He agrees
4. He does not care
5. He does not know
6. Something else _____

_____

36. Have you got enough information that you were interested in from the leaflets
    1. No
    2. Would have wanted more information about _____
    3. Yes

37. Have you got enough information that you were interested in from the midwife
    4. No
    5. Would have wanted more information about _____
    6. Yes

38. Have you got enough information that you were interested in from the study physician
    7. No
    8. Would have wanted more information about _____
    9. Yes

39. Do you have any suggestions how we can make the trial better
    1. No
    2. Yes
       How _____

40. Do you participate in some other research study
yes, which ___
no

LIFE SITUATION

41. Are you currently in paid work
    1. No, I am retired
    2. No, I am unemployed/ looking for a job
    3. Yes, I am in paid work outside home
    4. Yes, I am working at home
    5. Something else,
       specify _____

42. What is your current marital status
    1. Single
    2. Married
    3. Cohabitant
    4. Divorced
    5. Widow

43. If you are married or a cohabitant, what is your partner's age: _____ years

44. Who is/are living with you in the same household? Encircle the right alternative(s) (you may choose more than one alternative)
    1. I live alone
    2. Husband or cohabitant
    3. Child/children
    4. My own parent(s)
    5. My husband's/cohabitant's parent(s)
    6. Others, who? _____

45. How many rooms do you have in your residence (kitchen included): ____

Do you think that the following corresponds with your view/are true?

46. It is a relief for me that I do not have to be afraid of pregnancy any more.
    1. I totally agree
    2. I somewhat agree
    3. I don't know
    4. I somewhat disagree
    5. I totally disagree

47. It is sad that I do not have the possibility for pregnancy any more.
    1. I totally agree
    2. I somewhat agree
    3. I don't know
    4. I somewhat disagree
    5. I totally disagree

48. My partner thinks that my problems are due to climacteric
    1. I totally agree
    2. I somewhat agree
    3. I don't know
    4. I somewhat disagree
    5. I totally disagree

49. In my age sexual life is not so important any more.
    1. I do not have a husband/cohabitant
    2. I totally agree
    3. I somewhat agree
    4. I don't know
    5. I somewhat disagree
    6. I totally disagree

50. Women's Health Questionnaire
please indicate how you are feeling now, or how you have been feeling in the **past few days**, **circle the appropriate answer in every row.**

		Yes definitely	Yes sometimes	No not much	No not at all
1.	I wake early then sleep badly for the rest of the night	1	2	3	4
2.	I get very frightened or panic feelings for apparently no reason at all	1	2	3	4
3.	I feel miserable and sad	1	2	3	4
4.	I feel anxious when I go out of the house on my own	1	2	3	4
5.	I have lost interest in Things	1	2	3	4
6.	I get palpitations or a sensation of 'butterflies' in my stomach or chest	1	2	3	4
7.	I still enjoy the things I used to	1	2	3	4
8.	I feel life is not worth living	1	2	3	4
9.	I feel tense or 'wound up'	1	2	3	4
10.	I have a good appetite	1	2	3	4
11.	I am restless and can't keep still	1	2	3	4
12.	I am more irritable than usual	1	2	3	4
13.	I worry about growing old	1	2	3	4
14.	I have headaches	1	2	3	4
15.	I feel more tired than usual	1	2	3	4
16.	I have dizzy spells	1	2	3	4
17.	My breasts feel tender and uncomfortable	1	2	3	4
18.	I suffer from backache or pains in my limbs	1	2	3	4
19.	I have hot flushes	1	2	3	4
20.	I am more clumsy than usual	1	2	3	4
21.	I feel full of pride	1	2	3	4
22.	I have abdominal cramps or discomfort	1	2	3	4
23.	I feel sick or nauseous	1	2	3	4
24.	I have lost interest in sexual activity	1	2	3	4
25.	I have feelings of well-being	1	2	3	4
26.	I have heavy periods	1	2	3	4
27.	I suffer from night sweats	1	2	3	4
28.	My stomach feels bloated	1	2	3	4
29.	I have difficulty in getting off to sleep	1	2	3	4
30.	I often notice pins and needles in my hands and feet	1	2	3	4
31.	I am satisfied with my current sexual relationship (please omit if not sexual active)	1	2	3	4
32.	I lack pride in myself	1	2	3	4
33.	I have difficulty in concentrating	1	2	3	4
34.	As a result of vaginal dryness sexual intercourse has become uncomfortable (please omit if not sexual active)	1	2	3	4
35.	I need to pass urine/water more frequently than usual	1	2	3	4
36.	My memory is poor	1	2	3	4
37.	I am happy with the way I look	1	2	3	4
38.	I wish I was someone else	1	2	3	4
39.	I feel I have lots of good qualities	1	2	3	4

D:\Data\HORMOONITRIAL\KOKOUSASIAKIRJAT\KOKOUS191099\WHQ&SEST.doc

51. Date of completing the questionnaire _ _ _ _ _ _
dd mm yy

Thank you very much for your co-operation and using your time to fill this questionnaire.

Appendix 11. Second year questionnaire in the EPHT trial

MENOPAUSE AND WOMEN'S HEALTH

Dear respondent. typically circle only one option, the one which most closely corresponds to your view or situation. Those questions in which you may choose more than one alternative are indicated

1. Study number _ _ _ _ _ _

2. Your birthday _ _ _ _ _ _ _ _ _ _
dd mm yy

HEALTH

3. How do you assess your current health
1. very good
2. good
3. average
4. satisfactory
5. poor
6. very poor

4. In the **past 12 months** have you been found to have any of these diseases as diagnosed by a physician (if yes, circle the alternative, you may choose more than one alternative)

		No	Yes	Do not know
1.	myocardial infarction	1	2	3
2.	angina pectoris	1	2	3
3.	heart failure	1	2	3
4.	any type of stroke including TIA	1	2	3
5.	gall-bladder disease	1	2	3
6.	diabetes mellitus	1	2	3
7.	bone fracture(s)	1	2 which? _____	
	_____			
8.	other diseases	1	2 which? _____	
	_____			

5. In the **past 12 months** have you had any of these symptoms

		No	Yes
1.	sudden loss of vision	1	2
2.	diplopia	1	2
3.	other symptoms	1	2 which ___
	_____		
4.	confinement to wheel chair	1	2

6. Have you within the **last 4 weeks** used any prescribed medicines
   1. No,
   2. Yes, What are the names of the medicines?_____
      _____

7. Have you had the following operations within the **past 12 months?**
   You may choose more than one alternative.

   1. Oophorectomy one side,
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

   2. Oophorectomy both sides
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

   3. Hysterectomy,
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,
      Was the hysterectomy
      1. Total
      2 subtotal
      3 I do not know,

   4. Operation of breast
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

8. Have you had menstrual bleeding within **past 12 months**?

1. No
2. Yes, how many times? ____,
   Was the bleeding bothersome?
   1 No
   2 Yes

9. Your current weight _____ kg

10. How much have you exercised during your free-time within past 3 months?
    1. Not at all
    2. A little
    3. Somewhat
    4. Rather much
    5. Much

11. Have you within the **past 2 weeks** had following symptoms or trouble ?

	No	Yes
dizzy spells (1)	1	2
lack of energy (2)	1	2
diarrhoea or constipation (3)	1	2
irritability (4)	1	2
persistent cough (5)	1	2
feeling of blue or depressed (6)	1	2
backaches (7)	1	2
upset stomach (8)	1	2
headaches (9)	1	2
cold sweats (10)	1	2
aches/stiffness in the joints (11)	1	2
shortness of breath (12)	1	2
hot flashes (13)	1	2
sore throat (14)	1	2
trouble sleeping (15)	1	2
loss of apetite (16)	1	2
fluid (water) retention (17)	1	2

12. Which of these symptoms bother(ed) you (Write here the numbers of the symptoms above which bothered you)
    _____

USE OF HEALTH SERVICES

13. In the **past 12 months** how many times have you seen the study physician _____

14.What were the reasons for these visits to the study physician?

_____

_____

15. In the **past 12 months** how many times have you seen other physicians (excluding dentist)

_____

16.What were the reasons for these visits to other physicians?

_____

_____

17. In the **past 12 months**, have you been in a hospital ward over night?

1. no
2. Yes _____ times, in total _____ days
   Hospital's name _____
   reason _____
   Hospital's name _____
   reason _____

18. In the **past 3 months** how many days have you been so sick that you could not go to work or do your normal duties at home?

1. Not at all
2. _____ days

TRIAL

19. During the **past 12 months**, have you stopped taking trial drugs

1. no
2. yes, ➔ **19B**. when? ➔_____ / _____
   month / year
   what were you reasons for it_____

3. I have not even started using them,
   what were your reasons for it_____
4. I belong to the control group where trial drugs are not used.

20. If you stopped the trial drugs have you started using them again?

1. No
2. Yes

21. Have been taking the trial drugs during the **past 4 weeks**?

1. No
2. Yes, (almost) every day
3. Yes, every now and then
4. I belong to the control group where trial drugs are not used

22. If you have within the **past 4 weeks** taken trial drugs less than advised what were your reasons for this? You can choose several alternatives.
1. I did not get any trial drugs
2. Pills were too few
3. I did not consider them necessary
4. I have forgotten
5. I have had side effects
6. something else _____
   _____
7. I do not know
8. I have taken trial drugs according to advice

23. Have the trial drugs caused you side effects
1. no
2. yes, **23.B** what? encircle the suitable alternatives (you may choose many)
   1. vaginal bleeding
   2. weight loss
   3. weight gain
   4. mastodynia
   5. vaginal discharge
   6. nausea
   7. other, what _____

24. Have the trial drugs had some positive consequences
1. no
2. yes, **24.B** what? encircle the suitable alternatives (you may choose many)
   1. menopausal symptoms disappeared
   2. weight loss

3. better mood
4. better sleep
5. sexual life improved
6. health status improved
7. I feel myself well/normally
8. Cannot say
9. Other, what _____

25. If you belong to the control group (where women did not get trial drugs), have you used hormone replacement therapy?

1. No
2. Yes. Give the time ➔ **23.B** From ____/____ to ____/_____
   mo year mo year

23.C What were the reasons to start (You may choose several)

1. Hot flushes
2. Sleeping disorders
3. Dryness of vagina
4. Doctor advised
5. Other, what _____

26. Do you have any suggestions how we can make the trial better?

1. No
2. Yes, ➔ 26B. Which? _____
   _____

27. Do you participate in some other research study

1. No
2. Yes, ➔ 27B. Which _____

CURRENT LIFE SITUATION

28. Are you currently in paid work

1. Yes, I am in paid work outside home
2. Yes. I am doing paid work at home
3. No, I am retired
4. No, I am unemployed/ looking for a job
5. No, I am a housewife

6. Something else,
   specify _____

29. What is your current marital status
    1. Single
    2. Married
    3. Cohabitant
    4. Divorced
    5. Widow

Finally we ask you to answer the questions on your general health status and daily living. Please encircle the statements which best describe your health state today. (only one alternative in each question)

30. Mobility
    1. I have no problems in walking about
    2. I have some problems in walking about
    3. I am confined to bed

31. Self-Care
    1. I have no problems with self-care
    2. I have some problems washing or dressing myself
    3. I am unable to wash or dress myself

32. Usual Activities (e.g. work, study, housework, family or leisure activities)
    1. I have no problems with performing my usual activities
    2. I have some problems with performing my usual activities
    3. I am unable to perform my usual activities

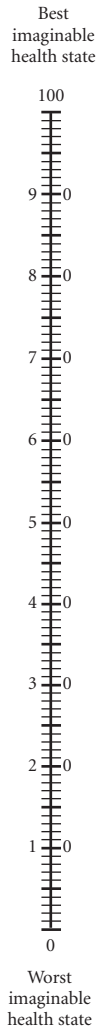
33. Pain/Discomfort
    1. I have no pain or discomfort
    2. I have moderate pain or discomfort
    3. I have extreme pain or discomfort

34. Anxiety/Depression
    1. I am not anxious or depressed
    2. I am moderately anxious or depressed
    3. I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



36.

The questionnaire was filled in: date/month/year

Thank you for filling in the questionnaire and for the pleasant co-operation!

Appendix 12. Third year questionnaire in the EPHT trial

MENOPAUSE AND WOMEN'S HEALTH

Third year questionnaire

Dear respondent. Typically circle only one option, the one which most closely corresponds to your view or situation. Those questions in which you may choose more than one alternative are indicated

1. Study number _ _ _ _ _ _

2. Your birthday _ _ _ _ _ _ _ _ _ _
dd mm yy

HEALTH

3. How do you assess your current health
1. very good
2. good
3. average
4. satisfactory
5. poor
6. very poor

4. In the **past 12 months** have you been found to have any of these diseases as diagnosed by a physician (if yes, circle the alternative, you may choose more than one alternative)

		No	Yes	Do not know
1.	myocardial infarction	1	2	3
2.	angina pectoris	1	2	3
3.	heart failure	1	2	3
4.	any type of stroke including TIA	1	2	3
5.	gall-bladder disease	1	2	3
6.	diabetes mellitus	1	2	3
7.	bone fracture(s)	1	2 which? _____	
	_____			
8.	other diseases	1	2 which? _____	
	_____			

5. In the **past 12 months** have you had any of these symptoms

		No	Yes
1.	sudden loss of vision	1	2
2.	diplopia	1	2
3.	other symptoms	1	2 which ___
4.	confinement to wheel chair	1	2

6. Have you within the **last 4 weeks** used any prescribed medicines
   1. No,
   2. Yes, What are the names of the medicines?_____

7. Have you had the following operations within the **past 12 months?**
   You may choose more than one alternative.

   1. Oophorectomy one site,
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      3 I do not know,
   2. Oophorectomy both sites
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      3 I do not know,
   3. Hysterectomy,
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      3 I do not know,
      Was the hysterectomy
      1. Total
      2 subtotal
      3 I do not know,
   4. Operation on breast
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      3 I do not know,

8. Have you had vaginal bleeding within **past 12 months**?

1. No
2. Yes, how many times? ____,
   Was the bleeding bothersome?
   1 No
   2 Yes

9. Your current weight _____ kg

10. How much have you exercised during your free time within the past 3 months?
    1. Not at all
    2. A little
    3. Somewhat
    4. Rather much
    5. Much

11. Have you within the **past 2 weeks** had the following symptoms or troubles?

	No	Yes
dizzy spells (1)	1	2
lack of energy (2)	1	2
diarrhoea or constipation (3)	1	2
irritability (4)	1	2
persistent cough (5)	1	2
feeling of blue or depressed (6)	1	2
backaches (7)	1	2
upset stomach (8)	1	2
headaches (9)	1	2
cold sweats (10)	1	2
aches/stiffness in the joints (11)	1	2
shortness of breath (12)	1	2
hot flashes (13)	1	2
sore throat (14)	1	2
trouble sleeping (15)	1	2
loss of appetite (16)	1	2
fluid (water) retention (17)	1	2

USE OF HEALTH SERVICES

13. In the **past 12 months** how many times have you seen the study physician _____ times

14. What were the reasons for these visits to the study physician?
1. There were no extra visits
2. _____

_____

15. In the future, would you like to receive an invitation to the study physician with a fixed date and time?

1 no

2 yes

16. In the **past 12 months** how many times have you seen other physicians (excluding dentist)
1. Not once
2. _____ times

17.What were the reasons for these visits to other physicians?

_____

_____

18. Have you had a mammogram within the past 12 months?

1 no

2 yes

18.A

1 the finding was normal

2 I was referred for further investigations

19. In the **past 12 months**, have you been in a hospital ward over night?

1. no
2. Yes _____ times, in total _____ days
   Hospital's name _____
   reason _____
   Hospital's name _____
   reason _____

20. In the **past 3 months** how many days have you been so sick that you could not go to work or do your normal duties at home?

1. Not at all
2. _____ days

TRIAL

21. During the **past 12 months**, have you stopped taking trial drugs

1. no
2. yes, ➔ when? Year and month _____ what were your reasons for the interruption ?_____
3. I have not even started using them, what were your reasons for it___ _____
4. I belong to the control group where trial drugs are not used.

22. If you stopped the trial drugs have you started using them again?

1. No
2. Yes

23. If you belong to the control group (where women did not get trial drugs), have you used hormone replacement therapy?

1. No
2. Yes. Give the time ➔ From ____/____ to ____/_____
   mo year mo year

23.A➔ What were the reasons to start (You may choose several)

1. Hot flushes
2. Sleeping disorders
3. Vaginal dryness
4. Doctor advised
5. Other, what _____

24. What were your expenses in the trial during **past 12 months?**

1 I spent_____ working hours (my salary is___)
2 I spent _____ hours of my spare time
3 My friends or relatives spent _____working hours
4 My friends or relatives spent _____hours of their spare time
5 I spent

24.A 1 _____ for transportation
2 _____ for phone calls
3 _____for napkins
4 other expenses, what _____

25. Do you participate in some other study

1. No
2. Yes, ➔ 27B. Which _____

26. EuroQoL Visual Analogue Scale

27. The questionnaire was filled in date/month/year

Thank you!

Appendix 13. Final (fourth year) questionnaire in the EPHT trial

MENOPAUSE AND WOMEN'S HEALTH

Fourth year questionnaire

Dear respondent. Typically circle only one option, the one which most closely corresponds to your view or situation. Those questions in which you may choose more than one alternative are indicated

1. Study number _ _ _ _ _ _

2. Your birthday _ _ _ _ _ _ _ _ _ _
dd mm yy

HEALTH

3. How do you assess your current health
1. very good
2. good
3. average
4. satisfactory
5. poor
6. very poor

4. In the **past 12 months** have you been found to have any of these diseases as diagnosed by a physician (if yes, circle the alternative, you may choose more than one alternative)

		No	Yes	Do not know
1.	myocardial infarction	1	2	3
2.	angina pectoris	1	2	3
3.	heart failure	1	2	3
4.	any type of stroke including TIA	1	2	3
5.	gall-bladder disease	1	2	3
6.	diabetes mellitus	1	2	3
7.	bone fracture(s)	1	2 which? _____	
	_____			
8.	other diseases	1	2 which? _____	
	_____			

5. In the **past 12 months** have you had any of these symptoms

		No	Yes
1.	sudden loss of vision	1	2
2.	diplopia	1	2
3.	other symptoms	1	2 which ___
	_____		
4.	confinement to wheel chair	1	2

6. Have you within the **last 4 weeks** used any prescribed medicines
   1. No,
   2. Yes, What are the names of the medicines?_____
      _____

7. Have you had the following operations within the **past 12 months?**
   You may choose more than one alternative.

   1. Oophorectomy one side,
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

   2. Oophorectomy both sides
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

   3. Hysterectomy,
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,
      Was the hysterectomy
      1. Total
      2 Subtotal
      3 I do not know,

   4. Operation on breast
      1 No
      2 Yes, when? Month and year _____Why was it performed? _____
      _____
      3 I do not know,

8. How old you were when your first child was born
   1. _____yrs
   2. I have not given birth

9. Have you had vaginal bleeding within **past 12 months**?
   1. No
   2. Yes, how many times_____

   9.A Was the bleeding bothersome?
      1. Yes
      2. No

10. Your current weight _____ kg

11. How much have you exercised during your free-time within the **past 3 months**?
   1. Not at all
   2. A little
   3. Somewhat
   4. Rather much
   5. Much

12. Have you within the **past 2 weeks** had following symptoms or troubles?
   (if yes, circle the alternative, you may choose more than one alternative)

	No	Yes
dizzy spells (1)	1	2
lack of energy (2)	1	2
diarrhoea or constipation (3)	1	2
irritability (4)	1	2
persistent cough (5)	1	2
feeling of blue or depressed (6)	1	2
backaches (7)	1	2
upset stomach (8)	1	2
headaches (9)	1	2
cold sweats (10)	1	2
aches/stiffness in the joints (11)	1	2
shortness of breath (12)	1	2
hot flashes (13)	1	2
sore throat (14)	1	2
trouble sleeping (15)	1	2
loss of appetite (16)	1	2
fluid (water) retention (17)	1	2

13. Which of these symptoms have disturbed you? Please, write here the number in brackets of the disturbing symptom/s. _____

14. At the end of the day do you feel emotionally exhausted?

1 never or almost ever
2 rather seldom
3 Rather often
4 Always or almost always

15. At the end of the day do you feel physically exhausted?

1 never or almost ever
2 rather seldom
3 Rather often
4 Always or almost always

16**.** During the past two weeks

	sometimes	usually	always
Have you had difficulties in finding the right word?	1	2	3
Have you had difficulties tracking what is being said in a conversation?	1	2	3
Have you easily forgot things just told to you?	1	2	3
Have you missed appointments, meetings, deadlines?	1	2	3

USE OF HEALTH SERVICES

17. In the **past 12 months** how many times have you seen the study physician _____ times

18. What were the reasons for these visits to the study physician?

1. There were no extra visits
2. _____

_____

19. In the **past 12 months** how many times have you seen other physicians (excluding dentist)

1. Not a single time
2. _____ times

20. What were the reasons for these visits to other physicians?

_____

_____

21. In the past 12 months have you had a mammogram examination?

1. No

2. Yes➔ **21A**
   1. The result was normal
   2. I got a referral for further examinations

22. In the **past 12 months**, have you been in a hospital ward over night?

1. no
2. Yes _____ times, in total _____ days
   Hospital's name _____
   reason _____
   Hospital's name _____
   reason _____
   Hospital's name _____
   reason _____

23. In the **past 3 months** how many days have you been so sick that you could not go to work or do your normal duties at home?

1. Not at all
2. _____ days

TRIAL

24. During the **past 12 months**, have you stopped taking trial drugs
1. no
2. yes, ➔ **24 B** when? Year and month _____
   ➔ **24 C** what were you reasons for the interruption? _____
   _____
3. I have not even started using them,
   ➔ 24 D what were your reasons for it___ _____
4. I belong to the control group where trial drugs are not used.

25. If you stopped the trial drugs have you started using them again?

1. No
2. Yes ➔ 25A. When _____/ _____
   mo year

26. What were the reasons for restarting trial treatment (you may encircle more than one alternative) ?
   1. Hot flushes
   2. cold sweat
   3. sleeping problems
   4 Trial staff recommended
   5. some other doctor recommended
   6. to prevent osteoporosis

7. to cure osteoporosis
8. Other reason. What _____

27. If you belong to the control group (where women did not get trial drugs), have you used hormone replacement therapy?

1. No
2. Yes. Give the time, regimen and reasons:

➔ **27A** From ____/____ to ____/_____
mo year mo year

➔ **27B** Drug name _____

➔ **27C** What were the reasons to start (You may choose several)

1. Hot flushes
2. cold sweats
3. sleeping problems
4 Trial staff recommended
5. some other doctor recommended
6. to prevent osteoporosis
7. to cure osteoporosis
8. Other reason. What _____

28. Have your opinion on hormone treatment changed during the trial

1. No
2. Yes ➔ **24A** How have they changed _____
_____

PERSONAL LIFE

29. About how many families in your neighbourhood are you well enough acquainted with, so that you visit each other?
_____ families

30. About how many **close** friends do you have - people you feel at ease with and can talk with about what is on your mind? (You may include relatives.) /Enter number on line)
_____ close friends

31. Over the period of a year, about how often do you get together with friends or relatives, like going out together or visiting each other's homes?

1. Every day
2 Several days a week
3. About once a week
4. 2 or 3 times a month
5. About once a month
6. 5 to 10 times a year
7. Less than 5 times a year

32. About how often were you on the telephone with close friends or relatives during the **past month**?

1. Every day
2. Several times a week
3. About once a week
4. 2 or 3 times
5. Once
6. Not at all

33. About how often did you write a letter to a friend or relative during the **past month**?

1. Every day
2. Several times a week
3. About once a week
4. 2 or 3 times in past month
5. Once in past month
6. Not at all in past month

34. About how often did you write an electronic letter (email) to a friend or relative during the **past month**?

1. Every day
2. Several times a week
3. About once a week
4. 2 or 3 times in past month
5. Once in past month
6. Not at all in past month

35. How active are you in the affairs of these groups or clubs you belong to? (If you belong to a great many, just count those you feel closest to. If you do not belong to any, circle 4.)

1. Very active, attend most meetings
2. Fairly active, attend fairly often
3. Not active, belong but hardly ever go
4. Do not belong to any groups or clubs

36. Do you find it difficult becoming old?

1. Not at all
2. A little
3. Rather much
4. Very much
5. I do not know

37. In your ageing, what did you find positive? _____
_____

38.In your ageing, what did you find negative? _____
_____

39. Are you currently in paid work
    1. No, I am retired
    2. No, I am unemployed/ looking for a job
    3. Yes, I am in paid work outside home
    4. Yes. I am working at home
    5. Something else, ➔ **39 A** specify _____

40. What is your current marital status
    1. Single
    2. Married
    3. Cohabitant
    4. Divorced
    5. Widow

41. Are you satisfied with your partner as a friend?
    1. Not at all
    2. A little
    3. Rather much
    4. Very much
    5. I have no partner

42. Are you satisfied with your partner as a lover?
    1. Not at all
    2. A little
    3. Rather much
    4. Very much
    5. I have no partner

43. Does your partner experience difficulty in sexual performance? (e.g. erectile problems, ejaculation difficulties, low arousal
    1. Not at all
    2. A little
    3. Rather much
    4. Very much
    5. I have no partner

44. During the past year (12 months) have you had pain during sexual intercourse?
    1. No
    2. Yes
    3. I have had no intercourse in past 12 months

45-49. EuroQoL 5D in Estonian.
50. EuroQoL VAS
51. The questionnaire was filled in date/month/year

Thank you!

Appendix 14. Long-term (over 12 months) randomised clinical trials of hormone therapy according to their outcomes

Author, publi-cation year	Name of the trial; recruitment period	Participants (N; mean age)	Treatment	Follow-up	Outcome	Result
Trials of HT and bone fractures						
Komulai-nen et al, 1998	Kuopio Osteoporosis Study; 1989	464 healthy women; 53 yrs	Estradiol + cyproterone acetate; placebo	5 yrs	Bone fractures	Decreased risk (RR 0.29; 95 % CI: 0.10–0.90)
Hulley et al; 1998	Heart and Estrogen/Progestin Study (HERS I); 1993–1994	2 763 with CHD; 67 yrs	CEE + MPA	4.1 yrs	Bone fractures	No difference (RR 0.95; 95% CI: 0.75–1.21)
Hulley at al, 2002	HERS II; 1993–1994	2 763 with CHD; 67 yrs	CEE + MPA	6.8 yrs	Bone fractures	No difference (RR 1.04; 95% CI: 0.87–1.25)
The Esprit team; 2001	ESPRIT; 1996–2000	1 017 women with MI; 63 yrs	Estradiol; placebo	2 yrs	Bone fractures	Non-significantly decreased risk (RR 0.60; 95% CI: 0.29–1.26)
WHI team; 2002	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16 608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs	Hip fractures	Decreased risk (HR 0.66; 95% CI: 0.45–0.98)
WHI team; 2004	Estrogen arm of the Women's Health Initiative (WHI) Trial; 1993–1998	10 739 healthy hysterec-tomised women; 64 yrs	CEE; placebo	6.8 yrs	Hip fractures	Decreased risk (HR 0.61; 95% CI: 0.41–0.91)
Trials of HT and coronary heart disease						
Hulley et al; 1998	Heart and Estrogen/Progestin Study (HERS I); 1993–1994	2 763 with CHD; 67 yrs	CEE + MPA	4.1 yrs	MI / CHD death	No difference (RR 0.99; 95% CI:0.80–1.22); improved lipids (p < 0.001)
The Esprit team; 2001	ESPRIT; 1996–2000	1 017 women with MI; 63 yrs	Estradiol; placebo	2 yrs	Rein-farction, cardiac death	Non-significantly increased risk (RR 0.99; 95% CI: 0.70–1.41)
Grady et al; 2002	HERS II; 1993–1994	2 763 with CHD; 67 yrs	CEE + MPA	6.8 yrs	MI / CHD death	No difference (RR 0.99; 95% CI: 0.84–1.17)
Clarke et al; 2002	Papworth HRT Atherosclerosis Enquiry (PHASE)	255 with coronary heart disease; 67 yrs	Estradiol + - norethisterone; no treatment	3 yrs	Unstable angina, MI or cardiac death	No difference (HR 1.29; 95% CI: 0.84–1.95)

Author, publi-cation year	Name of the trial; recruitment period	Participants (N; mean age)	Treatment	Follow-up	Outcome	Result
WHI team; 2002	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16 608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs	CHD	Increased risk (HR 1.29; 95% CI: 1.02–1.63)
WHI team; 2004	Estrogen arm of the Women's Health Initiative (WHI) Trial; 1993–1998	10 739 healthy hysterec-tomised women; 64 yrs	CEE; placebo	6.8 yrs	CHD	No difference (HR 0.91; 95% CI: 0.75–1.12)
Trials of HT and stroke						
Viscoli et al; 2001	Women's Estrogen for Stroke Trial (WEST); 1993–1998	664 with ischemic stroke or TIC; 71 yrs	Estradiol; placebo	3 yrs	Com-bined stroke and death	No difference (RR 1.1; 95% CI: 0.8–1.4)
The Esprit team; 2001	ESPRIT; 1996–2000	1 017 women with MI; 63 yrs	Estradiol; placebo	2 yrs	Stroke, TIC	Increased risk for stroke (RR 1.64; 95% CI: 0.60–4.47) and TIC (RR 1.13; 95% CI: 0.54–2.36)
WHI team; 2002	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16 608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs	Stroke	Increased risk (HR 1.41; 95 % CI: 1.07–1.85)
WHI team; 2004	Estrogen arm of the Women's Health Initiative (WHI) Trial; 1993–1998	10 739 healthy hysterec-tomised women; 64 yrs	CEE; placebo	6.8 yrs	Stroke	Increased risk (HR 1.39; 95% CI: 1.10–1.77)
Trials of HT and DVT						
Hulley et al; 1998	Heart and Estrogen/Progestin Study (HERS I); 1993–1994	2 763 with CHD; 67 yrs	CEE + MPA	4.1 yrs	Thromb-embolic events	Increased risk (RR 2.89; 95% CI:1.50–5.58)
Hoibraaten et al; 2000	Estrogen in venous thromboembo–lism trial (EVTET); 1996–1998	140 women with previous VTE;	Estradiol + NETA; placebo		VTE	Increased risk of VTE
The Esprit team; 2001	ESPRIT; 1996–2000	1 017 women with MI; 63 yrs	Estradiol; placebo	2 yrs	DVT, PE	Increased risk of DVT (RR 1.96; 95% CI: 0.18–21.6) and PE (RR 0.98; 95% CI: 0.20–4.84)

Author, publication year	Name of the trial; recruitment period	Participants (N; mean age)	Treatment	Follow-up	Outcome	Result
WHI team; 2002	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16 608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs	Pulmonary embolism	Increased risk (HR 2.13; 95% CI: 1.39–3.25)
WHI team; 2004	Estrogen arm of the Women's Health Initiative (WHI) Trial; 1993–1998	10 739 healthy hysterectomised women; 64 yrs	CEE; placebo	6.8 yrs	Pulmonary embolism	Non-significantly increased risk (HR 1.34; 95% CI: 0.87–2.06)
Trials of HT and breast cancer						
The Esprit team; 2001	ESPRIT; 1996–2000	1 017 women with MI; 63 yrs	Estradiol; placebo	2 yrs	Breast cancer	Increased risk (RR 0.98; 95% CI: 0.25–3.91)
WHI team; 2002	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs	Breast cancer	Increased risk (HR 1.26; 95 % CI: 1.00–1.59)
WHI team; 2004	Estrogen arm of the Women's Health Initiative (WHI) Trial; 1993–1998	10 739 healthy hysterectomised women; 64 yrs	CEE; placebo	6.8 yrs	Breast cancer	Non-significantly decreased risk (HR 0.77; 95% CI: 0.59–1.01)
Trials of HT and gynecologic cancers						
The Writing Group for the PEPI Trial; 1996	Postmenopausal Estrogen/Progestin Interventions Trial (PEPI); 1989–1991	875 (596 with uterus); 56 yrs	CEE alone; three CEE + P regimens; placebo	3 yrs	Endometrial changes	Unopposed estrogens add risk of endometrial hyperplasia and cancer ($p < 0.001$)
WHI team; 2002	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16 608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs	Endometrial cancer	No difference (HR 0.83; 95% CI: 0.47–1.47)
Anderson et al, 2003	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16 608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs	Ovarian cancer	Non-significantly increased risk (HR 1.58; 95% CI: 0.77–3.24)
Trials of HT and colorectal cancer						
WHI team; 2002	Estrogen plus progestin arm of the Women's Health Initiative (WHI) Trial; 1993–1998	16 608 healthy women; 63 yrs	CEE+MPA; placebo	5.2 yrs	Colorectal cancer	Decreased risk (HR 0.63; 95% CI: 0.43–0.92)

Author, publi-cation year	Name of the trial; recruitment period	Participants (N; mean age)	Treatment	Follow-up	Outcome	Result
WHI team; 2004	Estrogen arm of the Women's Health Initiative (WHI) Trial; 1993–1998	10 739 healthy hysterec-tomised women; 64 yrs	CEE; placebo	6.8 yrs	Colo-rectal cancer	No difference (HR 1.08, 95% CI: 0.75–1.55)
Trials of HT and arterial events*						
Herrington et al ; 2000	Estrogen Replacement and Atherosclerosis (ERA); 1995–1996	309 with CHD; 66 yrs	CEE +- MPA; placebo	3.2 yrs	Mean mini-mum coronary artery diameter	No difference (1.87+ – 0.02 mm; 1.84+– 0.02 mm; 1.87 +– 0.02 mm); improved lipids (p < 0.01)
Waters et al; 2002	The Women's Angiographic Vitamin and Estrogen Trial (WAVE); 1997–1999	423 with CHD; 65 yrs	CEE + -MPA or placebo; Vit E + Vit C or placebo; factorial design	2.8 yrs	MLD of coronary lesions	No benefit with HT (p = 0.17) or vitamins (p = 0.32)
De Kleijn et al; 1999	Name not reported; duration 1992–1995	121 healthy women; 47 yrs	Estradiol + cyclic desogestrel; CEE + cyclic norgestrel; placebo	2 yrs	Carotid IMT and end-diastolic lumen diameter	No difference
Hodis et al; 2001	Estrogen and Prevention of Atherosclerosis Trial (EPAT)	222 healthy women; 62 yrs	Estradiol; placebo; LLMs if indicated	2 yrs	Carotid IMT	Less progression with 17– ß-estradiol without LLMs (p = 0.002); no difference in those taking LLMs (p > 0.2)
Hodis et al; 2003	Women's Estrogen–Progestin Lipid–Lowering Hormone Atherosclerosis Regression Trial (WELL–HART); 1995–2000	226 women with coronary artery lesion; 64 yrs	Estradiol; Estradiol + cyclic MPA; placebo	3.3 yrs	Percent stenosis	No effect
Waters et al; 2002	The Women's Angiographic Vitamin and Estrogen Trial (WAVE); 1997–1999	423 with CHD; 65 yrs	CEE + -MPA or placebo; Vit E + Vit C or placebo; factorial design	2.8 yrs	MLD of coronary lesions	No benefit with HT (p = 0.17) or vitamins (p = 0.32)

* Only statistical signifance has been reported from these trials

Trials of HT and dementia						
Shumaker et al, 2004	The Women's Health Initiative Memory Study; 1995–2002	4 532 healthy women; 65-79 yrs	CEE+MPA or placebo	7 yrs	Dementia	Increased risk (HR 2.05; 95% CI: 1.21–3.48)
Shumaker et al, 2004	The Women's Health Initiative Memory Study; 1995–2004	2 947 healthy women; 65-79 yrs	CEE or placebo	9 yrs	Dementia or MCI	Increased risk (HR 1.38; 95% CI: 1.01–1.89)

Author, publi-cation year	Name of the trial; recruitment period	Participants (N; mean age)	Treatment	Follow-up	Outcome	Result
Trials of HT and diabetes						
Kanaya et al, 2003	HERS I	2 763 women with CHD; 67 yrs	CEE+MPA	4.1 yrs	Diabetes	Decreased risk (RR 0.65; 95% CI: 0.48–0.89)
Margolis et al, 2004	WHI	15 641 healthy women; 63 yrs	CEE+MPA	5.6 yrs	Treated diabetes	Decreased risk (HR 0.79; 95% CI: 0.67–0.93)
Trials of HT and biliary tract disease						
Hulley et al, 1998	HERS I	2 763 with CHD; 67 yrs	CEE + MPA	4.1 yrs	Gall-bladder disease	Increased risk (RR 1.38; 95% CI: 1.50–5.58)
Hulley et al, 2002	HERS II	2 763 with CHD; 67 yrs	CEE + MPA	6.8 yrs	Biliary tract surgery	Increased risk (RR 1.48; 95 % CI: 1.12–1.95)

CEE = conjugated equine estrogen; CHD = coronary heart disease; CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; HT = hormone therapy; IMT = intima-media thickness; LLMs = lipid-lowering medications; MCI = mild cognitive impairment; MI = myocardial infarction; MLD = minimal lumen diameter; MPA = medroxyprogesterone acetate; NETA = - norethisterone acetate; PE = pulmonary embolism; RR = relative risk; TIC = transitory ischaemic attacks; VTE = venous thromboembolism

I

Available online at www.sciencedirect.com
ScienceDirect
Maturitas 55 (2006) 162–173
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Results from the Estonian postmenopausal hormone therapy trial [ISRCTN35338757]

Piret Veerus[a,b,e,*], Sirpa-Liisa Hovi[c,e], Krista Fischer[d], Mati Rahu[a,b], Matti Hakama[e], Elina Hemminki[b]

[a] *Department of Epidemiology and Biostatistics, National Institute for Health Development (TAI), Tallinn, Estonia*
[b] *Estonian Center of Excellence in Behavioral and Health Sciences, Tallinn, Estonia*
[c] *Department of Health and Social Services, National Research and Development Centre for Welfare and Health (STAKES), Helsinki, Finland*
[d] *Department of Public Health, University of Tartu, Tartu, Estonia*
[e] *Tampere School of Public Health, University of Tampere, Tampere, Finland*

Received 3 October 2005; received in revised form 26 January 2006; accepted 30 January 2006

Abstract

Objectives: At present the Women's Health Initiative trial is the only reported randomised controlled trial studying the effects of hormone therapy among healthy postmenopausal women. The Women's Health Initiative reports have been criticized for lacking in generalisability, due to the characteristics of the trial population. We aimed to compare the health effects of oral continuous combined hormone therapy with a placebo and non-treatment among healthy Estonian women.
Methods: Eligible women were randomised into a blind group of hormone therapy versus placebo and into a non-blind group of open label hormone therapy versus non-treatment. One thousand seven hundred and seventy-eight postmenopausal women aged 50–64 at the time of sampling were recruited in 1999–2001 at three clinical centers in Estonia. Participants received conjugated equine oestrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or conjugated equine oestrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 5 mg/d, if less than 3 years had passed since menopause at recruitment, or matched placebo or non-treatment. Trial treatment was stopped gradually from 1 January 2004 to 31 May 2004.
Results: After a follow-up period from 2.0 to 5.0 years the combined hazard ratio, stratified by blinding and adjusted for age at recruitment and former oral contraceptive use was 1.12 (95% confidence interval [CI]: 0.90–1.40) for coronary heart disease, 1.24 (95% CI: 0.85–1.82) for cerebrovascular disease, 1.36 (95% CI: 0.73–2.52) for total cancer, and 0.61 (95% CI: 0.42 to 0.89) for bone fractures.
Conclusions: The results from the Estonian Postmenopausal Hormone Therapy randomised trial are consistent with the Women's Health Initiative findings.

Keywords: Postmenopausal hormone therapy; Randomised trial with blind and non-blind controls; Follow-up by means of database linkages

* Corresponding author. Tel.: +372 6 593 941; fax: +372 6 593 901.
E-mail address: piret.veerus@tai.ee (P. Veerus).

0378-5122/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2006.01.012

1. Introduction

Several randomised controlled trials studying the effects of postmenopausal hormone therapy on the health status of women with prior coronary heart disease, stroke, or venous thromboembolism have been reported. They found that hormone therapy does not reduce the risk of coronary heart disease events in postmenopausal women with coronary disease [1–7], or the risk of stroke in postmenopausal women with cerebrovascular disease [8], and that it increases the risk of venous thromboembolism in women who have previously suffered from venous thromboembolism [9] or coronary heart disease [1,10,11]. In women with coronary disease, it was found that hormone therapy reduces the incidence of diabetes [12].

As a primary prevention trial among relatively healthy postmenopausal women, the Women's Health Initiative trial found that combined postmenopausal hormone therapy increases the risk of coronary heart disease [13,14], stroke [13,15], breast cancer [13,16], and dementia [17], but reduces the risk of bone fractures [13,18] and colorectal cancer [13,19]. The Women's Health Initiative trial did not confirm that hormone therapy protects against peripheral arterial disease [20]. The Women's Health Initiative trial has been criticized as being in part a secondary cardiovascular prevention trial which could not test the hypothesis that hormone therapy may be cardioprotective when started around menopause [21,22].

The aim of this randomised controlled trial was to ascertain harms and benefits of combined continuous hormone therapy among healthy Estonian postmenopausal women. Most women in the Estonian Postmenopausal Hormone Therapy trial used the same regimen as women in the Women's Health Initiative combined hormone treatment randomised trial. The trial consisted of two sub-trials—a blind and a non-blind one. The results are presented as combined hazard ratios for coronary heart disease, cerebrovascular disease, total cancer and bone fractures.

2. Materials and methods

2.1. Participants

The names, personal identification numbers and addresses of all 39 713 women living in two Estonian counties of Tartu and Harju – including Tallinn, the capital of Estonia – and aged 50–64 years in March 1999 were obtained from the Estonian Population Registry. These women were mailed information about the trial and a questionnaire. The questionnaire included questions about health status and willingness to join a randomised trial. Of the 14 743 women who returned the questionnaire, 6606 respondents were interested in participating (Fig. 1). Among these, 2311 women were found to be ineligible (38% were still menstruating, 26% had reported a condition defined by the study group as a medical contraindication for hormone therapy, 22% were already using hormone therapy, 7% had no health insurance, 6% asked for open-label hormone therapy or for no treatment, and 1% had moved to a new location). Altogether 4170 eligible women were randomised for the main trial.

In order to study the impact of blinding on the recruitment process, adherence, and health care costs (not reported here), the trial used a non-blind sub-trial in parallel to the blind one. Randomisation was therefore carried out before recruitment and receipt of consent. There were four study arms: (1) blind drug arm; (2) placebo arm; (3) non-blind drug arm; (4) non-blind control arm. Randomisation to four arms was carried out in permuted blocks, each of a size 16 and each block of the three clinics separately, at the National Research and Development Centre for Welfare and Health in Finland. The treatment allocation was enclosed in a non-transparent sealed envelope and sent to trial clinics.

The 4170 randomly assigned women were mailed a doctor's invitation, revealing whether the woman had been randomised to the blind or to the non-blind sub-trial. Only 2323 actually responded by visiting the doctor. Of these, 1778 proved to be eligible, and their randomisation envelope was opened. Unopened randomisation envelopes were collected from the clinics by the research team in order to detect deviations from the trial protocol.

Trained trial physicians conducted a thorough medical examination during the recruitment visits, including questioning about reproductive and health history, risk factors for coronary heart disease, and medication use, as well as measurement of blood pressure, examination of breasts, pelvic examination, a Pap-smear for all women, and transvaginal sonography for women in the treatment arms. The inclusion criteria for joining the

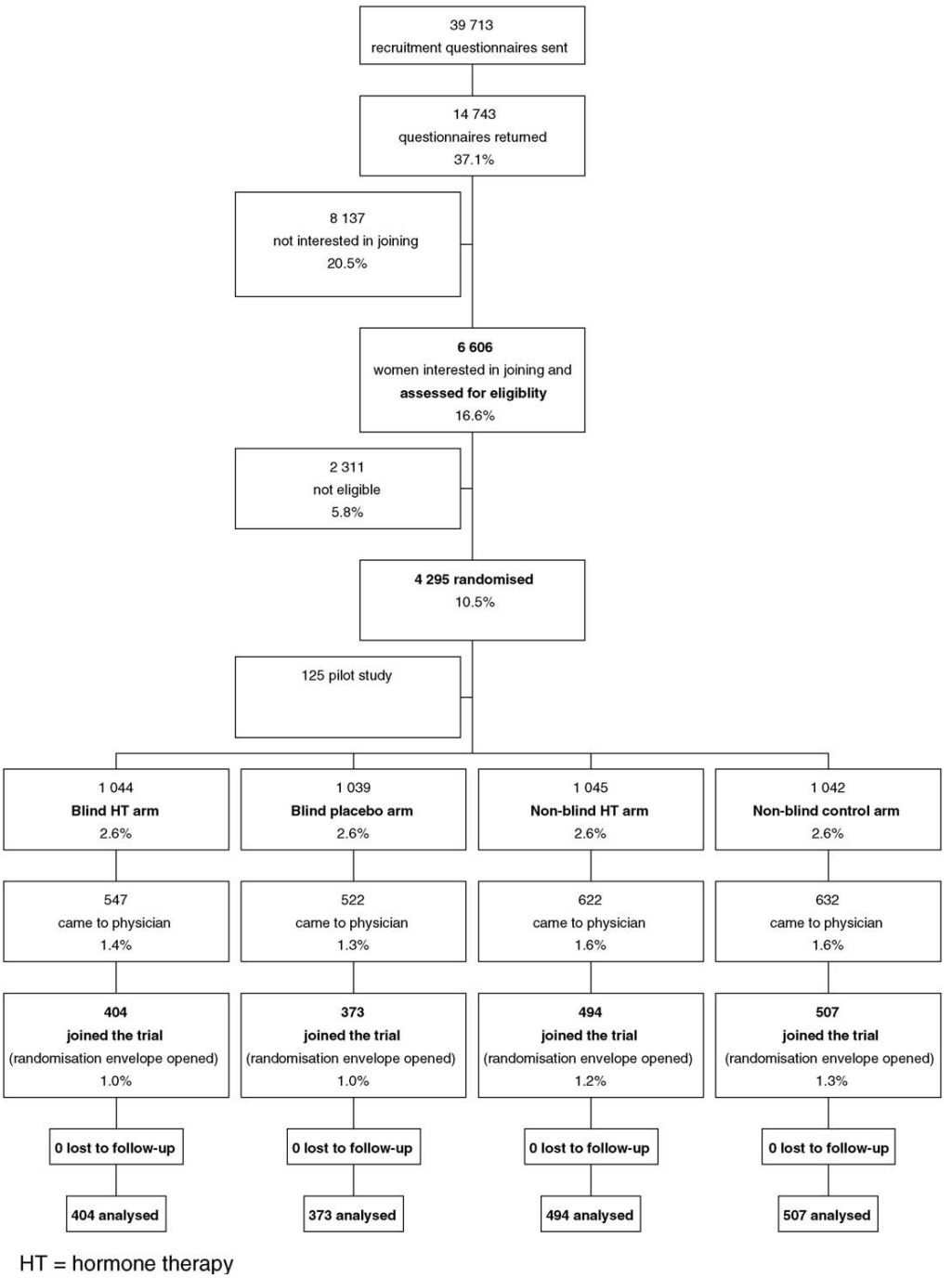


Fig. 1. Trial profile of the Estonian Postmenopausal Hormone Therapy trial.

trial were an age of 50–64 at the time of sampling from the Estonian Population Registry and an elapsed time of 12 months or more since the last period at the randomisation stage. The exclusion criteria were as follows: use of hormone therapy during the past 6 months; untreated endometrial adenomatosis or atypical hyperplasia of the endometrium; a history of breast cancer, endometrial cancer or ovarian cancer; any other cancer treated less than 5 years ago; a history of meningioma; myocardial infarction within the last 6 months; a history of hepatitis or functional liver disorders in the last 3 months; a history of deep vein thrombosis, pulmonary embolism, or cerebral infarction; porphyria; hypertension of more than 170/110 mmHg despite medication; laparoscopically or histologically confirmed endometriosis.

Recruitment lasted from January 1999 to December 2001. The recruitment process has been described in detail elsewhere [23]. All participants gave written informed consent. The study protocol was approved by the Tallinn Medical Research Ethics Committee, Estonia, and by the Ethics Committee of University Clinic of Tampere, Finland.

The Estonian Postmenopausal Hormone Therapy trial was originally planned to be a part of the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM) in the United Kingdom which would have taken the overall sample size in WISDOM together with other international collaborators from 18 000 to 34 000 [24]. No sample size calculations were made for health outcomes in the Estonian trial. Drugs were donated by Wyeth Ayerst Company via WISDOM and the outcomes of the Estonian trial were meant to contribute to WISDOM.

The main outcome measures reported in this paper are coronary heart disease, cerebrovascular disease, total cancer and bone fractures. Coronary heart disease was defined as diagnoses I20–I25 according to the 10th revision of the International Classification of Diseases (ICD-10) [25] (angina pectoris, acute myocardial infarction, subsequent myocardial infarction, current complications following acute myocardial infarction, other acute ischaemic heart disease, chronic ischaemic heart disease). Cerebrovascular disease was defined as diagnoses I60–I69 according to ICD-10 (subarachnoid haemorrhage, intracerebral haemorrhage, other nontraumatic intracranial haemorrhage, cerebral infarction, stroke, occlusion and stenosis of precerebral arteries, occlusion and stenosis of cerebral arteries, other cerebrovascular diseases, cerebrovascular disorders, sequelae of cerebrovascular disease). Total cancer was defined as diagnoses C00–C97 according to ICD-10 (all malignant neoplasms). Bone fractures were defined as diagnoses S12, S22, S32, S42, S52, S62, S72, S82, S92 according to ICD-10 (fracture of neck, fractures of ribs, sternum and thoracic spine, fracture of lumbar spine and pelvis, fracture of shoulder and upper arm, fracture of forearm, fracture at wrist and hand level, fracture of femur, fracture of lower leg, including ankle).

2.2. Procedures

After the woman's health status had been checked and the informed consent had been signed, the sealed non-transparent randomisation envelope was opened. In the blind sub-trial, the women were told that they would be using either hormone therapy or a placebo; in the non-blind sub-trial, they were told that they would be receiving hormone therapy or non-treatment.

The drug in oral daily use in the treatment arms contained 0.625 mg of conjugated oestrogens and 2.5 mg of medroxyprogesterone acetate (or matched placebo in the placebo arm). Altogether 251 women within 3 years of their last period were randomised to daily 0.625 mg of oral conjugated oestrogens and 5.0 mg of oral medroxyprogesterone acetate or matched placebo in the placebo arm or non-treatment in the control arm to reduce the risk of uterine bleeding. The drug bottles had a unique bottle number; in the non-blind sub-trial the label contained information about the composition of the drug.

Study participants were asked to fetch their drug bottles every 7 months after recruitment, and were invited to annual clinical examinations by means of mailed letters. The annual medical examination included measurement of weight and arterial blood pressure, pelvic examination and breast inspection. A Pap-smear was taken every second year. Other examinations (endometrial biopsy, blood sample) were made only on clinical indications. Vaginal bleeding was managed by an algorithm that accounted for time and severity of bleeding, and sonographically determined endometrial thickness. The trial midwives had fixed calling hours in order to answer any questions by the trial women.

Permanent discontinuation of trial medication was required by protocol for women who developed breast

cancer, invasive cancer at any other site, meningioma, deep vein thrombosis, pulmonary embolism, retinal vein occlusion, porphyria, stroke or brain haemorrhage, hypertension over 170 mmHg/110 mmHg despite medication, renal failure, or for whom any other hormone therapy regimen was prescribed. Medication was temporarily discontinued in patients who experienced sudden loss of vision, proptosis or diplopia, liver functional disorders, active hepatitis or active gall bladder disease, angina pectoris, myocardial infarction, hospitalisation for other cardiovascular conditions, heart failure, cerebrovascular accident, subarachnoid haemorrhage, transient ischaemic attacks, pancreatitis, or long-term immobilization.

Adherence was assessed by the number of collected and returned drugs and by the information from annual questionnaires and weekly reports from the clinics. Women taking more than 80% of the allocated drugs were considered to be adherent, whilst women in the control arm were considered to be adherent if they were not taking hormone therapy for 80% of the time.

The intervention was originally planned to last 5 years. The Data Monitoring Committee[1] made interim analyses once a year. On 2 December 2003 the Data Monitoring Committee recommended stopping trial treatment which was started in January 2004 by gradually informing the participants individually and was completed on 31 May 2004. The decision was based upon published reports of the Women's Health Initiative trial and the Million Women Study findings [13–18,26–29], not on the results of the interim analyses of trial data. As the Trial Steering Committee[2] wanted to offer a thorough medical check-up at the closure visit to all trial participants, as also requested in the study protocol, it took 6 months to schedule the final clinic visits. Participants in the blind sub-trial received information on their treatment allocation within 1 month of their final visit. The trial staff remained blinded until the end of the trial.

The trial cohort was monitored by means of annual mailed questionnaires, annual medical check-ups and annual linkages to the Estonian Health Insurance Fund database, the Estonian Cancer Registry database, and the Estonian Mortality Database (via the Estonian Cancer Registry). Cancer cases were identified by linkages to the Estonian Cancer Registry. Cardiovascular endpoints and bone fractures were identified by linkages to the Estonian Health Insurance Fund database. The last follow-up date for the present analysis was 31 December 2003 for the Health Insurance Fund database and for the Cancer Registry, and 31 December 2002 for the Mortality Database. The Estonian Cancer Registry database has been validated for completeness of registration, with the overall completeness of registration being 90.8% in 1998 [30].

The Estonian Health Insurance Fund covers the costs of health services required by an individual in the case of illness, regardless of the amount of social tax paid for the person concerned [31]. The Fund stores information about all health care contacts in a centralized, computerized database, using an individual's personal identification code. In the data file, the unit is one disease episode. For each disease episode, up to three medical diagnoses of insured persons as the cause for care according to the 10th revision of the International Classification of Diseases are recorded. The data is transferred electronically from clinics to the database of the Health Insurance Fund. As the compensation depends on the transmission of data from clinics to the central database and not on the diagnosis, the process is quick, and the probability of missing data is small. The persons doing linkages with the Health Insurance Fund database and the Estonian Cancer Registry were unaware of the treatment allocation.

2.3. Statistical analysis

The data was analyzed by time-to-event methods for the outcomes, and the analysis was based on the intention-to-treat principle. All participants whose randomisation envelope was opened during the recruitment visit and who signed the informed consent were included in the analysis.

[1] T. Aro, M. Jylhä, T. Hakulinen (chair).

[2] K. Fischer, University of Tartu, Estonia; M. Hakama, Tampere School of Public Health, Finland; E. Hemminki, National Research and Development Centre for Welfare and Health, Finland; S.-L. Hovi, National Research and Development Centre for Welfare and Health, Finland; H. Karro, University of Tartu, Estonia; F. Kirss, University of Tartu, Estonia; M. Rahu, National Institute for Health Development, Estonia; T. Sevon, National Research and Development Centre for Welfare and Health, Finland; R. Tuimala, Tampere University Women's Clinic, Finland; P. Veerus, National Institute for Health Development, Estonia; S. Vorobjov, National Institute for Health Development, Estonia.

For a given outcome, the time of the first event in each disease group was defined as the number of days from recruitment to the first diagnosis in this disease group, as registered in the Health Insurance Fund database or in the Estonian Cancer Registry database. Participants without a diagnosis were censored for that event at 1 January 2004.

Hazard ratios with 95% confidence intervals for main outcomes were calculated within the blind and the non-blind sub-trial using Cox proportional hazards modelling, adjusted by age at recruitment and former oral contraceptive use. For the statistical analysis of the main outcomes, the hormone therapy arms were then combined, as well as the placebo arm and non-blind control arm. Outcome comparisons are presented as crude and adjusted combined hazard ratios with 95% confidence intervals. The analyses were based on Cox proportional hazards modelling, adjusted on the basis of stratification by blinding for the crude combined hazard ratio and using stratification by blinding and adjustment by age at recruitment and former oral contraceptive use for the adjusted combined hazard ratio. Interaction between treatment group and blinding was tested but not included in the model. The assumption of proportionality was tested and met.

Table 1
Number and percentage distribution of women by trial arms and baseline characteristics[a] in the Estonian Postmenopausal Hormone Therapy trial

Characteristic	Open HT ($n = 494$)	Control ($n = 507$)	Blind HT ($n = 404$)	Placebo ($n = 373$)
Age, mean (S.D.) (year)	58.6 (4.0)	58.9 (4.0)	58.5 (3.9)	59.0 (3.9)
Age at recruitment (year)				
50–54	122 (24.7)	108 (21.3)	95 (23.5)	74 (19.8)
55–59	182 (36.8)	176 (34.7)	158 (39.1)	128 (34.3)
60–64	164 (33.2)	201 (39.7)	138 (34.2)	154 (41.3)
65–70	26 (5.3)	22 (4.3)	13 (3.2)	17 (4.6)
Age at menopause, mean (S.D.)	50.2 (3.9)	50.5 (4.0)	50.4 (3.8)	50.3 (3.9)
Prior OC use[b]	36 (7.3)	19 (3.7)	37 (9.2)	24 (6.4)
BMI, mean (S.D.) (kg/m^2)	27.2 (4.5)	26.9 (4.6)	27.0 (4.8)	26.9 (4.2)
BMI (kg/m^2)				
<25	175 (35.4)	189 (37.3)	150 (37.1)	133 (35.7)
25–29.9	193 (39.1)	203 (40.0)	156 (38.6)	156 (41.8)
≥30	123 (24.9)	107 (21.1)	89 (22.0)	77 (20.6)
Parity[b]				
No term pregnancy	44 (9.7)	49 (10.3)	33 (8.9)	28 (8.1)
≥1 term pregnancy	410 (90.3)	429 (89.7)	338 (91.1)	318 (91.9)
Education[b]				
<4 years	13 (2.6)	21 (4.1)	17 (4.2)	12 (3.2)
4–7 years (basic)	34 (6.9)	42 (8.3)	27 (6.7)	28 (7.5)
8–11 years (secondary)	276 (55.9)	280 (55.3)	228 (56.7)	216 (58.1)
University	171 (34.6)	164 (32.3)	130 (32.4)	116 (31.2)
Hysterectomy (self-reported)	65 (13.2)	66 (13.0)	46 (11.4)	48 (12.9)
Current smoking	65 (13.2)	82 (16.2)	66 (16.3)	52 (13.9)
Treated for hypertension	75 (15.2)	63 (12.4)	53 (13.1)	45 (12.1)
History of angina	11 (2.2)	13 (2.6)	6 (1.5)	4 (1.1)
History of MI	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.3)
Systolic BP, mean (S.D.) (mmHg)	136.5 (17.5)	137.0 (16.6)	136.5 (17.3)	137.0 (15.9)
Diastolic BP, mean (S.D.) (mmHg)	86.7 (11.2)	86.1 (10.9)	85.7 (11.0)	86.2 (10.2)
Female relative with breast cancer	28 (5.7)	41 (8.1)	29 (7.2)	26 (7.0)

HT = hormone therapy, OC = oral contraceptives, BMI = body mass index, MI = myocardial infarction, BP = blood pressure.
[a] For selected variables also mean and standard deviation (S.D.) are indicated.
[b] Among women for whom data was available.

Kaplan–Meier curves of cumulative hazard in four trial arms were plotted for the main outcomes. A subgroup analysis for women within 3 years of menopause and an additional analysis omitting women with prior history of angina pectoris were performed.

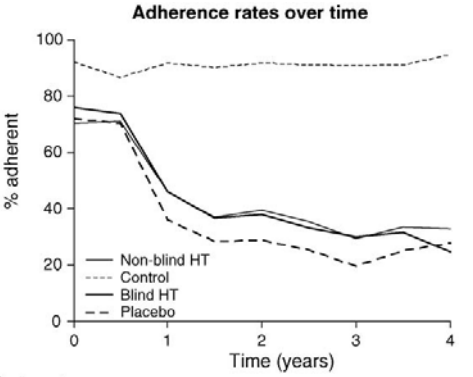
The software used was *R* for Windows, version 1.9.0 [32].

3. Results

The number of women attending the recruitment visit was higher in the non-blind sub-trial, and more women were recruited into the non-blind sub-trial by trial physicians. The impact of blinding on recruitment has been described elsewhere [23]. In the blind sub-trial, the socio-economic background characteristics of women who did not attend the recruitment reception were not different of those who did, but in the non-blind sub-trial, more women with higher education declined participation at this stage. Age, social status, marital status, living place and having a relative with breast cancer had no impact on trial participation in neither of the sub-trials.

Comparing the baseline characteristics in the four arms showed a difference in the former use of oral contraceptives, comparing the hormone therapy and no hormone therapy arms showed a difference in the age at recruitment (Table 1). The mean follow-up time from recruitment was 3.43 years; the potential follow-up time was from 2.00 to 4.97 years. There were seven deaths among participating women—one in the blind hormone therapy arm, one in the blind placebo arm, two in the non-blind hormone therapy arm, and three in the non-blind control arm. The adherence rates over time are presented in Fig. 2. Women were not persuaded by the research team to use trial treatment which explains the loss to adherence at the beginning of the trial and the dramatic fall in adherence within the first trial year when the women had to fetch their second drug bottle.

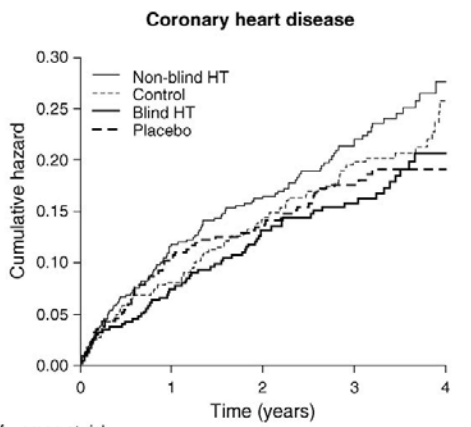
The main trial outcomes by 1 January 2004 after a follow-up period from 2 to 5 years are presented in Table 2. The combined hazard ratio for coronary heart disease events after stratification by blinding and adjustment by age at recruitment and former oral contraceptive use was 1.12 (95% CI: 0.90–1.40). The cumulative hazard rate of coronary heart disease is shown in Fig. 3. The combined hazard ratio for cere-



No of adherent women:					
Non-blind HT	347	227	195	107	27
Control	466	465	464	347	88
Blind HT	307	186	153	89	15
Placebo	268	134	107	54	17

HT = hormone therapy

Fig. 2. Adherence rates by four trial arms in the Estonian Postmenopausal Hormone Therapy trial.



No of women at risk:					
Non-blind HT	494	438	417	285	62
Control	507	468	439	314	72
Blind HT	404	374	353	246	44
Placebo	373	336	323	227	52

HT = hormone therapy

Fig. 3. Cumulative rates of coronary heart disease by four trial arms in the Estonian Postmenopausal Hormone Therapy trial.

Table 2
The main trial outcomes and hazard ratios with 95% confidence intervals by trial arm for all women

Outcome	Blind			Non-blind			Blind and non-blind	
	Hormone therapy[a] ($n = 404$)	Placebo[a] ($n = 373$)	Hazard ratio[b] (95% CI)	Hormone therapy[a] ($n = 494$)	Control[a] ($n = 507$)	Hazard ratio[b] (95% CI)	Hazard ratio, crude[c] (95% CI)	Hazard ratio, adjusted[d] (95% CI)
Coronary heart disease	66 (16.3)	62 (16.6)	1.03 (0.73–1.46)	105 (21.3)	97 (19.1)	1.17 (0.88–1.54)	1.07 (0.87–1.33)	1.12 (0.90–1.40)
Myocardial infarction only	2 (0.5)	0	–	1 (0.2)	2 (0.4)	0.55 (0.05–6.01)	1.48 (0.25–8.86)	1.62 (0.27–9.69)
Cerebrovascular disease	23 (5.7)	9 (2.4)	2.46 (1.14–5.34)	35 (7.1)	39 (7.7)	0.95 (0.60–1.50)	1.22 (0.83–1.78)	1.24 (0.85–1.82)
Stroke only	1 (0.2)	1 (0.3)	1.06 (0.07–17.2)	5 (1.0)	3 (0.6)	1.88 (0.34–10.4)	1.51 (0.43–5.36)	1.61 (0.38–6.77)
Total cancer	6 (1.5)	4 (1.1)	1.59 (0.45–5.65)	17 (3.4)	14 (2.8)	1.30 (0.64–2.64)	1.31 (0.71–2.43)	1.36 (0.73–2.52)
Breast cancer only	1 (0.2)	2 (0.5)	0.55 (0.05–6.06)	3 (0.6)	4 (0.8)	0.82 (0.18–3.68)	0.68 (0.19–2.40)	0.72 (0.20–2.56)
Bone fractures	15 (3.7)	25 (6.7)	0.52 (0.27–0.98)	29 (5.9)	44 (8.7)	0.67 (0.42–1.07)	0.62 (0.43–0.91)	0.61 (0.42–0.89)

CI = confidence interval.
[a] Data is presented as number (percentage) of women.
[b] Hazard ratio, obtained by Cox proportional hazards modelling, adjusted by age at recruitment and prior oral contraceptive use.
[c] Combined hazard ratio, obtained by Cox proportional hazards modelling, adjusted on the basis of stratification by blinding.
[d] Combined hazard ratio, obtained by Cox proportional hazards modelling, adjusted by age at recruitment and prior oral contraceptive use and stratified by blinding.

Fig. 4. Cumulative rates of cerebrovascular disease by four trial arms in the Estonian Postmenopausal Hormone Therapy trial.

brovascular disease was 1.24 (95% CI: 0.85–1.82), and for total cancer 1.36 (95% CI: 0.73–2.52). There were two cases of colorectal cancer in the non-blind hormone therapy arm. No pulmonary embolism or deep vein thrombosis events occurred. The combined hazard ratio for bone fractures in the hormone treatment arms was 0.61 (95% CI: 0.42–0.89). There were no hip fractures among the trial participants. The cumulative hazard rates of cerebrovascular disease, total cancer and bone fractures are presented in Figs. 4–6.

For almost all diseases, there were more events in the non-blind sub-trial. No significant interactions were detected between treatment and blinding except on risk for cerebrovascular disease ($p = 0.03$). Among 39 women diagnosed with cerebrovascular disease in the control arm, 10 had been using prescribed hormone therapy. The hazard ratio of cerebrovascular disease after including the interaction term in the model was 2.52 (95% CI: 1.16–5.45) in the blind sub-trial and 0.94 (95% CI: 0.59–1.48) in the non-blind one.

In the subgroup analysis of 251 women within 3 years of menopause at recruitment the adjusted hazard ratio was 1.09 (95% CI: 0.48–2.46) for coronary heart disease, 3.26 (95% CI: 0.35–29.95) for cancer and 0.44 (95% CI: 0.13–1.56) for bone fractures.

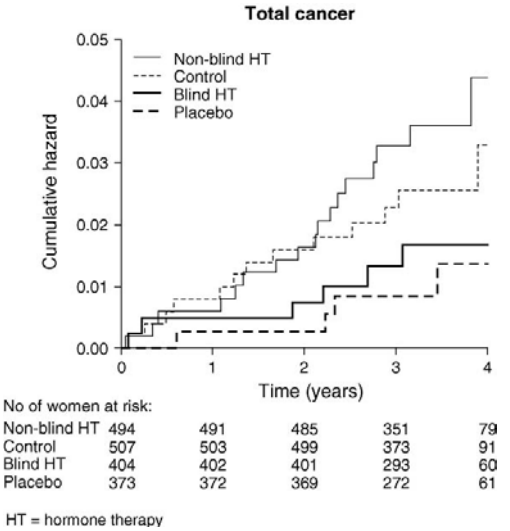


Fig. 5. Cumulative rates of total cancer by four trial arms in the Estonian Postmenopausal Hormone Therapy trial.

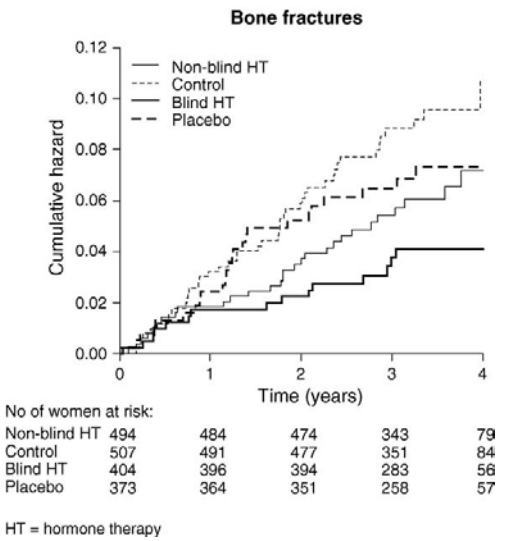


Fig. 6. Cumulative rates of bone fractures by four trial arms in the Estonian Postmenopausal Hormone Therapy trial.

For women without prior history of angina pectoris, the hazard ratio for coronary heart disease was 0.95 (95% CI: 0.66–1.36) in the blind sub-trial and 1.23 (95% CI: 0.92–1.65) in the non-blind sub-trial, the adjusted combined hazard ratio being 1.12 (95% CI: 0.89–1.40).

4. Discussion

The main outcome results in this trial concerning coronary heart disease, cerebrovascular disease, and bone fractures are consistent with the results of the Women's Health Initiative trial. For total cancer, the hazard ratio was higher than in the Women's Health Initiative trial. The harmful effects of postmenopausal hormone therapy include coronary heart disease, stroke, thromboembolic events, breast cancer and cholecystitis [33]. The protective effect of hormone therapy on postmenopausal bone fractures is well established [13,18,34,35], and a potential protective effect on colorectal cancer has been reported [13,19,36].

In comparison with women participating in the Women's Health Initiative trial, women in the Estonian trial were younger and healthier. On average they were 4.4 years younger on entering the trial (58.8 years versus 63.2 years), and their mean body mass index at screening was 1.5 units smaller (27.0 kg/m^2 versus 28.5 kg/m^2); only 22.2% had a body mass index equal or more than 30, as compared with 34.1% in the Women's Health Initiative trial. In the Estonian trial, 14.9% were current smokers, as compared with 10.5% in the Women's Health Initiative trial. Fewer women in the Estonian trial had been treated for hypertension before recruitment (13.2% versus 36.1%). Fewer women in the Estonian trial had a history of angina (1.9% versus 2.8%), a history of myocardial infarction (0.3% versus 1.7%), a history of diabetes (1.6% versus 4.4%), and a female relative with breast cancer (7.0% versus 15.7%). Women with a history of stroke or deep venous thrombosis were excluded from our trial. Prior hormone therapy was not checked in the Estonian trial, but according to the State Agency of Medicine, oestrogen use in Estonia was low in the years 1999–2001 [37]. In the Women's Health Initiative trial, prior hormone therapy use was nearly 26%. Prior use of oral contraceptives was 43.0% in the Women's Health Initiative and 7.1% in the Estonian trial.

More than half of the randomly assigned women were lost before recruitment. This was not unexpected, because the trial design was based on the assumption that there would be differences between the blind and non-blind sub-trials, but not between the trial arms, since the allocation happened without the woman or the trial staff knowing to which arm the woman belonged. However, there were two baseline imbalances in the prior use of oral contraceptives and age at recruitment, possibly due to variation. The possible bias was corrected for by using adjustment for former oral contraceptive use and age at recruitment. After the adjustment, we believe that the loss before opening the randomisation envelopes did not endanger comparability but increased the random error in estimates of effect.

We assume that none of the participants was lost for the follow-up as the probability of missing data in the Health Insurance Fund database is small. The data processing in the registries had no information on women's participation in the trial. Electronically captured routine clinical data have been shown to be valid for health technology assessment [38].

There was a wide discrepancy in event rates in the blind and the non-blind sub-trial. This may be due to chance, or may have resulted from women who were more ill being more eager and willing to participate or being accepted by trial physicians in the non-blind sub-trial. It may also have resulted from less care seeking in the blind sub-trial, perhaps due to the placebo effect.

The discontinuation rate in treatment arms was about the same as in real life circumstances [39]. This may have caused dilution of the differences between the groups as regards trial results. The reasons for non-adherence have been reported elsewhere [40].

The closing date for the Estonian Mortality Database was 12 months earlier than the closing date for the Estonian Health Insurance Fund database and Estonian Cancer Registry database. We assume that it does not have any practical effect on the estimation of outcomes.

The outcomes are presented as combined results from the blind and non-blind sub-trials although the patient populations might have been slightly different and the results of the non-blind sub-trial may have included women's and physicians' behaviour in addition to the biological effects of hormone therapy.

The results of the Estonian hormone trial showed a statistically significant reduction in bone fractures. The risk of coronary heart disease, cerebrovascular disease and cancer was not significantly affected, probably due to the small number of events. The results of the Estonian Postmenopausal Hormone Therapy trial adds to evidence that hormone therapy reduces bone fractures in healthy women, and provides no evidence of benefits for coronary heart disease, cerebrovascular disease, or total cancer. The results are consistent with Women's Health Initiative findings. The impact of blinding on trial outcomes deserves more attention in the medical research.

Acknowledgments

We sincerely thank each woman for her participation in the trial. We also express our gratitude to our trial staff, Dr. Anne-Mary Rumma, Dr. Reet Sokk, Eevi Beldsinsky, Piia Reisman from West Tallinn Central Hospital; Dr. Maret Ramm, Dr. Fred Kirss, Dr. Aira Peri, Jelena Konoshina, Pille Joonas, Marge Mahla from Tartu University Clinic; Dr. Zinaida Kuznetshikova, Dr. Reet Laasik, Dr. Tiiu Mäss, Dr. Reeli Saaron, Made Bambus, Õie-Maret Leetberg, Piia Heiman, Riina Pajula from East-Tallinn Central Hospital, as well as to collaborators from the National Institute for Health Development, Tallinn and from the National Research and Development Centre for Welfare and Health, Helsinki. Our special thanks to Maie Thetloff from the Estonian Health Insurance Fund and to Pille Härmaorg from the Estonian Cancer Registry. The trial was funded by the Academy of Finland (grant nos. 69838 and 201490), STAKES (National Research and Development Centre for Welfare and Health), Finland, and the Estonian Ministry of Education and Research (target funding 0192112s02). PV and SLH received a fellowship from Finnish Ministry of Education (Doctoral Programs in Public Health). The work of KF was partially supported by Estonian Science Foundation grant no. 5203. Drugs were donated by Wyeth Ayerst Company via the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM) in the United Kingdom. The funding bodies had no role in the study design, data collection, data analysis, data interpretation, writing of the report or in the decision to submit the paper for publication.

References

[1] Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605–13.

[2] Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/Progestin Replacement Study follow up (HERS II). JAMA 2002;288:49–57.

[3] The ESPRIT Team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. Lancet 2002;360:2001–8.

[4] Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofield PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT Atherosclerosis Study. Br J Obstet Gynaecol 2002;109: 1056–62.

[5] Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary–artery atherosclerosis. N Engl J Med 2000;343:522–9.

[6] Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women. A randomized controlled trial. JAMA 2002;288:2432–40.

[7] Hodis HN, Mack WJ, Azen SP, et al. Hormone therapy and the progression of coronary–artery atherosclerosis in postmenopausal women. N Engl J Med 2003;349:535–45.

[8] Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 2001;345:1243–9.

[9] Hoibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrom E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy: results of the randomised, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost 2000;84:961–7.

[10] Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and estrogen/progestin replacement study follow-up (HERS II). JAMA 2002;288:58–66.

[11] Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the heart and estrogen/progestin replacement study. Ann Intern Med 2000;132:689–96.

[12] Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the heart and estrogen/progestin replacement study: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2003;138:1–9.

[13] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.

[14] Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523–34.

[15] Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effects of estrogen plus progestin on stroke in postmenopausal women. The Women's Health Initiative: a randomized trial. JAMA 2003;289:2673–84.

[16] Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The Women's Health Initiative randomized trial. JAMA 2003;289:3243–53.

[17] Shumaker S, Legault C, Rapp S, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2651–62.

[18] Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density. The Women's Health Initiative Randomized Trial. JAMA 2003;290:1729–38.

[19] Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004;350:991–1004.

[20] Hsia J, Criqui MH, Rodabough RJ, et al. Estrogen plus progestin and the risk of peripheral arterial disease. The Women's Health Initiative. Circulation 2004;109:620–6.

[21] McDonough P. The randomized world is not without its imperfections: reflections on the Women's Health Initiative Study. Fertil Steril 2002;78:951–6.

[22] MacLennan A, Sturdee D. The end of WISDOM. Climacteric 2002;5:313–6.

[23] Hemminki E, Hovi SL, Veerus P, Tuimala R, Rahu M, Hakama M. Impact of blinding on recruitment—The Estonian Postmenopausal Hormone Therapy Trial. J Clin Epidemiol 2004;57:1237–43.

[24] Vickers M, Meade T, Darbyshire J. WISDOM: history and early demise—was it inevitable? Climacteric 2002;5:317–25.

[25] International Statistical Classification of Diseases and Related Health Problems, 1989 Revision. Geneva: World Health Organization; 1992.

[26] Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.

[27] Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2663–72.

[28] Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med 2003;348:1839–54.

[29] Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. The Women's Health Initiative randomized trial. JAMA 2003;290:1739–48.

[30] Lang K, Mägi M, Aareleid T. Study of completeness of registration at the Estonian cancer registry. Eur J Cancer Prev 2003;12:153–6.

[31] Estonian Health Insurance Fund. Available at: http://www.haigekassa.ee/HK/in_english.htm. Accessed October 14, 2004.

[32] The R Project for Statistical Computing. Available at: http://www.r-project.org. Accessed August 9, 2005.

[33] Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JP. Postmenopausal hormone replacement therapy. Scientific review. JAMA 2002;288:872–81.
[34] Torgerson DJ, Bell-Seyer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA 2001;285:2891–7.
[35] Writing Group for the PEPI Trial. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. JAMA 1996;275: 1389–96.
[36] Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 1999;106:574–82.
[37] Hovi SL, Karttunen T, Karro H, Hemminki E. Comparison of Estonian and Finnish physicians' opinions of menopause and hormone therapy. Maturitas 2004;49:107–13.
[38] Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT. Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment. Health Technol Assess 2003;7:1–117.
[39] Thorp JM, Gavin NI, Ohsfeldt RL. Hormone replacement therapy in postmenopausal women: utilization of health care resources by new users. Am J Obstet Gynecol 2001;185:318–26.
[40] Vorobjov S, Hovi S-L, Veerus P, Pisarev H, Rahu M, Hemminki E. Treatment adherence in the Estonian postmenopausal hormone therapy (EPHT) trial [ISRCTN35338757]. Maturitas 2005;52:286–95.

II

Symptom reporting and quality of life in the Estonian Postmenopausal Hormone Therapy trial

P Veerus, K Fischer, SL Hovi, H Karro, M Rahu, E Hemminki

Abstract

Background: To determine the effect of postmenopausal hormone therapy on women's symptom reporting and quality of life in a randomized trial.

Methods: 1823 women participated in the Estonian Postmenopausal Hormone Therapy (EPHT) trial between 1999 and 2004. Women were randomized to open-label continuous combined hormone therapy or no treatment, or to blind hormone therapy or placebo. The average follow-up period was 3.6 years. Prevalence of symptoms and quality of life according to EQ-5D were assessed by annually mailed questionnaires.

Results: In the hormone therapy arms, less women reported hot flushes (OR) 0.20; 95% CI: 0.14–0.28), sweating (OR 0.56; 95% CI: 0.43–0.73), and sleeping problems (OR 0.71; 95% CI: 0.55–0.92), but more women reported episodes of vaginal bleeding (OR 8.40; 95% CI: 3.27–27.43) and backache (OR 1.27; 95% CI: 1.02–1.59). There was no difference between the trial arms in the prevalence of other symptoms over time. Quality of life did not depend on hormone therapy use.

Conclusions: Postmenopausal hormone therapy decreased vasomotor symptoms and sleeping problems, but increased episodes of vaginal bleeding and backache, and had no effect on quality of life.

[**ISRCTN35338757**]

III

American Journal of Obstetrics and Gynecology (2006) **195**, 62–71

ELSEVIER

American Journal of
Obstetrics & Gynecology
www.ajog.org

Postmenopausal hormone therapy increases use of health services: Experience from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]

Piret Veerus, MD,[a,b,c,*] Krista Fischer, PhD,[d] Sirpa-Liisa Hovi, Lic NSc,[c,e] Matti Hakama, PhD,[c] Mati Rahu, PhD,[a,b] Elina Hemminki, MD, Dr PH[e]

Department of Epidemiology and Biostatistics, National Institute for Health Development (TAI), Tallinn, Estonia[a]*; Estonian Center of Excellence in Behavioral and Health Sciences, Tallinn-Tartu, Estonia*[b]*; Tampere School of Public Health, Tampere, Finland*[c]*; Department of Public Health, University of Tartu, Tartu, Estonia*[d]*; Department of Health and Social Services, National Research and Development Centre for Welfare and Health (STAKES), Helsinki, Finland*[e]

Received for publication August 11, 2005; revised November 17, 2005; accepted December 19, 2005

KEY WORDS
Postmenopausal hormone therapy
Utilization of health services
Health care costs

Objective: This study was undertaken to compare utilization of health services and health care costs in a randomized hormone therapy trial.
Study design: A total of 1823 healthy postmenopausal women aged 50 to 64 years at the time of sampling were allocated to combined continuous hormone therapy or placebo or no treatment. The analysis was based on routinely collected electronic data in the Estonian Health Insurance Fund database during a follow-up period from 2 to 5 years.
Results: In the nonblind subtrial, the number of all health care visits was 10% higher and the number of visits to family practitioners 16% higher per person-year in the hormone therapy arm. Per person-year, the number of vaginal sonograms was 14% and the number of electrocardiograms 19% higher in the nonblind hormone therapy arm. Outpatient health care costs and drug expenses were higher in the nonblind hormone therapy arm. In the blind subtrial, the number of gynecologic operations, vaginal sonograms and total health care costs was higher in the hormone therapy arm.
Conclusion: Hormone therapy caused additional expenses on health care.

Supported by the Academy of Finland (grants 69838 and 201490), STAKES (National Research and Development Centre for Welfare and Health), Finland, and the Estonian Ministry of Education and Research (target funding 0192112s02). Drugs were donated by Wyeth Ayerst Company via the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM) in the United Kingdom.

The funding bodies had no role in the study design, data collection, data analysis, data interpretation, writing of the report or in the decision to submit the paper for publication.

* Reprint requests: Piret Veerus, Department of Epidemiology and Biostatistics, National Institute for Health Development (TAI), Hiiu 42, 11619 Tallinn, Estonia.
E-mail: piret.veerus@tai.ee

0002-9378/$ - see front matter © 2006 Mosby, Inc. All rights reserved.
doi:10.1016/j.ajog.2005.12.037

The health effects of postmenopausal hormone therapy (HT) include increases in cardiovascular disease and breast cancer, and decreases in bone fractures and colorectal cancer.[1] Although HT prescriptions declined after the publication of the Women's Health Initiative trial results, millions are still prescribed annually.[2] Therefore, policymakers and clinicians need information about the costs of therapies in addition to their clinical benefits.

Before the publication of the Women's Health Initiative trial results, postmenopausal HT was considered to be relatively cost-effective.[3-5] Computer simulations were set up to study hypothetical cohorts of menopausal women and to calculate the corresponding lifetime differences in direct health care costs and health effects.[6,7] Annual health care utilization was calculated according to data about women who self-initiated HT[8-11] or from computer model studies.[12,13] Health care use in a randomized trial of tibolone and HT was estimated by retrospectively interviewing a panel of general practitioners and gynecologists and by modeling these data.[14] The results of these studies are contradictory.

The objective of this study was to compare the health care use of women who used open-label postmenopausal HT with women who did not use it in a randomized nonblind trial. Treatment allocation was revealed only after enrollment into the trial. The aim of unveiling the treatment allocation was to capture the consequences resulting from the subjects' knowledge of whether the patient was receiving HT or not, as well as the care providers' response to this knowledge, so that the results would be relevant to ordinary settings. The results from the blind subtrial are presented for comparison.

The use of health services was analyzed from the viewpoint of the provider institutions and the purchaser of health care. The analysis was based on the results of linkages with the Estonian Health Insurance Fund database that includes data about all provided health services. The health effects of the Estonian Postmenopausal Hormone Therapy trial will be reported separately.

Material and methods

Screening, randomization, recruitment, and clinical follow-up

Screening, randomization, and recruitment of participants in the Estonian Postmenopausal Hormone Therapy Trial have been described in detail elsewhere.[15] To study the impact of blinding on recruitment and for logistic reasons, randomization was nontraditionally carried out after initial expression of interest before signing the informed consent. Randomization to 4 groups was carried out as a central randomization service in permuted blocks, each of a size 16. Women were randomly assigned to 4 trial arms: (1) blind HT arm, (2) blind placebo arm, (3) nonblind HT arm, or (4) nonblind control arm.

The inclusion criteria for joining the trial were an age of 50 to 64 years at the time of sampling from the Estonian Population Registry and an elapsed time of 12 months or more since the last period at the randomization stage. The exclusion criteria were as follows: use of HT during the past 6 months; untreated endometrial adenomatosis or atypical hyperplasia of the endometrium; a history of breast cancer, endometrial cancer or ovarian cancer; any other cancer treated less than 5 years ago; a history of meningioma; myocardial infarction within the last 6 months; a history of hepatitis or functional liver disorders in the last 3 months; a history of deep vein thrombosis, pulmonary embolism, or cerebral infarction; porphyria; hypertension of more than 170/110 mm Hg despite medication; and laparoscopically or histologically confirmed endometriosis.

The treatment allocation was enclosed in a nontransparent sealed envelope with a woman's study number and name on it, and sent to the trial clinic. During the 2 recruitment visits, everyone received a thorough medical examination, including a Papanicolaou (Pap) test smear. In addition, transvaginal sonography was carried out on the eligible women allocated to trial treatment. The randomization envelope was opened only after checking the woman's eligibility criteria and after signing the informed consent. Recruitment visits and clinical investigations before enrollment were not included in the present analysis.

There were 494 women in the nonblind HT arm, 507 women in the nonblind control arm, 404 in the blind HT arm, and 373 in the blind placebo arm. The mean age of participants was 58.8 years at recruitment, 23% of the women were 50 to 54 years, 36% were from 55 to 59 years, 37% from 60 to 64 years, and 4% were from 65 to 70 years. The mean body mass index of participating women was 27.0 kg/m^2 and 15% were current smokers. About 13% of women were treated for hypertension, and 2% had a history of angina.

Women were invited to the trial physician once a year. Annual visits to trial physicians were included in the analysis. We assume that these visits would normally appear in everyday practice as well. In the nonblind subtrial, the percentage of women attending the first annual examination was higher in the HT arm, but was not significantly different in the 2 trial arms in the following years. In the blind subtrial, the proportion of women attending annual visits did not differ in the 2 trial arms.

The recruitment period lasted from January 1999 to December 2001. All participants gave written informed consent. The trial protocol was approved by the Tallinn Medical Research Ethics Committee, Estonia, and by the Ethical Committee of Tampere University Hospital, Finland.

The intervention was originally planned to last 5 years, but on December 2, 2003, the Data Monitoring Committee recommended stopping trial treatment that was started gradually by informing the participants individually and was completed on May 31, 2004. The decision was based on published reports of the Women's Health Initiative trial findings.[1,16-23] As the Trial Steering Committee wanted to offer a thorough medical check-up at the closure visit to all trial participants, as also requested in the study protocol, it took 6 months to schedule the final clinic visits. All participants were regularly informed about the published results of the Women's Health Initiative trial since September 2002.

Intervention

The drug in oral daily use in the treatment arms contained 0.625 mg of conjugated estrogens and 2.5 mg of medroxyprogesterone acetate or matched placebo in the placebo arm. Altogether 251 women within 3 years of their last period were randomly assigned to daily 0.625 mg of oral conjugated estrogens and 5.0 mg of oral medroxyprogesterone acetate or matched placebo in the placebo arm or nontreatment in the control arm. The drug bottles had a unique bottle number, in the nonblind subtrial the label contained information about the composition of the drug.

If HT was prescribed to women in the control arm, or if women in the trial treatment arms stopped or restarted trial treatment, they were asked to inform the trial staff about the date and reason for stopping or starting HT.

Women in the trial treatment arms taking more than 80% of the allocated drugs were considered to be adherent, whereas women in the control arm were considered to be adherent if they were not taking HT for 80% of the time. Adherence rates and reasons for nonadherence have been described in detail elsewhere.[24]

Health care system in Estonia

The Estonian Health Insurance Fund is the only organization in Estonia dealing with compulsory health insurance.[25] The Fund guarantees health care to all insured Estonian citizens. The Fund uses the social tax paid by the working population, which also covers the cost of health services provided to persons who have no income with regard to working activities.

The Health Insurance Fund pays for all health care visits, diagnostic examinations, preventive and treatment procedures, hospital stays, surgeries, technical aids during or after surgery, and compensations for medicinal products. It also pays benefits for temporary incapacity for work. All participants in the trial were insured.

Every person has a freely chosen family practitioner. Usually a person needs a referral from the family practitioner to visit a medical specialist, but no referral is needed to visit a psychiatrist, gynecologist, dermatovenerologist, ophthalmologist, dentist, pulmonologist (for tuberculosis treatment), infection specialist (for HIV/AIDS treatment), surgeon, or orthopedist (for traumatology). In the case of emergency treatment, a person may directly go to the emergency reception or call an ambulance regardless his or her insurance status. The attending physician decides whether the patient needs urgent inpatient treatment. Planned hospitalizations occur after a referral from a family practitioner or a medical specialist.

Data collection

Follow-up was performed by annual linkages to the database of the Estonian Health Insurance Fund. The linkages were made using personal identification numbers. No technical problems occurred while doing the linkages. The last follow-up date was December 31, 2003. The mean follow-up time in the trial was 3.4 years. The trial profile is presented in Figure 1.

The unit of registration at the Health Insurance Fund is one care episode, and the following data are recorded: dates of start and end of the episode, number of visits to the doctor or number of inpatient days in a hospital, diagnostic examinations, treatment procedures, surgical interventions, the cost of each service separately, up to 3 medical diagnoses as the cause for care according to the 10th revision of International Classification of Diseases[26] and the date of death if relevant. For prescribed drugs, the following information is recorded: data about the physician and the patient, name and ATC-code of the drug, diagnosis according to the International Classification of Diseases, and date of writing the prescription.

The main outcome measures were number of health care visits, number of visits to family practitioners, to all medical specialists and separately to gynecologists, number of hospitalizations and hospital days, number of sickness leave days, inpatient and outpatient health care costs, purchased cost of prescribed drugs, purchased cost of sickness leaves and number of women who used selected medical procedures, each calculated in both trial arms per person-year. Dental care was not included in the analysis. On the basis of previous literature,[1,10] we selected from the list of medical procedures vaginal ultrasonography, biopsies, gynecologic operations, mammography, breast operations, bone densitometry, Pap test smears, cytologic investigations, x-ray investigations, and electrocardiograms of the heart. A comparison of the 20 most often-used medical services in trial arms did not provide any additional information.

The cost of trial treatment, based on adherence rates in the HT arm, was calculated separately from the costs of prescribed drugs. Costs of prescribed drugs include HT prescribed in the control arm. All drug costs were analyzed as costs purchased by the Health Insurance Fund, not as the total costs of prescribed drugs. The rate

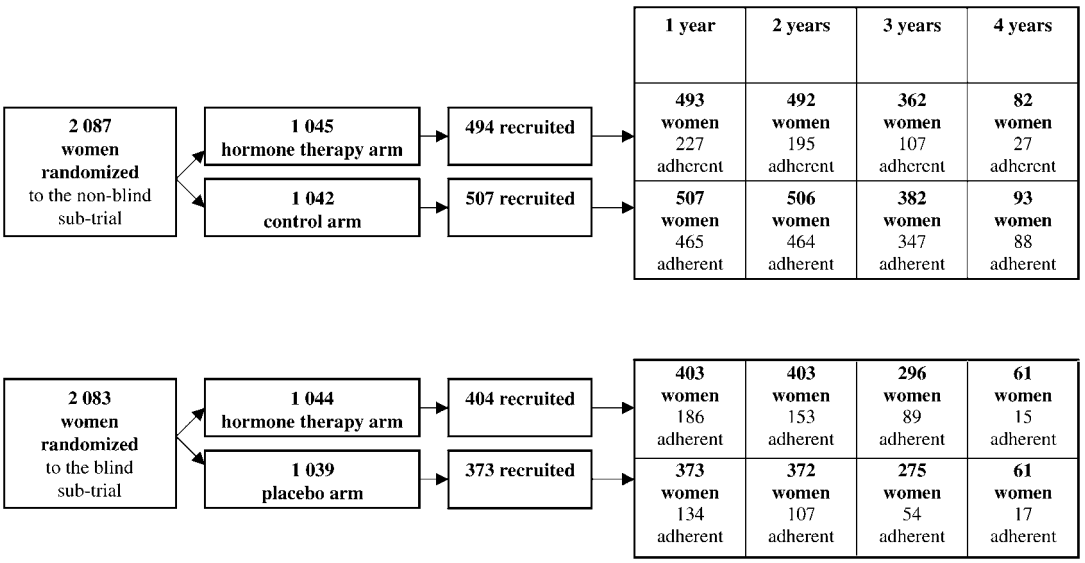


Figure 1 Trial profile.

of currency conversion was 12.63 Estonian kroon per $1 US. The average rise in the costs of the Estonian Health Insurance Fund from 1999 to 2004 was about 15% (unpublished data).

Annual linkages to the Estonian Mortality Database were used to detect deaths. The last follow-up date for the linkage with the Mortality Database was December 31, 2002. There were 2 deaths in the nonblind HT arm, 3 deaths in the control arm, 1 death in the blind HT arm, and 1 in the placebo arm during the trial.

Statistical analysis

The data were analyzed according to the intention-to-treat principle.

All baseline characteristics were compared by using χ^2 tests (categorical variables) or analysis of variance (continuous variables). No significant differences between the 2 arms in either subtrials were detected.

Log-linear Poisson regression was used for a statistical comparison of the number of health care visits and instances of health services used within the nonblind and blind subtrial. The total number of visits in each 6-month period in each of the 5-year interval age groups at recruitment was used as a dependent variable, using the total number of person-years observed in this interval as the denominator. The model was adjusted for period since recruitment and age group at recruitment. Interactions between age and treatment, age and time, time and treatment were tested for. No interactions were detected. To adjust for overdispersion in cases in which repeated health care visits or repeated procedures such as electrocardiograms of heart at each disease instance per woman are likely to occur, the iterative algorithm proposed by Breslow was used.[27]

The software used was R for Windows, version 2.0.0 with the contributed package dispmod to adjust for overdispersion in the log-linear models.[28]

Results

As the distribution of health care visits, hospital care days, hospitalizations, and sickness days per person-year was strongly skewed, the numbers are presented by quartiles in Table I. Half of the women in the nonblind HT arm had up to 5.9 health care visits per person-year, whereas in the control arm the corresponding figure was 5.5. Half of the women in the nonblind HT arm had up to 2.5 visits to family practitioner per person-year, the corresponding figure in the control arm being 2.2. Per person-year, the number of all health care visits was 10% higher and number of visits to family practitioners 16% higher in the nonblind HT arm. In the blind subtrial no statistically significant differences were found in regard to these outcomes. The number of visits to all medical specialists or separately to gynecologists did not differ significantly between the arms. The number of hospitalizations, hospital care days, and days on sickness leave did not differ between the arms.

Figure 2 shows the mean number of health care visits to family practitioners and medical specialists per

Table I Health services utilization per person-year in the nonblind and blind subtrial

	Minimum	First quartile	Median	Third quartile	Maximum	Rate ratio	95% CI
All health care visits*							
Nonblind HT arm	0	3.35	5.90	9.68	31.02	1.10	1.02-1.18
Control arm	0	2.87	5.51	8.59	35.25		
Blind HT arm	0	2.92	5.33	8.37	26.45	0.96	0.89-1.04
Placebo arm	0	2.70	5.53	9.14	41.14		
Visits to a family practitioner*							
Nonblind HT arm	0	1.00	2.49	4.34	13.94	1.16	1.06-1.26
Control arm	0	0.89	2.19	4.07	15.34		
Blind HT arm	0	1.01	2.33	4.39	15.67	0.99	0.90-1.10
Placebo arm	0	0.97	2.37	4.13	12.37		
Visits to all specialists*							
Nonblind HT arm	0	1.60	3.09	5.30	24.81	1.04	0.96-1.13
Control arm	0	1.41	2.80	4.79	25.32		
Blind HT arm	0	1.48	2.45	4.41	19.33	0.94	0.86-1.04
Placebo arm	0	1.36	2.68	4.89	32.31		
Visits to a gynecologist*							
Nonblind HT arm	0	0	0.53	1.06	4.61	1.15	0.97-1.36
Control arm	0	0	0.47	0.88	5.27		
Blind HT arm	0	0	0.51	1.01	3.78	0.98	0.82-1.18
Placebo arm	0	0	0.47	1.03	5.07		
Number of hospitalizations							
Nonblind HT arm	0	0	0	0.25	2.10	0.94	0.79-1.12
Control arm	0	0	0	0.26	2.19		
Blind HT arm	0	0	0	0.26	4.16	0.96	0.78-1.19
Placebo arm	0	0	0	0.25	3.72		
Hospital care days*							
Nonblind HT arm	0	0	0	0.53	23.09	1.01	0.76-1.35
Control arm	0	0	0	0.63	34.36		
Blind HT arm	0	0	0	0.48	44.14	0.96	0.87-1.38
Placebo arm	0	0	0	0.26	115.24		
Hospital care days per hospitalized woman							
Nonblind HT arm	0.22	0.89	2.03	3.53	23.09	0.92	0.62-1.37
Control arm	0.22	0.81	1.79	3.66	34.36		
Blind HT arm	0.22	0.65	1.47	2.71	44.14	1.27	0.72-2.25
Placebo arm	0.24	0.72	1.39	3.49	115.24		
Number of days on sickness leave*							
Nonblind HT arm	0	0	0	4.37	119.51	0.92	0.63-1.32
Control arm	0	0	0	4.76	91.47		
Blind HT arm	0	0	0	3.67	86.77	0.74	0.48-1.12
Placebo arm	0	0	0	4.81	54.62		

* Accounted for overdispersion.

person-year in both arms of the nonblind subtrial. The number of visits to family doctors increased in time, and the rise was more remarkable in the HT arm.

The use of selected medical procedures in the 2 nonblind trial arms is presented in Table II. Women using HT were 14% more often investigated by vaginal sonography. They had 19% more electrocardiograms during the trial. There was no significant difference in the number of gynecologic or breast operations, in the numbers of bone densitometry, mammograms, Pap test smears, cytologic investigations, x-ray investigations, or biopsies between the 2 groups. In the blind subtrial, the number of vaginal sonograms was 38% higher in the HT arm and women in the HT arm had 2.5 times more gynecologic operations. There were no differences in the use of other medical procedures between the arms of the blind subtrial.

The distribution of health care costs was skewed. Quartiles of health care costs in US dollars per person-year in both subtrials are presented in Table III. Outpatient health care costs were higher in the nonblind HT arm. Half of the women in this arm used outpatient health care for up to $56 US per person-year, whereas the corresponding figure in the control arm was $50 US per person-year. Inpatient health care costs did not differ in the 2 nonblind arms. Half of the women in

Figure 2 *HT,* hormone therapy arm; *C,* control arm; *Spec,* visits to medical specialists; *FP,* visits to family practitioners.

both arms did not use inpatient care per person-year at all. Inpatient health care costs for 75% of women were up to $65 US per person-year in the nonblind HT and up to $62 US per person-year for 75% of women in the control arm. Total cost of prescribed drugs per person-year became significantly higher in the HT arms after including cost of trial treatment in the calculations, reaching $73 US for half of the women in the nonblind HT arm, and $21 US in the control arm, the corresponding figures being $72 US in the blind HT arm and $18 US in the placebo arm. Benefits for temporary incapacity for work were similar in all arms. Because of increased expenses on drugs and added costs on outpatient health care in the nonblind HT arm, total health care costs were higher in the HT arms. For half of the women in the nonblind HT arm, health care costs were up to $161 US per person-year ($140 US in the blind HT arm), the corresponding figure in the control arm was $121 US ($111 US in the placebo arm).

Comment

Results of the Estonian Postmenopausal Hormone Therapy trial show that HT users cause additional expenses in health care and use different subcategories of health services in comparison with women not using HT.

This article is not an economic evaluation study because we wanted to report the use of different health services in a randomized HT trial and to disaggregate the costs as far as possible. Cost-effectiveness league

Table II Use of selected medical procedures in the nonblind subtrial

	HT arm N = 494	Control arm N = 507	Rate ratio*	95% CI	*P* value
Gynecologic operations			1.30	0.88-1.92	.18
0	446 (90.3)	474 (93.5)			
1	38 (7.7)	22 (4.3)			
2+	10 (2.0)	11 (2.2)			
Operations on breasts			1.28	0.38-4.27	.68
0	488 (98.8)	502 (99.0)			
1	5 (1.0)	5 (1.0)			
2+	1 (0.2)	0 (0)			
Vaginal sonograms			1.14	1.05-1.25	.002
0	311 (63.0)	392 (77.3)			
1	120 (24.3)	85 (16.8)			
2+	63 (12.7)	30 (5.9)			
Bone densitometry			0.88	0.67-1.17	.37
0	426 (86.2)	429 (84.6)			
1	49 (9.9)	57 (11.2)			
2+	19 (3.9)	21 (4.2)			
Mammograms			1.23	0.90-1.68	.18
0	133 (26.9)	169 (33.3)			
1	219 (44.3)	216 (42.6)			
2+	142 (28.8)	122 (24.1)			
Pap test smears			1.07	0.83-1.37	.61
0	117 (23.7)	132 (26.1)			
1	187 (37.9)	205 (40.4)			
2+	190 (38.4)	170 (33.5)			
X-ray of trunk or extremities			0.96	0.86-1.07	.49
0	184 (37.3)	191 (37.7)			
1	146 (29.5)	141 (27.8)			
2+	164 (33.2)	175 (34.5)			
ECG†			1.19	1.03-1.36	.01
0	208 (42.1)	221 (43.6)			
1	116 (23.5)	133 (26.2)			
2+	170 (34.4)	153 (30.2)			
Biopsies			1.07	0.74-1.55	.70
0	446 (90.3)	463 (91.3)			
1	41 (8.3)	35 (6.9)			
2+	7 (1.4)	9 (1.8)			
Cytologic investigations			1.26	0.91-1.74	.16
0	434 (87.9)	455 (89.7)			
1	46 (9.3)	39 (7.7)			
2+	14 (2.8)	13 (2.6)			

ECG, Electrocardiogram; *0,* number (percentage) of women with no operation or investigation; *1,* number (percentage) of women with 1 operation or investigation; *2+,* number (percentage) of women with 2 or more operations or investigations.

* Per person-year.

† Accounted for overdispersion.

tables cannot be the sole basis for resource allocation.[29] The use of a single outcome fails to recognize the variety of important effects.[30]

The analysis is focused on the results from the nonblind subtrial. The subjects and the investigators were not blinded in the nonblind subtrial, only persons doing linkages in the registries were blinded. Blind assessment of the trial outcome is more important than blinding the treatment.[31] Trial doctors were aware of the treatment allocation, and women were asked to inform other physicians about their participation in the trial. In clinical practice, the placebo response creates a possible effect on outcomes, and may thus affect the use of health services.[32]

More than half of the randomly assigned women were lost before recruitment. As this occurred before the randomization envelope was opened, we assume the loss was independent of the trial arm.[15] According to recruitment questionnaires, the women interested in participating in the trial were not healthier than women who were

Table III Health care costs in US dollars per person-year in the nonblind and blind subtrial

	Minimum	First quartile	Median	Third quartile	Maximum	*P* value*
Outpatient health care costs						.04
Nonblind HT arm	0	30	56	102	1483	
Control arm	0	26	50	90	2810	
Blind HT arm	0	28	49	81	3427	.58
Placebo arm	0	26	48	97	623	
Inpatient health care costs						.88
Nonblind HT arm	0	0	0	65	3933	
Control arm	0	0	0	62	8922	
Blind HT arm	0	0	0	52	3144	.36
Placebo arm	0	0	0	18	10210	
Costs of prescribed drugs†						.93
Nonblind HT arm	0	4	24	82	633	
Control arm	0	4	21	92	1077	
Blind HT arm	0	3	16	77	2006	.83
Placebo arm	0	3	18	82	949	
Cost of trial treatment						NA
Nonblind HT arm	0	11	35	65	76	
Control arm						
Blind HT arm	0	11	38	65	76	NA
Placebo arm						
Total cost of drugs						<.001
Nonblind HT arm	0	39	73	121	637	
Control arm	0	4	21	92	1077	
Blind HT arm	0	35	72	122	2077	<.001
Placebo arm	0	3	18	82	949	
Costs of sickness leaves						.69
Nonblind HT arm	0	0	0	30	1744	
Control arm	0	0	0	28	2094	
Blind HT arm	0	0	0	22	604	.55
Placebo arm	0	0	0	29	1083	
Total‡						<.001
Nonblind HT arm	0	91	161	345	4156	
Control arm	0	48	121	290	9519	
Blind HT arm	10	85	140	286	4645	<.001
Placebo arm	0	35	111	241	10383	

NA, Not applicable.
* According to Wilcoxon test.
† Excluding trial treatment.
‡ Including inpatient health care, outpatient health care, costs of sickness leaves, prescribed drugs, and trial treatment.

not interested in participation.[33] There were no significant differences in the baseline characteristics of women participating in the 2 arms of the nonblind and blind subtrials.

We assume the number of missing data to be minimal in the Estonian Health Insurance Fund database, as the compensations to health care institutions and to apothecaries depend on the rapidity and accuracy of the electronically forwarded data. For the year 1999, it was not possible to determine how many of the visits to medical specialists were to gynecologists. The last follow-up date for the Estonian Mortality database was 12 months earlier than for the Estonian Health Insurance Fund. We assume this does not have a major effect on the estimation of outcomes.

Our results give the minimal estimation of the increase in health care utilization. Recruitment visits and medical procedures carried out before recruitment were not included in the statistical analysis. If they were, it would have added to the number of visits to gynecologists and vaginal sonograms in the HT arm. It is difficult to predict whether there would have been an even larger increase in vaginal sonograms or gynecologic operations if no ultrasonography had been carried out before recruitment.

The annual trial visits were included in the analysis. It is possible that without the trial, the number of visits to gynecologists would have been smaller in the control arm. If adherence would have been higher, the increase in health service utilization and health care costs might have been even greater in HT arms.

The effect of waiting times and different hospitalization rates in different geographic regions is supposed to be similar in all trial arms.

The comparison of the results from the blind and nonblind subtrial suggests that the number of health care visits results from the context of being on HT and that health care visits in the placebo arm could have been influenced by the trial effect. Instead, the use of prescription drugs and selected medical procedures suggests that those are related to the biologic effects of HT only.

In addition to the available risk-benefit profile of HT, prospectively collected data in the Estonian Postmenopausal Hormone Therapy randomized trial provide decision makers with information on the utilization of health services by HT users. The results of this analysis cannot be directly transferred to any other country, but they can be calibrated to other health care systems and health behavior. A longer follow-up may reveal more differences in the use of health services by women who use and who did not use postmenopausal HT.

Acknowledgments

We thank each woman for her participation in the trial, our trial staff for their contribution, collaborators from the National Institute for Health Development, Tallinn and from the National Research and Development Centre for Welfare and Health, Helsinki for help and support. Our special thanks to Maie Thetloff from the Estonian Health Insurance Fund.

References

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomised controlled trial. JAMA 2002;288:321-33.
2. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy. JAMA 2004;291:47-53.
3. Daly E, Roche M, Barlow D, Grady A, McPherson K, Vessey M. HRT: an analysis of benefits, risks and costs. Br Med Bull 1992;48: 368-400.
4. Samsioe G. The menopause revisited. Int J Gynaecol Obstet 1995; 51:1-13.
5. Townsend J, Buxton M. Cost effectiveness scenario analysis for a proposed trial of hormone replacement therapy. Health Policy 1997;39:181-94.
6. Cheung AP, Wren BG. A cost-effectiveness analysis of hormone replacement therapy in the menopause. Med J Aust 1992;156: 312-6.
7. Daly E, Vessey MP, Barlow D, Gray A, McPherson K, Roche M. Hormone replacement therapy in a risk-benefit perspective. Maturitas 1996;23:247-59.
8. Hurley JS, Frost EJ, Trinkaus KM, Buatti MC, Emmett KE. Relationship of compliance with hormone replacement therapy to short-term healthcare utilization in a managed care population. Am J Manag Care 1998;4:1691-8.
9. Hoerger TJ, Downs KE, Lakshmanan MC, Lindrooth RC, Plouffe L Jr, Wendling B, et al. Healthcare use among U.S. women aged 45 and older: total costs and costs for selected postmenopausal health risks. J Womens Health Gend Based Med 1999;8:1077-89.
10. Thorp JM, Gavin NI, Ohsfeldt RL. Hormone replacement therapy in postmenopausal women: utilization of health care resources by new users. Am J Obstet Gynecol 2001;185:318-26.
11. Ohsfeldt RL, Gavin NI, Thorp JM. Medical care costs associated with postmenopausal estrogen plus progestogen therapy. Value Health 2004;7:544-53.
12. Zethraeus N, Johannesson M, Jonsson B. A computer model to analyse the cost-effectiveness of hormone replacement therapy. Int J Technol Assess Health Care 1999;15:352-65.
13. Mullins CD, Ohsfeldt RL. Modeling the annual costs of postmenopausal prevention therapy: raloxifene, alendronate, or estrogen-progestin therapy. J Manag Care Pharm 2003;9:150-8.
14. Plumb JM, Guest JF. Economic impact of tibolone compared with continuous-combined hormone replacement therapy. Pharmacoeconomics 2000;18:477-86.
15. Hemminki E, Hovi SL, Veerus P, Sevon T, Tuimala R, Rahu M, et al. Blinding decreased recruitment in a prevention trial of postmenopausal hormone therapy. J Clin Epidemiol 2004;57:1237-43.
16. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523-34.
17. Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. Effects of estrogen plus progestin on stroke in postmenopausal women—The Women's Health Initiative: a randomized trial. JAMA 2003;289:2673-84.
18. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women—The Women's Health Initiative randomized trial. JAMA 2003;289: 3243-53.
19. Shumaker S, Legault C, Rapp S, Thal L, Wallace R, Ockene J, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women—The Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2651-62.
20. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density—The Women's Health Initiative Randomized Trial. JAMA 2003;290:1729-38.
21. Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women—The Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2663-72.
22. Hays J, Ockene JK, Brunner RL, Kotchen JM, Manson JE, Patterson RE, et al. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med 2003;348:1839-54.
23. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SAA, Pettinger M, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures—The Women's Health Initiative randomized trial. JAMA 2003;290: 1739-48.
24. Vorobjov S, Hovi SL, Veerus P, Pisarev H, Rahu M, Hemminki E. Treatment adherence in the Estonian postmenopausal hormone therapy (EPHT) trial [ISRCTN35338757]. Maturitas 2005;52: 286-95.
25. Estonian Health Insurance Fund. Available at: http://www.haigekassa.ee/eng/ehif. Accessed on August 10, 2004.
26. International Statistical Classification of Diseases and Related Health Problems, 1989 Revision. Geneva: World Health Organization; 1992.
27. Breslow NE. Extra-Poisson variation in log-linear models. Applied Statistics 1984;33:38-44.
28. The R Project for Statistical Computing. Available at: http://www.r-project.org. Accessed on January 3, 2005.

29. Drummond M, Torrance G, Mason J. Cost-effectiveness league tables: more harm than good? Soc Sci Med 1993;37:33-40.
30. Coast J. Is economic evaluation in touch with society's health values? BMJ 2004;329:1233-6.
31. Day SJ, Altman DG. Blinding in clinical trials and other studies. BMJ 2000;321:504.
32. Hyland ME. Using the placebo response in clinical practice. Clin Med 2003;3:347-50.
33. Hovi SL, Hakama M, Veerus P, Rahu M, Hemminki E. Who wants to join into preventive trials—experience from the Estonian Postmenopausal Hormone Therapy trial. BMC Med Res Methodol 2005;5:12.

IV

DOI: 10.1111/j.1471-0528.2007.01292.x
www.blackwellpublishing.com/bjog

Does hormone replacement therapy affect the use of prescription medicines in postmenopausal women: experience from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]

P Veerus,[a,b,c] K Fischer,[d] S-L Hovi,[c,e] H Karro,[f] E Hemminki[e]

[a] Department of Epidemiology and Biostatistics, National Institute for Health Development (TAI), Tallinn, Estonia [b] Estonian Center of Excellence in Behavioral and Health Sciences, Tallinn-Tartu, Estonia [c] Tampere School of Public Health, Tampere, Finland [d] Department of Public Health, University of Tartu, Tartu, Estonia [e] Department of Health and Social Services, National Research and Development Centre for Welfare and Health (STAKES), Helsinki, Finland [f] Tartu University Women's Clinic, Tartu, Estonia
Correspondence: P Veerus, Department of Epidemiology and Biostatistics, National Institute for Health Development (TAI), Hiiu 42, 11619 Tallinn, Estonia. Email piret.veerus@tai.ee

Accepted 10 January 2007. Published OnlineEarly 12 March 2007.

Objective To determine how postmenopausal hormone therapy (HRT) is related to the use of other prescription medication.

Design Follow up of a randomised controlled trial with a blind subtrial of hormone therapy versus placebo and a nonblind subtrial of open label hormone therapy versus nontreatment.

Population A total of 1823 postmenopausal women aged 50–64 at the time of sampling participated in the trial from 1999 to 2004.

Methods Use of prescription medication was identified by records in the central computerised database of the Estonian Health Insurance Fund.

Main outcome measures The use of 21 classes of prescription medication was compared in the hormone therapy arms and placebo or nontreatment trial arms. The influence of women's socio-economic characteristics on the intensity of concomitant medication use was also examined.

Results The proportion of women using any prescription medication besides hormone therapy did not differ between the arms. However, the type of prescribed drugs varied between the arms. After combining data from both hormone therapy arms, for women using HRT the combined hazard ratio was 1.26 (95% CI: 1.05–1.53) for the use of calcium channel blockers, 1.48 (95% CI: 1.10–1.99) for local vaginal treatment, 0.70 (95% CI: 0.50–0.99) for hypnotics and sedatives and 0.77 (95% CI: 0.60–0.99) for selective serotonin reuptake inhibitors (SSRIs). Women who were older, who had a higher body mass index, who were unemployed and who lived outside the capital used more prescription drugs in comparison with others.

Conclusions Hormone therapy did not increase the overall use of prescription medication other than hormone therapy, but the types of drugs used in hormone therapy and nontherapy arms varied, with increased use of calcium channel blockers for hypertension and local vaginal treatments for vaginal candidiasis and decreased use of hypnotics, sedatives and SSRIs in the HRT arms.

Keywords Hormone replacement therapy, randomised controlled trial, prescription medication.

Please cite this paper as: Veerus P, Fischer K, Hovi S, Karro H, Hemminki E. Does hormone replacement therapy affect the use of prescription medicines in postmenopausal women: experience from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]. BJOG 2007;114:548–554.

Introduction

Prescription drug use has been reported to be higher in current and former hormone therapy users in certain countries.[1–3] Based on data from administrative databases or surveys, hormone therapy was associated with an increased use of thyroid hormone preparations and antimigraine preparations,[1] antacids and antihistaminic drugs[3] and antihypertensive medication.[4] No difference in the use of cardiac drugs or bisphosphonates has been reported.[4] The use of antidepressants and sedatives is reported to be higher among hormone therapy nonusers.[4,5]

Unlike observational data, results from randomised trials are not confounded by social and behavioural factors.[6] Only baseline medication use has been reported in the Heart and Estrogen/Progestin Study[7] and the Women's Health Initiative trial.[8] Details of concomitant medication use have not been reported from these trials.

The aim of this paper was to analyse the use of prescription drugs by participants in the Estonian Postmenopausal Hormone Therapy (EPHT) trial. This randomised trial consisted of two subtrials, a blind and a nonblind one. According to EPHT trial data, the expenses of prescription medication were higher in the hormone therapy arms.[9] Using the centralised electronic database of the Estonian Health Insurance Fund, prescription medication was analysed in hormone therapy arms and nontreatment arms during a mean follow-up time of 4.4 (SD 0.7) years.

Methods

Participants

Postmenopausal women aged 50–65 years and living in Tartu, Tartu county, Tallinn and Harju county were asked to participate in a postmenopausal hormone therapy trial. Eligible women were randomised into four trial arms: 1) blind hormone therapy arm, 2) blind placebo arm, 3) nonblind hormone therapy arm and 4) nonblind control arm. Randomisation occurred prior to consent in order to study the impact of blinding on recruitment (Figure 1). The nonblind subtrial was designed to study the impact of hormone therapy on health service utilisation.

Participants were recruited at three clinical centres in Estonia from January 1999 to December 2001. Randomisation, eligibility criteria, recruitment and clinical follow up of participants have been described in detail elsewhere.[10] Trial treatment was stopped by May 2004. The follow-up period for trial participants was from 2 to 5 years. All participants gave written informed consent. The trial design was approved by the Tallinn Medical Research Ethics Committee, Estonia and by the Ethics Committee of the University Clinic of Tampere, Finland.

On average, women were 58.2 years of age on entering the trial. Their mean body mass index was 27.0 kg/m^2 at recruitment and average age at menopause was 50.2 years. At the time of recruitment, 69% of the women were employed, and 33% had a higher education, 52% of them were living in the capital, 17% in the surrounding area, 21% in a smaller town and 10% in rural areas. Of the participating women, 15% were current smokers, 13% had been treated for hypertension, 1.9% had a history of angina, 0.3% a history of myocardial infarction and 1.6% a history of diabetes. There was no difference in the baseline medical conditions between the arms. Use of prescription drugs prior to enrolment was similar in all four trial arms.

Trial treatment

Participants in the hormone therapy arms received 0.625 mg of combined estrogens plus 2.5 mg of medroxyprogesterone acetate daily orally or a matched placebo in the placebo arm or no treatment in the control arm. The 251 participants who were within 3 years from their last menstrual period received 0.625 mg of combined estrogens plus 5.0 mg of

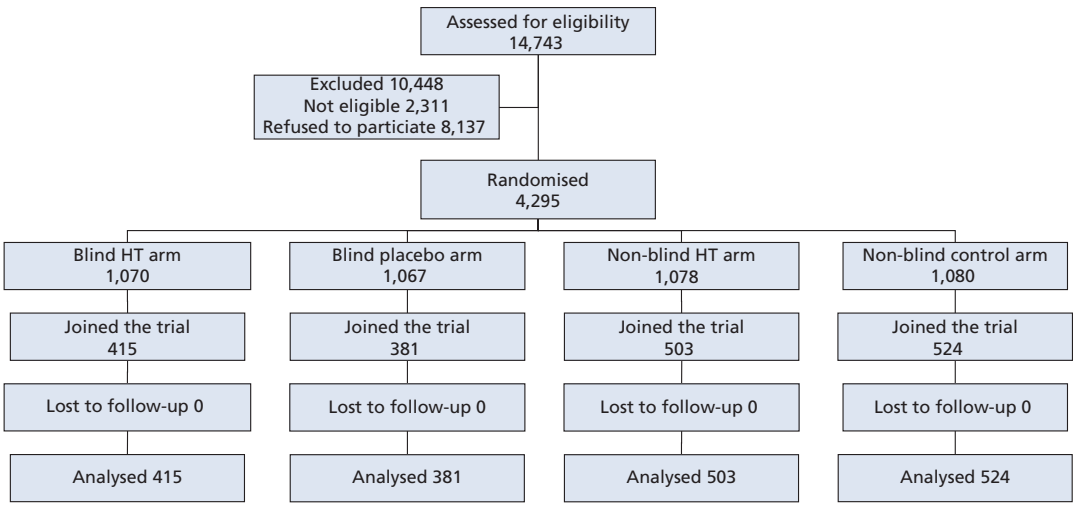


Figure 1. Flow chart of the EPHT trial.

medroxyprogesterone acetate daily orally or matched placebo or no treatment.

In the nonblind subtrial, participants and trial staff were aware of the treatment allocation, and women were asked to inform other physicians about their hormone therapy usage. In the blind subtrial, participants and physicians were blinded about the composition of trial treatment. Women participating in the blind subtrial were asked to inform other physicians about their participation in a blind hormone therapy trial. These women were informed about the nature of their trial drug within 1 month of the closure visit.

At the end of the first trial year, less than half of the participants took over 80% of their assigned trial medication.[11] At the end of the second year, the number of women taking trial treatment had decreased approximately a further 13%. At the end of the third trial year, the proportion of women taking over 80% of trial treatment was 36% on average. The proportion of women in the control arm who did not start hormone therapy remained at about 90% throughout the trial. The proportion of women who started prescribed hormone replacement therapy (HRT) in the placebo arm was 5%. Reasons for nonadherence have been reported separately.[11]

Primary and secondary outcomes

Based on previous literature[1–5] and on the outcomes of hormone therapy trials,[12,13] 21 types of prescription medication according to the anatomical therapeutic chemical (ATC)[14] classification of drugs were selected to calculate the drug usage in hormone therapy versus nontherapy arms throughout the trial. In addition, drug usage was compared between the arms within the blind and nonblind subtrial. The numbers of women using no prescription drugs, one, two, three and four or more prescription drugs were compared in four trial arms during the first three trial years. The duration of usage for prescribed antidepressants, hypnotics and sedatives, and calcium channel blockers was compared between the trial arms. The background characteristics of participating women were analysed to check their influence on the intensity of concomitant drug use.

Data collection

Women's background characteristics were obtained from recruitment questionnaires. Use of prescription drugs was obtained by linkages to the electronic database of the Estonian Health Insurance Fund, using an individual's personal identification code.[15] All participants in the trial were insured. The person doing linkages in the Health Insurance Fund was unaware of the treatment allocation.

The Estonian Health Insurance Fund stores information about all sold prescription drugs in a centralised, computerised database. Patients pay a certain amount of the drug price, the rest is compensated to the pharmacy by the Health Insurance Fund. As the compensation to pharmacies depends on the quick and accurate transmission of data, the probability of missing data is small. For each drug, the following information is recorded: personal data of the physician and the patient, name and ATC code of the drug, diagnosis according to the 10th revision of the International Classification of Diseases[16] and date of writing the prescription. Even though most of the drugs in Estonia are issued under a medical prescription written by a doctor, some painkillers, antacids, ointments and other simple drugs are obtained over-the-counter and they are not included in our analysis. The last follow-up date was 31 December 2004.

Statistical analysis

Numbers of women using no prescription medication, one, two, three and four or more prescribed drugs during the first three trial years were compared in each arm.

Cox proportional hazards modelling was used to compare the use of 21 classes of selected drugs in different trial arms throughout the trial. The data were analysed according to the intention-to treat principle. Use of prescription drugs in the same 21 classes 3 months prior to enrolment was compared between all four trial arms using chi-squared test or Fisher's exact test, where appropriate.

Group means of numbers of prescriptions per woman by trial arms were compared for antidepressants, hypnotics and sedatives and calcium channel blockers.

Logistic regression was used to compare the use of calcium channel blockers, selective serotonin reuptake inhibitors and anxiolytics between adherent and nonadherent women. Cox proportional hazards modelling was used to compare the time-point for starting such treatment between adherent and nonadherent women. Women taking more than 90% of allocated trial treatment in the first trial year were defined to be adherent.

Log-linear regression was used for a statistical comparison of the background characteristics of women using four or more prescription drugs during the first 2 years of participation in both subtrials. The models were adjusted for age group at recruitment, education, employment status, body mass index and living place. Interactions with blinding and treatment indicators were tested for. No interactions were detected.

The software used was R for Windows, version 2.1.1.[17]

Results

During the first trial year, about one-third of the women did not use any prescription drugs, and a quarter of women used more than four prescription drugs. During the second and the third participation year, the proportion of women using prescription drugs increased. The proportion of women using prescribed drugs in different trial years did not differ between the four trial arms (Table 1).

Table 1. Number and percentage of women using prescription drugs in four trial arms per participation year

	Trial arm				
	Blind HT, *n* = 415	**Blind placebo, *n* = 381**	**Nonblind HT, *n* = 503**	**Nonblind control, *n* = 524**	**Total, *n* = 1823**
Using no prescription drugs					
1st year	154 (37.1%)	135 (35.4%)	176 (35.0%)	177 (33.8%)	642 (35.2%)
2nd year	128 (30.8%)	114 (29.9%)	143 (28.4%)	135 (25.8%)	520 (28.5%)
3rd year	119 (28.7%)	96 (25.2%)	132 (26.2%)	134 (25.6%)	481 (26.4%)
Using one prescription drug					
1st year	64 (15.4%)	66 (17.3%)	94 (18.7%)	92 (17.6%)	316 (17.3%)
2nd year	72 (17.4%)	62 (16.3%)	78 (15.5%)	89 (17.0%)	301 (16.5%)
3rd year	72 (17.4%)	71 (18.6%)	94 (18.7%)	95 (18.1%)	332 (18.2%)
Using two prescription drugs					
1st year	62 (14.9%)	48 (12.6%)	60 (11.9%)	72 (13.7%)	242 (13.3%)
2nd year	58 (14.0%)	61 (16.0%)	79 (15.7%)	75 (14.3%)	273 (15.0%)
3rd year	72 (17.4%)	57 (15.0%)	64 (12.7%)	74 (14.1%)	267 (14.6%)
Using three prescription drugs					
1st year	38 (9.2%)	32 (8.4%)	42 (8.4%)	62 (11.8%)	174 (9.6%)
2nd year	52 (12.5%)	44 (11.6%)	55 (10.9%)	68 (12.9%)	219 (12.0%)
3rd year	29 (6.9%)	48 (12.6%)	72 (14.3%)	56 (10.7%)	205 (11.3%)
Using four or more prescription drugs					
1st year	97 (23.4%)	100 (26.3%)	131 (26.0%)	121 (23.1%)	449 (24.6%)
2nd year	105 (25.3%)	100 (26.2%)	148 (29.5%)	157 (30.0%)	510 (28.0%)
3rd year	123 (29.6%)	109 (28.6%)	141 (28.1%)	165 (31.5%)	538 (29.5%)

HT, hormone therapy.

Table 2 presents the use of prescription drugs for the cardiovascular system during the trial. In the blind subtrial, the use of any antihypertensive drugs did not differ between the hormone therapy arm and the placebo arm, but in the nonblind subtrial, hormone therapy users used antihypertensive treatment more commonly. The use of calcium channel blockers was higher in the hormone therapy arm of the blind subtrial (hazard ratio [HR] 1.38; 95% CI: 1.02–1.86) and after combining the data for both hormone therapy arms (HR 1.26; 95% CI: 1.05–1.53). For the majority of prescriptions, hypertensive diseases were the reason for the use of calcium channel blockers. The numbers of prescriptions with different reasons for the use of calcium channel blockers were the following: for hypertensive diseases 4004, for angina pectoris 33 and for cardiac arrhythmias 14 prescriptions altogether. The combined odds ratio between hormone therapy arms and nontherapy arms for hypertensive diseases as the reason for the use of calcium channel blockers was 1.25 (95% CI: 1.03–1.51)

Table 2. Numbers of women and HRs with 95% confidence intervals for using drugs for the cardiovascular system

Drug class, ATC code	**Blind HT, 415**	**Blind placebo, 381**	**HR (95% CI)**	**Nonblind HT, 503**	**Nonblind control, 524**	**HR (95% CI)**	**Combined HR (95% CI)**
Any drugs for hypertension (C02, C03, C07, C08 or C09)	187	169	1.03 (0.83–1.27)	249	230	1.20 (1.00–1.44)	1.12 (0.98–1.29)
Antihypertensives C02	22	21	0.97 (0.53–1.75)	30	29	1.08 (0.65–1.81)	1.03 (0.70–1.52)
Diuretics C03	61	50	1.14 (0.79–1.66)	75	83	0.95 (0.70–1.30)	1.03 (0.81–1.30)
Beta-blocking agents C07	105	111	0.86 (0.66–1.12)	157	146	1.18 (0.94–1.48)	1.03 (0.87–1.23)
Calcium channel blockers C08	105	72	1.38 (1.02–1.86)	131	119	1.19 (0.93–1.53)	1.26 (1.05–1.53)
Agents acting on the renin–angiotensin system C09	110	83	1.25 (0.94–1.67)	124	115	1.14 (0.89–1.48)	1.19 (0.99–1.44)
Organic nitrates C01DA	31	24	1.18 (0.69–2.01)	44	52	0.88 (0.59–1.32)	0.98 (0.71–1.35)
Serum lipid reducing agentsC10	26	32	0.74 (0.44–1.25)	42	53	0.82 (0.55–1.23)	0.79 (0.57–1.09)

HT, hormone therapy.

and the combined odds ratio for angina pectoris as the reason for the use of calcium channel blockers was 2.84 (95% CI: 0.75–10.72). There were no significant differences in the use of other drugs for hypertension, in the use of drugs for coronary heart disease or drugs lowering serum cholesterol.

There was no difference in the overall use of antidepressants between the trial arms, but the use of selective serotonin reuptake inhibitors was lower in the hormone therapy arms after combining data from both subtrials (HR 0.77; 95% CI: 0.60–0.99). After combining data from both subtrials, the use of hypnotics and sedatives was lower in hormone therapy arms (HR 0.70; 95% CI: 0.50–0.99), especially in women in the hormone therapy arm of the blind subtrial (HR 0.55; 95% CI: 0.33–0.92). The use of anxiolytics did not differ significantly between the trial arms (Table 3).

There was no difference between the arms in the use of nonsteroid anti-inflammatory drugs, antacids, antiallergic drugs, thyroid replacement therapy, painkillers, bisphosphonates, antidiabetic drugs, antithrombotic agents or antimigraine preparations during the trial (Table 4). The use of local gynaecological anti-inflammatory drugs was higher among women randomised to the blind hormone therapy arm (HR 1.73; 95% CI: 1.08–2.79) and after combining data from hormone therapy arms of both subtrials (HR 1.48; 95% CI: 1.10–1.99). After combining data from both hormone therapy arms, the reasons for the increased use of local vaginal treatment in the HRT arms were more frequent vaginal candidiasis (HR 1.93; 95% CI: 1.20–3.11) and acute vulvitis or vaginitis (HR 1.09; 95% CI: 0.96–1.20).

There was no difference in the group means of prescriptions per woman for antidepressants, hypnotics and sedatives, or calcium channel blockers in different trial arms throughout the trial. There was no difference between drop-outs and continuers in the treatment arms as regards the use of calcium channel blockers, selective serotonin reuptake inhibitors and anxiolytics or the time of starting such treatment.

As the women stopped trial treatment gradually from January 2004 to May 2004, a data analysis was also completed using data until 31 December 2003 as the last follow-up date. The results of the analysis including data until 31 December 2003 did not differ significantly from the results using data until 31 December 2004.

Factors affecting prescription drug use were analysed in both subtrials. This analysis was restricted to the first two trial years only, as this was the maximum follow-up time for all participants. In the blind subtrial, women who used four or more prescription drugs during the first two trial years were older, not employed, had a higher body mass index and lived around the capital area. In the nonblind subtrial, women using four or more prescription drugs were older, had a higher body mass index and lived in a small town or in countryside in comparison with women who used up to three prescription drugs during the first two trial years (Table 5). There was no difference in regard to being randomised to hormone therapy arm or not in either subtrials. Blinding had no effect on the use of prescribed drugs.

Discussion and conclusion

The use of prescription medication in the EPHT trial showed that hormone therapy had no effect on the overall use of prescribed drugs in addition to the hormone therapy used within the trial, but the types of drugs differed for women randomised to using and not using hormone therapy.

In comparison with other studies, we found no increase in the use of thyroid or antimigraine preparations, antihistaminic drugs or antacids. Our data showed no decrease in the overall use of antidepressants among hormone therapy users. The increased use of selective serotonin reuptake inhibitors and sedatives in the placebo and control arms may be due to their effectiveness to treat menopausal symptoms,[18–20] showing that hormone therapy and certain psychiatric drugs are used alternatively.

The results show an increase in the use of calcium channel blockers in the hormone therapy arms. Calcium channel blockers are among the most often prescribed drugs for the treatment of hypertension.[21] There is no evidence about the risk of developing hypertension during hormone therapy,[22] but an increased use of antihypertensive therapy during hormone therapy has been reported.[23]

Table 3. Numbers of women and HRs with 95% confidence intervals for using selected psycholeptics and psychoanaleptics

Drug class, ATC code	Blind HT, 415	Blind placebo, 381	HR (95% CI)	Nonblind HT, 503	Nonblind control, 524	HR (95% CI)	Combined HR (95% CI)
Antidepressants N06A	61	79	0.72 (0.52–1.01)	93	105	0.93 (0.70–1.23)	0.84 (0.68–1.04)
Selective serotonin reuptake inhibitors N06AB	42	54	0.70 (0.47–1.04)	65	83	0.82 (0.59–1.13)	0.77 (0.60–0.99)
Hypnotics and sedatives N05C	24	39	0.55 (0.33–0.92)	33	40	0.86 (0.54–1.36)	0.70 (0.50–0.99)
Anxiolytics N05B	21	24	0.80 (0.44–1.43)	24	35	0.70 (0.42–1.19)	0.75 (0.51–1.10)

HT, hormone therapy.

Table 4. Numbers of women and HRs with 95% confidence intervals for other selected prescription medication

Drug class, ATC code	Blind HT, 415	Blind placebo, 381	HR (95% CI)	Nonblind HT, 503	Nonblind control, 524	HR (95% CI)	Combined HR (95% CI)
Nonsteroid anti-inflammatory drugs M01	201	183	1.01 (0.83–1.23)	252	251	1.06 (0.89–1.26)	1.04 (0.91–1.18)
Antacids A02	82	87	0.85 (0.63–1.15)	129	131	1.05 (0.82–1.34)	0.97 (0.80–1.17)
Antiallergic drugs R06	39	36	1.00 (0.63–1.56)	55	51	1.13 (0.78–1.66)	1.07 (0.80–1.43)
Thyroid hormone preparations H03A	22	24	0.83 (0.47–1.48)	25	25	1.05 (0.61–1.83)	0.94 (0.63–1.40)
Painkillers N02	20	19	0.96 (0.51–1.80)	19	32	0.62 (0.35–1.09)	0.75 (0.50–1.14)
Biphosphonates M05BA	19	18	0.98 (0.51–1.86)	16	23	0.73 (0.38–1.38)	0.84 (0.54–1.32)
Oral blood glycose lowering drugs A10B	16	10	1.48 (0.67–3.27)	11	24	0.49 (0.24–1.00)	0.80 (0.48–1.32)
Antithrombotic agents B01	6	3	1.75 (0.44–7.01)	7	6	1.24 (0.42–3.68)	1.42 (0.61–3.32)
Antimigraine preparations N02CC, N02CX	3	2	1.38 (0.23–8.27)	5	2	2.61 (0.51–13.45)	1.98 (0.60–6.59)
Local vaginal treatment G01	48	26	1.73 (1.08–2.79)	59	47	1.33 (0.91–2.00)	1.48 (1.10–1.99)

HT, hormone therapy.

Although vaginal lactobacilli are more prevalent among women receiving hormone therapy,[24,25] we found an increase in the use of local vaginal treatment in the hormone treatment group. Local administration of estrogens may be more effective than systemic administration in reducing genitourinary infections.[26]

More than half of the randomly assigned women were lost before recruitment. Because this happened without the woman or the trial staff knowing to which arm the woman belonged, this loss occurred independently of the trial arm and did not endanger comparability but increased the random error in estimates of effect. The impact of blinding on recruitment and the reasons for ineligibility in different trial arms has been described elsewhere.[10]

The central electronic database of the Estonian Health Insurance Fund is assumed to have complete data about purchased prescription drugs. We preferred it to survey data because the duration of medication use and the date of first use are subject to recall bias even if use of medication is not.[27]

The Estonian Health Insurance database contains data about sales figures for drugs, not the actual drug usage. We assumed that the proportion of women actually using purchased drugs was similar in all trial arms. We have no data about the use of over-the-counter drugs, vitamin D and calcium supplements among them, and were not able to analyse the use of these. Reflection of changes in existing drug use patterns versus new ones was assumed to be similar in all trial arms.

The last follow-up date was later than the date of stopping trial treatment, but the biological effect of estrogens and progestins may last longer.[28] Including only data prior to the date of stopping the trial treatment did not change the results. The results are presented as combined HRs for women randomised to hormone therapy. Results are also provided separately for the blind and the nonblind subtrial. Low adherence

Table 5. Comparison of women using four or more prescription drugs with women using less prescription drugs during the first two trial years

	Blind subtrial		Nonblind subtrial		Combined	
	OR*	95% CI*	OR*	95% CI*	OR**	95% CI**
Randomised to HT	1.00	0.75–1.35	1.05	0.81–1.36	1.03	0.85–1.25
Age over 60 years	1.50	1.08–2.07	2.06	1.54–2.75	1.78	1.44–2.21
Higher education	0.92	0.66–1.27	0.88	0.66–1.16	0.89	0.75–1.10
Employed	0.60	0.43–0.85	0.76	0.56–1.04	0.69	0.55–0.87
BMI	1.06	1.02–1.10	1.06	1.03–1.09	1.06	1.04–1.08
Living around the capital	1.57	1.04–2.38	1.23	0.86–1.77	1.37	1.04–1.79
Living in a small town	1.25	0.86–1.82	1.42	1.01–2.00	1.34	1.04–1.72
Living in the countryside	1.45	0.87–2.39	1.91	1.20–3.02	1.69	1.20–2.36
Blinding					0.83	0.69–1.02

OR, odds ratio; HT, hormone therapy; BMI, body mass index.
*Adjusted for age group at recruitment, education, employment status, body mass index, and living place.
**Adjusted for age group at recruitment, education, employment status, body mass index, living place and blinding.

may have diluted the difference between the hormone therapy and nontreatment arms.

Data about treatment variations derived from randomised controlled trials can be generalised to community patients.[29] Knowledge about the influence of hormone therapy on the use of prescription medication can be used for public health decisions. Further research is needed to improve knowledge about the influence of simultaneous medication on the outcomes of long-term randomised trials.

Acknowledgements

We thank each woman for their participation in the trial, our trial staff for their contribution and our colleagues from the National Institute for Health Development, Tallinn, and the National Research and Development Centre for Welfare and Health, Helsinki, for pleasant collaboration. Our special thanks to Mrs Maie Thetloff from the Estonian Health Insurance Fund.

The trial was supported by the Academy of Finland (grants 69838 and 201490), STAKES (National Research and Development Centre for Welfare and Health), Finland, the Estonian Science Foundation (grants 5203 and 6570) and the Estonian Ministry of Education and Research (target funding 0192112s02). Drugs were donated by Wyeth Ayerst Company via the Women's International Study of Long Duration Oestrogen after Menopause in the United Kingdom.

The funding bodies had no role in the study design, data collection, data analysis, data interpretation, writing the report or in the decision to submit the paper for publication. ■

References

1 Small R, Friedman GD, Ettinger B. Concomitant medication use in postmenopausal women using estrogen therapy. *Menopause* 2001;8:120–6.

2 Jacobs PA, Hyland ME. An evaluation of the benefits of taking hormone replacement therapy with other prescription drugs. *Maturitas* 2003;46:273–81.

3 Khatibi EA, Samsioe G, Li C, Lidfeldbt J, Agardh CD, Nerbrand C. Does hormone replacement therapy increase allergic reactions and upper gastrointestinal problems? Results form a population-based study of Swedish woman. The women's health in the Lund area (WHILA) study. *Maturitas* 2004;48:438–45.

4 Thorp JM, Gavin NI, Ohsfeldt RL. Hormone replacement therapy in postmenopausal women: utilization of health care resources by new users. *Am J Obstet Gynecol* 2001;185:318–26.

5 McIntyre RS, Konarski JZ, Grigoriadis S, Fan NC, Mancini DA, Fulton KA, *et al*. Hormone replacement therapy and antidepressant prescription patterns: a reciprocal relationship. *CMAJ* 2005;172:57–59.

6 Lawlor DA, Davey Smith G, Bruckdorfer KR, Kundu D, Ebrahim S. Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence? *Lancet* 2004; 363:1724–7.

7 Furberg CD, Vittinghoff E, Davidson M, Herrington DM, Simon JA, Wenger NK, *et al.* Subgroup interactions in the Heart and Estrogen/Progestin Replacement Study. Lessons learned. *Circulation* 2002;105:917–22.

8 Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, *et al*. The Women's Health Initiative Recruitment Methods and Results. *Ann Epidemiol* 2003;13:S18–S77.

9 Veerus P, Fischer K, Hovi SL, Hakama M, Rahu M, Hemminki E. Postmenopausal hormone therapy increases use of health services: experience from the Estonian Postmenopausal Hormone Therapy Trial [ISRCTN35338757]. *Am J Obstet Gynecol* 2006;195:62–71.

10 Hemminki E, Hovi SL, Veerus P, Sevon T, Tuimala R, Rahu M, *et al*. Blinding decreased recruitment in a prevention trial of postmenopausal hormone therapy. *J Clin Epidemiol* 2004;57:1237–43.

11 Vorobjov S, Hovi SL, Veerus P, Pisarev H, Rahu M, Hemminki E. Treatment adherence in the Estonian Postmenopausal Hormone Therapy (EPHT) trial [ISRCTN35338757]. *Maturitas* 2005;52:286–95.

12 Barrett-Connor E, Grady D, Stefanick ML. The rise and fall of menopausal hormone therapy. *Annu Rev Public Health* 2005;26:115–40.

13 Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33.

14 WHO Collaborating Centre for Drugs Statistics Methodology. ATC/DDD Index 2005 [http://www.whocc.no/atcddd/]. Accessed 12 September 2005.

15 Estonian Health Insurance Fund [http://www.haigekassa.ee/eng/]. Accessed 10 May 2005.

16 *International Statistical Classification of Diseases and Related Health Problems, 1989 Revision*. Geneva: World Health Organization, 1992.

17 The R Project for Statistical Computing [http://www.r-project.org]. Accessed 31 August 2005.

18 Hickey M, Davis SR, Sturdee DW. Treatment of menopausal symptoms: what shall we do now? *Lancet* 2005;366:409–21.

19 Antonijevic IA. Depressive disorders—is it time to endorse different pathophysiologies? *Psychoneuroendocrinology* 2006;31:16–22.

20 Rodstrom K, Bengtsson C, Lissner L, Milsom I, Sundh V, Bjorkelund C. A longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. *Menopause* 2002;9:151–2.

21 Muntwyler J, Follath F. Calcium channel blockers in treatment for hypertension. *Prog Cardiovasc Dis* 2001;44:207–16.

22 Mueck AO, Seeger H. Effect of hormone therapy on blood pressure in normotensive and hypertensive postmenopausal women. *Maturitas* 2004;49:189–203.

23 Karalis I, Beevers G, Beevers M, Lip G. Hormone replacement therapy and arterial blood pressure in postmenopausal women with hypertension. *Blood Press* 2005;14:38–44.

24 Devillard E, Burton JP, Hammond JA, Lam D, Reid G. Novel insight into the vaginal microflora in postmenopausal women under hormone replacement therapy as analyzed by PCR-denaturing gradient gel electrophoresis. *Eur J Obstet Gynecol Reprod Biol* 2004;117:76–81.

25 Pabich WL, Fihn SD, Stamm WE, Scholes D, Boyko EJ, Gupta K. Prevalence and determinants of vaginal flora alterations in postmenopausal women. *J Infect Dis* 2003;188:1054–8.

26 Palacios S, Castelo-Branco C, Cancelo MJ, Vazquez F. Low-dose, vaginally administered estrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in postmenopausal women on hormone therapy. *Maturitas* 2005;50:98–104.

27 Cotterchio M, Kreiger N, Darlington G, Steingart A. Comparison of self-reported and physician-reported antidepressant medication use. *Ann Epidemiol* 1999;9:283–9.

28 Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric* 2005;Suppl 1:3–63.

29 Gross CP, Garg PP, Krumholz HM. The generalizability of observational data to elderly patients was dependent on the research question in a systemic review. *J Clin Epidemiol* 2005;58:130–7.

