National Institute for Health and Care Excellence

FINAL

Menopause (update)

[C] Cardiovascular disease and stroke

NICE guideline NG23

Evidence review underpinning recommendations 1.5.27, 1.5.32, 1.6.2 (except the first bullet point), 1.6.3 (except the first bullet point), 1.6.4 and statements in tables 1 and 2 related to coronary heart disease and stroke (as well as related absolute numbers tables) and research recommendation 6, 8 and 9 in the NICE guideline

November 2024

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This evidence review was developed by NICE

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Contents

Cardiovascular disease and stroke 6

Review question 6

Introduction 6

Summary of the protocol 6

Methods and process 7

Effectiveness evidence 7

Summary of included studies 8

Summary of the evidence 24

Economic evidence 28

Summary of included economic evidence 28

Economic model 28

The committee's discussion and interpretation of the evidence 28

Recommendations supported by this evidence review 36

References – included studies 36

Appendices 42

Appendix A Review protocols 42

Review protocol for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 42

Appendix B Literature search strategies 49

Literature search strategies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 49

Appendix C Effectiveness evidence study selection 67

Study selection for: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 67

Appendix D Evidence tables 68

Evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 68

Appendix E Forest plots 264

Forest plots for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 264

Appendix F GRADE tables 340

GRADE tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 340

Appendix G Economic evidence study selection 381

Study selection for: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 381

Appendix H Economic evidence tables 382

Economic evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 382

Appendix I Economic model 383

Economic model for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 383

Appendix J Excluded studies 384

Excluded studies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 384

Appendix K Research recommendations – full details 399

Research recommendations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 399

K.1.1 Research recommendation 399

Why this is important 399

Rationale for research recommendation 399

Modified PICO table 400

K.1.2 Research recommendation 400

Why this is important 401

Rationale for research recommendation 401

Modified PICO table 401

K.1.3 Research recommendation 402

Why this is important 402

Rationale for research recommendation 402

Modified PICO table 403

Appendix L Absolute risk tables and calculations 404

Absolute risk tables and calculations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease? 404

Cardiovascular disease and stroke

Review question

What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

Introduction

Cardiovascular disease (CVD) (including coronary heart disease and stroke) is the most common cause of death in women worldwide (1 in 2) and the risk of developing CVD increases after the menopause. There has been controversy about the possible influence of hormone replacement therapy (HRT) on CVD risk where epidemiological data initially suggested a reduced risk of CHD with long-term HRT usage. However, subsequent randomised controlled trials (RCTs) suggested an increased risk if HRT is initiated after a long period post menopause. The aim of this review was to determine the risks and benefits associated with HRT use and CVD to empower healthcare providers, and women, non-binary, and trans people with menopause to make fully informed therapeutic decisions.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women, non-binary and trans people with menopause (including perimenopause and post-menopause)

Intervention	• HRT*
	  ○ Oestrogen-only
	  ○ Combined oestrogen and progestogen
	  - Sequential combined
	  - Continuous combined
	  - Any combined
	* Regulated bioidentical hormones are included but compounded bioidentical hormones are excluded.

Comparison	• Placebo treatment • No HRT
Outcome	**Critical** • Coronary heart disease (including myocardial infarction) • Cardiac event composite scores • Mortality (cardiovascular disease related) • Stroke **Important** • TIA

HRT: hormone replacement therapy; TIA: transient ischaemic attack

For further details see the review protocol in Appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document (Supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Overall 41 studies were included for this review, 30 randomised controlled trials (RCTs: Anderson 2004, Anonymous 1995, Cherry 2002, Cherry 2014, Collins 2006, Grady 2002, Hall 1998, Harman 2014, Heiss 2008, Hendrix 2006, Herrington 2000, Hodis 2001, Hoibraaten 2000, Hsia 2006, Hulley 1998, Hulley 2002, LaCroix 2011, Manson 2003, Manson 2013, Manson 2017, Nachtigall 1979, Prentice 2020, Rossouw 2002, Rossouw 2007, Simon 2001, Tierney 2009, Veerus 2006, Vickers 2007, Viscoli 2001 and Wassertheil-Smoller 2003) and 11 observational studies (Arana 2006, Bhupathiraju 2017, Canonico 2016, Chilvers 2003, Ferrara 2003, Grodstein 2006, Grodstein 2008, Kim 2006, Lemaitre 2006, Lokkegaard 2017, Renoux 2010).

16 RCTs compared combined hormone replacement therapy (HRT) with oestrogen and progestogen to placebo (Collins 2006, Grady 2002, Hall 1998, Harman 2014, Heiss 2008, Hoibraaten 2000, Hulley 1998, Hulley 2002, Manson 2003, Nachtigall 1979, Rossouw 2002, Simon 2001, Tierney 2009, Veerus 2006, Vickers 2007 and Wassertheil Smoller 2003) and 1 observational study compared combined HRT with oestrogen and progestogen to no HRT (Canonico 2016). Eight RCTs compared HRT with oestrogen-only to placebo (Anderson 2004, Cherry 2002, Cherry 2014, Hendrix 2006, Hodis 2001, Hsia 2006, LaCroix 2011 and Viscoli 2001) and 1 observational study compared HRT with oestrogen-only to no HRT (Arana 2006). 15 studies were multiple armed trials, where 6 RCTs compared both combined HRT with oestrogen and progestogen, and oestrogen-only HRT to placebo (Anonymous 1995, Herrington 2000, Manson 2013, Manson 2017, Prentice 2020 and Rossouw 2007) and 9 observational studies compared both combined HRT with oestrogen and progestogen, and oestrogen-only HRT to no HRT (Bhupathiraju 2017, Chilvers 2003, Ferrara 2003, Grodstein 2006, Grodstein 2008, Kim 2006, Lemaitre 2006, Lokkegaard 2017 and Renoux 2010).

Of the 32 studies that compared combined HRT with oestrogen and progestogen to either placebo or no HRT, 17 RCTs used continuous combined HRT (Collins 2006, Grady 2002, Heiss 2008, Herrington 2000, Hoibraaten 2000, Hulley 1998, Hulley 2002, Manson 2003, Manson 2013, Manson 2017, and Prentice 2020, Rossouw 2002, Rossouw 2007, Simon 2001, Veerus 2006, Vickers 2007 and Wassertheil Smoller 2003), four RCTs used sequential combined HRT (Hall 1998, Harman 2014, Nachtigall 1979 and Tierney 2009), one RCT and one observational study used sequential combined and continuous combined HRT (Anonymous 1995, Lokkegaard 2017) and nine observational studies did not report if combined HRT was prescribed sequentially or continuous (Bhupathiraju 2017, Canonico 2016, Chilvers 2003, Ferrara 2003, Grodstein 2006, Grodstein 2008, Kim 2006, Lemaitre 2006 and Renoux 2010).

31 studies reported outcomes related to cardiovascular disease (coronary heart disease including myocardial infarction, cardiac event composite scores and mortality) of which 26 were RCTs (Anderson 2004, Anonymous 1995, Cherry 2002, Cherry 2014, Collins 2006, Grady 2002, Hall 1998, Harman 2014, Heiss 2008, Herrington 2000, Hodis 2001, Hsia 2006, Hulley 1998, Hulley 2002, LaCroix 2011, Manson 2003, Manson 2013, Manson 2017, Nachtigall 1979, Prentice 2020, Rossouw 2002, Rossouw 2007, Tierney 2009, Veerus 2006, Vickers 2007, Viscoli 2001) and five observational studies (Bhupathiraju 2017, Chilvers 2003,

Ferrara 2003, Grodstein 2006, Lemaitre 2006). 24 studies reported outcomes related to stroke (stroke and TIA) which included 19 RCTs (Anderson 2004, Collins 2006, Grady 2002, Harman 2014, Heiss 2008, Hendrix 2006, Herrington 2000, Hoibraaten 2000, Hulley 1998, LaCroix 2011, Manson 2013, Prentice 2020, Rossouw 2002, Rossouw 2007, Simon 2001, Tierney 2009, Veerus 2006, Viscoli 2001, Wassertheil Smoller 2003) and 8 observational studies (Arana 2006, Bhupathiraju 2017, Canonico 2016, Grodstein 2008, Kim 2006, Lemaitre 2006, Lokkegaard 2017, Renoux 2010).

13 RCTs (Cherry 2002, Cherry 2014, Collins 2006, Grady 2002, Hall 1998, Herrington 2000, Hodis 2001, Hoibraaten 2000, Hulley 1998, Hulley 2002, Simon 2001, Tierney 2009 and Viscoli 2001) were classified as prevention studies and included participants with the following conditions: previous myocardial infarction, coronary heart disease, acute coronary syndromes, coronary artery disease, angiographically verified coronary disease, low-density lipoprotein cholesterol level of 3.37 mmol/L or greater, recent ischemic stroke or transient ischemic attack, previous deep vein thrombosis or pulmonary embolism and delayed verbal recall. Five observational studies (Canonica 2016, Chilvers 2003, Ferrara 2003, Kim 2006, and Lemaitre 2006) included participants with the following conditions: previous stroke, previous myocardial infarction, and diabetes.

Some studies did not specify the recency or duration of HRT use, and this is described throughout the report as unknown recency or duration where applicable.

Different statistical summary measures (hazard ratios, risk ratios, odds ratios and Peto odds ratios) are used throughout the report, including across the forest plots in Appendix E. The basis for the use of different summary measures is described in the methods document (Supplement 1 methods) for details.

The included studies are summarised in Table 2.

See the literature search strategy in Appendix B and study selection flow chart in Appendix C.

Excluded studies

Studies that did not report outcomes separately for participants receiving combined HRT or oestrogen-only were not included in this review. The Boardman 2015 Cochrane review was excluded from this review for this reason. Studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
Anderson 2004 (WHI) RCT	N=10,739 Postmenopausal women aged 50 to 79 years with prior hysterectomy.	Oestrogen-only • 0.625mg/d CEE	Placebo	• Coronary heart disease (including MI)

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
US	Mean age (SD): 63.6 (7.3) years			• Mortality (CVD related) • Stroke Duration • 6.8 years (mean) Recency • Current users
Anonymous 1995 (PEPI) RCT US	N=875 Postmenopausal women aged 45 to 64 years with or without a uterus. Mean age (SD): 56.1 (NR) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA • Sequential: 0.625 mg/d CEE + 10 mg/d MPA for the first 12 days or 200 mg/d MP for the first 12 days Oestrogen-only • 0.625mg/d CEE	Placebo	• Cardiac event composite scores Duration • 3 years Recency • Current users
Arana 2006 Retrospective cohort study UK	N=10920 Women aged 50-69 registered on General Practice Research Database (GPRD) Mean age (SD): 62.0 (NR) years	Oestrogen-only • Unopposed or opposed oestrogen; low dose: <0.625mg oral oestrogens or 25µg transdermal estradiol; medium dose: 0.625-1.24mg oral oestrogens or 50µg transdermal estradiol; high dose: ≥1.25mg oral oestrogens or	No HRT	• TIA **Confounders adjusted for** • Age • Past use of HT • History of smoking • Hypertension • Diabetes • Obesity • Hypercholesterolemia • Family history of cardiovascular disease

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
		100µg transdermal estradiol		• Surgical menopause • Lipid-lowering drug use • Anticoagulant drug use • Cardio-prophylactic use of aspirin Duration • NR Recency • Current users
Bhupathiraju 2017 (NHS) Retrospective cohort study US	N=48385 Postmenopausal women aged at least 50 years Mean age NR Mean age (SD) per group; combined oestrogen and progestogen: 53.4 (2.6) years; Oestrogen-only: 55.5 (2.4) years; no HRT and underwent hysterectomy: 55.2 (2.4) years; no HRT and intact uterus: 53.6 (2.6) years	Combined Oestrogen and progestogen • Continuous or sequential NR: 0.625mg/d CEE + less than 10mg/d MPA Oestrogen-only • 0.625mg/d CEE	No HRT	• Total MI • Mortality (CVD related) • Stroke **Confounders adjusted for** • Age • Calendar time • Smoking status • Alcohol intake • Physical activity • BMI • Aspirin use • History of high blood pressure • History of hypercholesterolemia • History of type 2 diabetes mellitus • Age at menopause • Parental history of early myocardial infarction

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
				• Parental history of cancer • Duration of HRT use Duration • NR Recency • Current users
Canonico 2016 Retrospective cohort study (Nested case control study) France	N=15302 Women aged 51-62 years with a hospitalisation for stroke Mean age NR Mean age (SD) per group; combined oestrogen and progestogen: 56.7 (2.8) years; no HRT: 56.6 (2.7) years	Combined Oestrogen and progestogen • Continuous or sequential NR: low; ≤1 mg/d of oral oestrogens or <50 µg/d of transdermal oestrogens, intermediate; 1.5 mg/d of oral oestrogens or 50 µg/d of transdermal oestrogens, high: ≥2 mg/d of oral oestrogens or >50 µg/d of transdermal oestrogens	No HRT	• Ischaemic stroke **Confounders adjusted for** • Age • Antidiabetic medication • Antihypertensive medication • Antidyslipidemia medication • Long-term chronic disease Duration • NR Recency • Current users
Cherry 2002 (ESPRIT) RCT UK	N=1,017 Postmenopausal women aged 50–69 years with and without hysterectomy who had survived a first myocardial infarction. (27% and 21% with hysterectomy) Mean age (SD): 62.6 (NR) years	Oestrogen-only • 2mg/d oestradiol valerate	Placebo	• Mortality (CVD related) Duration • 2 years Recency • Current users
Cherry 2014 (ESPRIT)	N=1,017 Postmenopausal women aged 50–69 years who	Oestrogen-only	Placebo	• Mortality (CVD related)

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
RCT UK	had survived a first myocardial infarction Mean age: NR	• 2mg/d oestradiol valerate		Duration • 2 years Recency • Past users of 14.1 years (mean)
Chilvers 2003 Prospective cohort study UK	N=1677 Postmenopausal women who had suffered an acute myocardial infarction Mean age: NR	Combined Oestrogen and progestogen • Continuous or sequential NR: Dose or constituent NR Oestrogen-only • Dose or constituent NR	No HRT	• Acute MI **Confounders adjusted for** • Diabetes • High blood pressure • Smoking • Alcohol consumption • Social class • Family history • Health-conscious score Duration • NR Recency • Current and past users
Collins 2006 (WHISP) RCT UK	N=100 Postmenopausal women aged >55 years with acute coronary syndromes. Mean age NR Mean age (SD) per group; combined oestrogen and progestogen: 69.4 (8.6) years; placebo: 68.3 (9.0) years	Combined Oestrogen and progestogen • Continuous: 1mg/d oestradiol + 0.5mg/d NETA	Placebo	• Coronary heart disease (including MI) • Cardiac event composite scores • Mortality (CVD related) • Stroke Duration • 1 year Recency • Current users
Ferrara 2003 Prospective cohort study	N=25000 Diabetic women aged 50 years or older	Combined oestrogen and progestogen	No HRT	• Acute MI **Confounders adjusted for**

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
US	Mean age: NR	• Continuous or sequential NR: Dose and constituent NR Oestrogen-only • Unopposed oestrogen low dose; <0.625mg oral oestrogens or <0.02mg estradiol, medium dose; 0.625mg oral oestrogens or 0.05mg estradiol, high dose; >0.625mg oral oestrogens or 0.1mg estradiol		• Age • Ethnicity • Education • Obesity • Diabetes duration • Hypoglycemic therapy • Glycosylated hemoglobin • Hypertension • Lipid-lowering medications • Smoking • Alcohol • Exercise Duration • NR Recency • Current users
Grady 2002 (HERS I and II) RCT US	N=2,763 Postmenopausal women aged <80 years with coronary heart disease (CHD) and no prior hysterectomy. Mean age (SD): 67 (7) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	• Coronary heart disease (including MI) • Cardiac event composite scores • Mortality (CVD related) • Stroke Duration • 4.1 years (HERS I) • 6.8 years (HERS I and II) Recency • Current users
Grodstein 2006 (NHS) Retrospective cohort study	N=754150 Postmenopausal women Mean age: NR	Combined oestrogen and progestogen • Continuous or sequential NR:	No HRT	• Nonfatal MI • Coronary death **Confounders adjusted for**

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
US		Dose and constituent NR Oestrogen-only • Dose and constituent NR		• Age • BMI • Hypercholesterolemia • Hypertension • Parental history of premature heart disease • Diabetes • Cigarette smoking • Husband's education • Alcohol intake • Physical activity • Vitamin E supplementation • Multivitamin supplementation • Aspirin use Duration • NR Recency • Current users
Grodstein 2008 (NHS) Retrospective cohort study US	N= 895616 Postmenopausal women Mean age: NR	Combined oestrogen and progestogen • Continuous or sequential NR: Dose and constituent NR Oestrogen-only • Dose and constituent NR	No HRT	• Any stroke **Confounders adjusted for** • Age • Body mass index • High cholesterol level • Diabetes • High blood pressure • Husband's education • Smoking

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
				• Family history of premature myocardial infarction Duration • NR Recency • Current users
Hall 1998 RCT Norway	N=60 Postmenopausal women with coronary artery disease aged 44-75 years (hysterectomy status not reported) Mean age (SD): 59.4 (6.7) years	Combined Oestrogen and progestogen • Sequential: 50ug transdermal oestradiol per 24h alone for 18 days + 5mg/d MPA orally for 10 days • Sequential: 0.625mg/d CEE alone for 18 days + 5mg/d MPA for the following 10 days	Placebo	• Mortality (CVD related) Duration • 1 year Recency • Current users
Harman 2014 (KEEPS) RCT US	N=727 Menopausal women aged 42 to 58 years between 6 and 36 months from last menses. Mean age (SD): 52.7 (2.6) years	Combined Oestrogen and progestogen • Sequential: 0.45mg/d CEE + 200mg MP for 12 days per month • Sequential: 50mcg/d transdermal oestradiol + 200mg MP for 12 days per month	Placebo	• Coronary heart disease (including MI) • Stroke Duration • 4 years Recency • Current users
Heiss 2008 (WHI) RCT US	N=15,730 Postmenopausal women aged 50 to 79 years without hysterectomy.	Combined Oestrogen and progestogen • Continuous: 0.625mg/d	Placebo	• Coronary heart disease (including MI)

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
	Mean age NR Mean age (SD) per group; combined oestrogen and progestogen: 63.1 (7.1) years; placebo: 63.3 (7.1) years	CEE + 2.5 mg/d MPA		• Cardiac event composite scores • Mortality (CVD related) • Stroke Duration • 5.6 years (mean) Recency • 2.4 years (mean)
Hendrix 2006 (WHI) RCT US	N=10,739 Postmenopausal women aged 50 to 79 years with prior hysterectomy. Mean age (SD): 63.6 (NR) years	Oestrogen-only • 0.625mg/d CEE	Placebo	• Stroke Duration • 7.1 years (mean) Recency • Current users
Herrington 2000 (ERA) RCT US	N=309 Postmenopausal women with angiographically verified coronary disease. Mean age (range): 65.8 (41.8 to 79.9) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA Oestrogen-only • 0.625mg/d CEE	Placebo	• Coronary heart disease (including MI) • Mortality (CVD related) • Stroke Duration • 3.2 years (mean) Recency • Current users
Hodis 2001 (EPAT) RCT US	N=222 Postmenopausal women aged ≥45 years with and without hysterectomy Mean age (range): 62.2 (46 to 80) years	Oestrogen-only • Unopposed 1mg/d micronized Oestradiol	Placebo	• Cardiac event composite scores • Mortality (CVD related) Duration • 2 years Recency • Current users
Hoibraaten 2000 (EVTET)	N=140 Postmenopausal women aged <70 years who had	Combined Oestrogen and progestogen	Placebo	• Stroke

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
RCT Norway	suffered a previous DVT or PE. Mean age (SD): 55.8 (NR) years	• Continuous: 2mg/d oestradiol + 2.5mg/d NETA		Duration • 1.3 years (mean) Recency • Current users
Hsia 2006 (WHI) RCT US	N=10,739 Postmenopausal women aged 50 to 79 years who had undergone prior hysterectomy. Mean age (SD): 63.6 (7.3) years	Oestrogen-only • 0.625mg/d CEE	Placebo	• Coronary heart disease (including MI) • Mortality (CVD related) Duration • 7.1 years (mean) Recency • Current users
Hulley 1998 (HERS) RCT US	N=2,763 Postmenopausal women aged <80 years with intact uterus and established coronary disease Mean age (SD): 67 (7) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA	Placebo	• Coronary heart disease (including MI) • Mortality (CVD related) • Stroke Duration • 4.1 years Recency • Current users
Hulley 2002 (HERS) RCT US	N=2,763 Postmenopausal women aged <80 years with intact uterus and established coronary disease. Mean age (SD): 67 (7) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	• Mortality (CVD related) Duration • 4.1 years (HERS I) • 6.8 years (HERS I and II) Recency • Current users
Kim 2006 Nested case-control study UK	N=166 310 Women registered with General Practice Research Data Base who reported a first diagnosis of MI	Combined oestrogen and progestogen • Continuous or sequential NR: Opposed therapy	No HRT	• MI **Confounders adjusted for** • Hyperlipidaemia

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
	Mean age: NR	Oestrogen-only • Unopposed therapy		• Hypertension • Atheroma • Diabetes • History of angina • Smoking • Alcohol • BMI • Aspirin use • Cardiovascular drug use • Consultation rate • Atrial fibrillation • Peripheral vascular disease • Stroke • Heart failure Duration • NR Recency • Current users
LaCroix 2011 (WHI) RCT US	N=10,739 Postmenopausal women aged 50 to 79 years with prior hysterectomy. Mean age: NR	Oestrogen-only • 0.625mg/d CEE	Placebo	• Coronary heart disease (including MI) • Cardiac event composite scores • Mortality (CVD related) • Stroke Duration • 5.9 years (median) Recency • Current and past users
Lemaitre 2006 Case Control study	N=4205	Combined oestrogen and progestogen	No HRT	• MI • Ischaemic stroke

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
US	Postmenopausal women with an incident of MI between 1986-2001 Mean age NR Mean age (SD) per group; combined oestrogen and progestogen CEE: 62.2 (NR) years; combined oestrogen and progestogen EE: 62.1 (NR) years; oestrogen-only CEE: 65.1 (NR) years; Oestrogen-only EE: 66.2 (NR) years; no HRT: 68.6 (NR) years	• Continuous or sequential NR: CEE + progestin or EE +progestin Oestrogen-only • CEE or EE		**Confounders adjusted for** • Age • Year • Hypertension • Diabetes mellitus • Angina • Current smoking • Systolic blood pressure Duration • NR Recency • Current users
Lokkegaard 2017 Retrospective cohort study Denmark	N=980 003 Women aged 51-70 years Mean age: NR	Combined oestrogen and progestogen • Sequential: Long cycle combined (progestin type NR) or cyclic combined medroxyprogesterone, norethisterone, cyproterone acetate or levinorgestrel • Continuous: Continuous combined norethisterone, dienogest, tibolone or raloxifene Oestrogen-only • Dose or constituent NR	No HRT	• Any stroke **Confounders adjusted for** • Age • Calendar year • Education • Type of medication for diabetes, arrythmia, hypertension, diuretics, hyperlipidemia, anticoalugation Duration • NR Recency • Current users
Manson 2003 (WHI) RCT	N=16,608 Postmenopausal women aged 50 to 79 years without hysterectomy.	Combined Oestrogen and progestogen	Placebo	• Coronary heart disease (including MI)

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
US	Mean age (SD): 63.3 (7.1) years	• Continuous: 0.625mg/d CEE + 2.5mg/d MPA		• Cardiac event composite scores • Mortality (CVD related) Duration • 5.6 years (mean) Recency • Current users
Manson 2013 (WHI) RCT US	N=27,347 Postmenopausal women aged 50 to 79 years with and without hysterectomy. Mean age NR Mean age (SD) per group; combined oestrogen and progestogen: 63.2 (7.1) years; oestrogen-only: 63.6 (7.3) years; placebo: 63.3 (7.1) and 63.6 (7.3) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA Oestrogen-only • 0.625mg/d CEE	Placebo	• Coronary heart disease (including MI) • Cardiac event composite scores • Mortality (CVD related) • Stroke Duration • 5.6 years (median: combined HRT) and 7.2 years (median: oestrogen-only HRT) Recency • Current and past users
Manson 2017 (WHI) RCT US	N=27,347 Postmenopausal women aged 50 to 79 years with and without hysterectomy. Mean age NR Mean age (SD) per group; combined oestrogen and progestogen: 63.2 (7.1) years; Oestrogen-only: 63.6 (7.3) years; placebo: 63.3 (7.1) and 63.6 (7.3) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA Oestrogen-only • 0.625mg/d CEE	Placebo	• Mortality (CVD related) Duration • 5.6 years (median: combined HRT) and 7.2 years (median: oestrogen-only HRT) Recency • Current and past users

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
Nachtigall 1979 (ERT) RCT US	N=168 Postmenopausal hospitalised women with unspecified chronic disease. Mean age NR Mean age per group; combined oestrogen and progestogen: 55.3 (NR) years; placebo: 54.9 (NR) years	Combined Oestrogen and progestogen • Cyclical: 2.5mg/d conjugated oestrogen + 10mg/d MPA for 7 days each month	Placebo	• Coronary heart disease (including MI) Duration • 10 years Recency • Current users
Prentice 2020 (WHI) RCT 2020	N=24,347 Postmenopausal women aged 50 to 79 years with and without hysterectomy. Mean age NR Mean age (SD) per group; oestrogen and progestogen: 63.2 (7.1) years; oestrogen-only: 63.6 (7.3); placebo: 63.3 (7.1) and 63.6 (7.3) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA Oestrogen-only • 0.625mg/d CEE	Placebo	• Coronary heart disease (including MI) • Stroke Duration • 5.6 years (median: combined HRT) and 7.2 years (median: oestrogen-only HRT) Recency • Current and past users
Renoux 2010 Case control study Canada	N= 75668 Postmenopausal women aged 50-79 years Mean age (SD): 70 (NR) years	Combined oestrogen and progestogen • Continuous or sequential NR: Dose and constituent NR Oestrogen-only • Dose and constituent NR	No HRT	• Any stroke **Confounders adjusted for** • Age • Body mass index • Smoking status • Alcohol misuse • Diabetes, hyperlipidaemia • Hypertension, atrial fibrillation • Cardiovascular disease

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
				• Transient ischaemic attack • Aspirin or other NSAID use • History of hysterectomy or oophorectomy Duration • NR Recency • Current users
Rossouw 2002 (WHI) RCT US	N=16,608 Postmenopausal women aged 50 to 79 years without hysterectomy. Mean age NR Mean age (SD) per group; oestrogen and progestogen: 63.2 (7.1) years; placebo: 63.3 (7.1) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	• Coronary heart disease (including MI) • Mortality (CVD related) • Stroke Duration • 5.2 years (mean) Recency • Current users
Rossouw 2007 (WHI) RCT US	N=27,347 Postmenopausal women aged 50 to 79 years with and without hysterectomy. Mean age: NR	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA Oestrogen-only • 0.625mg/d CEE	Placebo	• Coronary heart disease (including MI) • Stroke Duration • 5.2 years (mean) Recency • Current users
Simon 2001 (HERS) RCT US	N=2,763 Postmenopausal women with established coronary disease. Mean age (SD): 67 (7) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5 mg/d MPA	Placebo	• Stroke Duration • 4.1 years Recency • Current users

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
Tierney 2009 (EMS) RCT Canada	N=142 Menopausal women aged 61-87 years of age with or without a uterus and normal to mildly impaired memory functioning. Mean age NR Mean age (SD) per group; combined oestrogen and progestogen: 75 (6.4) years; placebo: 74.5 (7.4) years	Combined Oestrogen and progestogen • Sequential: 1mg/d oestradiol + 0.35mg norethindrone 3d/week	Placebo	• Coronary heart disease (including MI) • Mortality (CVD related) • Stroke Duration • 2 years Recency • Current users
Veerus 2006 (EPHT) RCT Estonia	N=1,778 Postmenopausal women aged 50–64 years with or without hysterectomy. Mean age NR Mean age (SD) per group; combined oestrogen and progestogen: 58.5 (3.9) years; placebo: 59 (3.9) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA or 5mg/d MPA if <3 years had passed since their last period	Placebo	• Coronary heart disease (including MI) • Stroke Duration • 3.4 years (mean) Recency • Current users
Vickers 2007 (WISDOM) RCT Australia, NZ, and UK	N=4,385 Postmenopausal women aged 50–69 years with or without a uterus. Mean age (SD): 62.8 (4.8) years	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	• Coronary heart disease (including MI) • Cardiac event composite scores • Mortality (CVD related) Duration • 12.8 months (median) Recency • Current users
Viscoli 2001 (WEST) RCT US	N=664 Postmenopausal women aged >44 years with and without hysterectomy who recently had an ischemic stroke or	Oestrogen-only • 1mg/d oestradiol	Placebo	• Coronary heart disease (including MI) • Mortality (CVD related) • Stroke

Study	Population	Intervention	Comparison	Outcomes, confounders adjusted for (where applicable) and duration and recency of HRT use
	transient ischemic attack. (44% and 45% with hysterectomy) Mean age (range): 71 (46 to 91) years			Duration • 2.8 years (mean) Recency • Current users
Wassertheil Smoller 2003 (WHI) RCT US	N=16,608 Postmenopausal women aged 50-79 years without hysterectomy. Mean age: NR	Combined Oestrogen and progestogen • Continuous: 0.625mg/d CEE + 2.5mg/d MPA	Placebo	• Stroke Duration • 5.6 years (mean) Recency • Current users

CEE: conjugated equine estrogens; CHD: coronary heart disease; CVD: cardiovascular disease; d: days; DOPS: Danish Osteoporosis Prevention Study; DVT: deep vein thrombosis; EE: esterified estrogen; EPAT: Estrogen in the Prevention of Atherosclerosis; ERA: Estrogen Replacement and Atherosclerosis study; ERT: Estrogen Replacement Therapy; EMS: Estrogen Memory Study; EPHT: Estonian Postmenopausal Hormone Therapy; ESPRIT: Estrogen for the Prevention of Re-Infarction Trial; EVTET: Estrogen in Venous Thromboembolism Trial; HERS: Heart and Estrogen Progestin Replacement Study; KEEPS: Kronos Early Estrogen prevention Study; mcg: microgram; MI: myocardial infarction; mg: milligrams; MP: micronized progesterone; MPA: medroxyprogesterone acetate; NETA: norethisterone acetate; NR: not reported; NZ: New Zealand; PE: pulmonary embolism; PEPI: Postmenopausal Estrogen/Progestin Interventions Trial; RCT: randomised controlled trial; ug: microgram; UK: United Kingdom; US: United States of America; VTE: venous thromboembolism; WEST: Women's Estrogen for Stroke Trial; WHI: Women's Health Initiative; WHISP: Women's Hormone Intervention Secondary Prevention Study; WISDOM: Women's International Study of long Duration Oestrogen after Menopause.

See the full evidence tables in Appendix D, the forest plots in Appendix E and outcome data in Supplement 17 (RCTs) and Supplement 18 (observational studies).

Summary of the evidence

Comparison 1: Combined oestrogen plus progestogen (continuous) versus placebo

Recency and duration of hormone replacement therapy (HRT) use

Most of the evidence from randomised controlled trials (RCTs) comparing combined oestrogen plus progestogen (continuous) to placebo was in current users (11 studies) with a duration of use of <1 year, 1-4 years, and 5-9 years. There was evidence from 1 study in past users of <5 years since last use with a duration of use of 5-9 years and evidence from 2 studies where the recency of use was unknown, and this group were reported as current and past users (unknown recency).

Most of the RCT evidence showed no important difference between combined oestrogen plus progestogen (continuous) and placebo across outcomes, however low-quality evidence from 2 RCTs showed an important harm for current users with <1 year duration of use for the outcome coronary heart disease (including MI). There was also high-quality evidence from 2 RCTs which showed an important harm for current users with 1-4 years duration of use and moderate quality evidence from 1 study which showed an important harm for current users

with 5-9 years duration of use for the outcome cardiac event composite scores, compared to placebo. There was low quality evidence from 2 RCTs which showed an important harm for current users with 5-9 years duration of use for the outcome stroke, compared to placebo. However, moderate quality evidence from 1 RCT showed no important difference for current and past users (unknown recency), or past users (<5 years since last use) with 5-9 years duration of use for the outcome stroke, compared to placebo.

Age at first use, time since menopause at first use, constituent (oestrogenic and progestogenic), and ethnicity

Moderate quality evidence from 1 RCT showed an important harm for current users with 5-9 years duration of use for the outcome stroke when combined oestrogen plus progestogen (continuous) was taken aged 60-69 years at first use, compared to placebo. High quality evidence from 1 RCT also showed an important harm for current users with 5-9 years duration of use for the outcome stroke when combined oestrogen plus progestogen (continuous) was taken aged 70-79 years at first use, compared to placebo.

Moderate quality evidence from 1 RCT showed an important harm for current users with 5-9 years duration of use for the outcome coronary heart disease (including MI) when combined oestrogen plus progestogen (continuous) was taken >10 years since menopause at first use, compared to placebo.

Moderate quality evidence from 1 RCT comparing combined oestrogen plus progestogen (continuous) to placebo showed an important harm for current users of white ethnicity with 5-9 years duration of use for the outcome stroke. High quality evidence from 1 RCT also showed an important harm for current users of black ethnicity taking combined oestrogen plus progestogen (continuous) for 5-9 years duration of use for the outcome stroke, compared to placebo. The magnitude of effect was strongest in people with black ethnicity.

There was no important difference for constituent (oestrogenic and progestogenic) from RCT evidence comparing combined oestrogen plus progestogen (continuous) to placebo for all outcomes where evidence was reported (nonfatal MI, mortality, and stroke).

Comparison 2: Combined oestrogen plus progestogen (sequential) versus placebo

Recency and duration of HRT use

All evidence from RCTs comparing combined oestrogen plus progestogen (sequential) to placebo was in current users (5 studies) with a duration of use of <1 year, 1-4 years, and 10-14 years. All RCT evidence showed no important difference between combined oestrogen plus progestogen (sequential) and placebo across outcomes.

Constituent (oestrogenic and progestogenic), and mode of administration

There was no important difference for constituent (oestrogenic and progestogenic) or mode of administration from RCT evidence comparing combined oestrogen plus progestogen (continuous) to placebo for all outcomes where evidence was reported (nonfatal MI, cardiac event composite score, mortality, stroke, and TIA).

Comparison 3: Combined oestrogen plus progestogen versus no HRT

Duration of HRT use

Very low-quality evidence from 1 observational study showed no important difference for the outcome coronary heart disease (including MI) when HRT was used for less than a year, and between 1 and 4 years, and an important benefit when used for more than 5 years.

Age at first use

Very low to low quality evidence from 2 observational studies showed important benefits for the outcome coronary heart disease (including MI) when HRT was started within 4 years of menopause; between the ages of 45-54 years, and 55-64 years. Very low-quality evidence from 1 study showed no important difference for the outcome coronary heart disease (including MI) when HRT was started between the ages 65-74 years and over 75 years. Very low-quality evidence from one study showed no important difference for the outcome coronary heart disease when HRT was started more than 10 years after menopause.

Low quality evidence from 2 observational studies mostly showed no important differences for the outcome of stroke and age at first use. The exceptions were low quality evidence from 1 observational study that showed important harm for the outcome of stroke if HRT use was started after the age of 60 years.

Oestrogen dose

Very low to moderate quality evidence from 1 observational study mostly showed no important difference for the outcome stroke in oestrogen doses used. Exception is very low-quality evidence from 1 observational study which showed important harm for the outcome stroke when oestrogen was used continuously combined in high dosage.

Type of progestogen

Very low to moderate quality evidence from 2 observational studies showed mixed results for the outcome stroke and type of progestogen used. For example, very low-quality evidence from 1 observational study showed important harm for stroke when norpregnane derivates were used. Low quality evidence from 1 observational study showed important harm for stroke when norethisterone or tibolone were used continuously combined. Very low-quality evidence from 1 observational study showed no important difference for the outcome stroke when progesterone or nortestosterone derivatives were used. Low quality evidence from 1 observational study showed no important difference for the outcome stroke when raloxifene was used continuously combined. All other very low to moderate quality evidence for outcome stroke and type of progesterone used showed no important difference.

Route of administration

Very low to low quality evidence from 2 observational studies mostly showed no important difference for outcome stroke by route of administration. Exception was low quality evidence from 1 observational study that showed important harm for the outcome stroke when administered orally continuously combined.

Unknown recency or duration

Very low to low quality evidence from 7 observational studies only showed important benefit for the outcome coronary heart disease (including MI) when using combined HRT with unknown recency or duration. No important difference was found for the outcome cardiovascular mortality and stroke when using combined HRT with unknown recency or duration. Evidence of very low quality also found no important difference for the outcome TIA with HRT use with unknown recency or duration.

Comparison 4: Oestrogen-only HRT versus placebo.

Recency and duration of HRT use

Most of the evidence from RCTs comparing oestrogen-only HRT to placebo was in current users (7 studies) with a duration of use of <1 year, 1-4 years, and 5-9 years. There was evidence from 1 study in past users of ≥10 years since last use with a duration of use of 1-4 years and evidence from 2 studies where the recency of use was unknown, and this group were reported as current and past users (unknown recency).

Most of the RCT evidence showed no important difference between oestrogen-only and placebo across outcomes, however moderate quality evidence from 1 RCT showed an important harm for current users with 5-9 years duration of use for the outcome coronary heart disease (including MI) and moderate quality evidence from 1 RCT showed an important harm for current users with 5-9 years duration of use for the outcome stroke. There was evidence from 1 RCT in past users of ≥10 years since last use which showed an important harm with a duration of use of 1-4 years for the outcome mortality, compared to placebo.

Age at first use, and time since menopause at first use

Moderate quality evidence from 1 RCT showed an important benefit for current and past users (unknown recency) with 5-9 years duration of use for the outcome coronary heart disease (including MI) at 13 years follow-up when oestrogen-only was taken aged 50-59 years at first use, compared to placebo. This effect was only seen at 13 years follow-up and not at the endpoint of the study, however, was close to significance at endpoint (p=0.07). Comparatively, moderate quality evidence from 1 RCT showed an important harm for current users with 5-9 years duration of use for both the outcomes cardiac event composite scores and stroke when oestrogen-only was taken aged 60-69 years at first use, compared to placebo.

Moderate quality evidence from 1 RCT showed an important harm for current users with 5-9 years duration of use for the outcome stroke when oestrogen-only was taken >10 years since menopause at first use, compared to placebo.

Comparison 5: Oestrogen-only versus no HRT.

Duration of HRT use

Very low-quality evidence from 1 observational study for oestrogen-only users compared to non-users showed no important difference for the outcome coronary heart disease when oestrogen was taken for <1 year, 1 to 4 years, and more than 5 years.

Age at first use, and time since menopause at first use

Two observational studies comparing oestrogen-only users to non-users, ranging from very low to low quality evidence showed important benefits for the outcome coronary heart disease (including MI) when oestrogen was started within 4 years of menopause, at the ages of 50-59, 55-64, and 65-74 years of age. Conversely, 1 observational study showed evidence of low quality with important harm for the outcome of stroke when oestrogen was started within 4 years of menopause, more than 10 years after menopause, at the ages of 50-59 and over 60 years.

Oestrogen dose

Very low-quality evidence from 1 observational study only showed important harm for the outcome of stroke when oestrogen was used as a high dose, while the low and middle dose showed no important differences.

Route of administration

Very low-quality evidence from 2 observational studies showed an important increased risk of stroke associated with oral oestrogen-only and no important difference in risk of stroke in transdermal route of administration.

Unknown recency or duration

Across the 7 observational studies most of the very low to low quality evidence showed no important differences between groups for the outcomes stroke and cardiovascular mortality. The exceptions were evidence of very low quality from 5 studies that showed important

benefits for the outcome of coronary heart disease (including MI) with use of oestrogen compared to no HRT. Very low-quality evidence from 1 observational study also showed no important difference for the outcome TIA.

See Appendix F for full GRADE tables and Appendix L for the absolute risk tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Coronary heart disease (including myocardial infarction), cardiac event composite scores, mortality (cardiovascular disease related) and stroke were prioritised as critical outcomes by the committee. This is because these health outcomes can seriously affect quality of life, cause disability and death.

Transient ischaemic attack (TIA) was identified as an important outcome by the committee. The committee noted that TIA typically has a less severe impact on quality of life than stroke and can be more difficult to detect.

The quality of the evidence

The quality of the evidence was assessed with GRADE and rated as high to very low quality.

There was variation in the quality of the RCT evidence according to the risk of bias. Studies that were downgraded for risk of bias were mainly due to the randomisation process (no information about allocation concealment and/or randomisation), deviations from the intended interventions (effect of assignment to intervention and effect of adhering to intervention) where there was a lack of clarity as to whether an appropriate analysis was used to estimate the effect of assignment to the intervention. There were also some concerns around deviations for the intended intervention, as prescription registries or women's self-reporting may indicate the use of HRT, but it cannot be fully confirmed that they took the HRT. Observational studies were only included where data on HRT use was

collected before the outcome of interest was known as this was identified as a particular source of bias by the committee. Studies were also downgraded for risk of bias for missing outcome data that was not always available for all participants and in some studies, there was a significant difference between treatment groups in those lost to follow-up, measurement of the outcomes that could have been influenced by knowledge of the intervention received and a lack of clarity on the selection of the reported result. The observational evidence was downgraded for risk of bias due to confounding where time-varying confounding was not controlled for and selecting of participants with characteristics observed after starting the intervention. The RCT and observational evidence was also downgraded for imprecision due to the 95% confidence interval crossing a threshold for minimally important difference (0.8 and 1.25 for all relative dichotomous outcomes) and for inconsistency due to serious heterogeneity unexplained by subgroup analysis. Studies on prevention were downgraded for indirectness because the population had existing conditions (such as coronary heart disease or a previous myocardial infarction) and HRT was provided for secondary prevention rather than a treatment for menopause symptoms. There were no concerns about publication bias in the evidence.

In cases where the outcomes were statistically significant the committee considered the GRADE default imprecision rating and the resulting overall quality rating as being an overly conservative estimate of quality. Statistical significance featured in their discussions as an additional factor during decision-making (see also the 'Guideline recommendations' section in the Supplement 1 – Methods).

Benefits and harms

The committee discussed the evidence on the use of hormone replacement therapy (HRT: oestrogen-only, and combined oestrogen and progesterone taken either continuously or sequentially) on the outcomes coronary heart disease (including myocardial infarction), cardiac event composite scores, mortality, stroke, and transient ischemic attack (TIA). They discussed the data from randomised controlled trials (RCTs) and observational studies separately at first but combined the evidence from both study designs to make overarching recommendations. The committee discussed that it is unclear how much the observational findings may have been influenced by residual confounding with factors such as sociodemographic status, smoking, prior morbidities, or other factors which may be related to both HRT use and cardiovascular risk. They noted that whilst confounding is a potential source of bias in all observational studies, the likely impact of confounding on any given association will vary depending on the strength of the association of potential confounders with both HRT and the outcome of interest, and how reliably such confounders are measured. Based on the committee's knowledge, previous studies have found that HRT users differ from non-users in terms of sociodemographic status, body mass index (BMI), and other behavioural factors such as smoking and physical activity. Many of these factors have a substantial effect on cardiovascular disease and for this reason, there is scope for residual confounding of associations of HRT with cardiovascular disease due to inadequate adjustment for such factors. On this basis, the committee agreed that the assessment of the evidence for the association of HRT with cardiovascular disease outcomes should take the potential for residual confounding into consideration, particularly where the findings from observational and randomised evidence differ.

The committee emphasised the importance of using an individualised approach in relation to the risk of cardiovascular disease and cross referenced the related NICE guideline to inform initial discussions (see the 'other factors the committee took into account' section below).

Coronary heart disease and cardiac composite scores

Combined HRT

RCT

The committee discussed the RCT evidence for combined HRT (continuous and sequential) compared to placebo, that was stratified by recency and duration of use, and noted that for most of the evidence there was no difference between groups. There was an isolated increase in coronary heart disease risk in current users taking continuous combined HRT for less than 1 year, however the test for subgroup differences between the different durations of use was not statistically significant. They also discussed an increase in cardiac event composite scores in current users taking continuous combined HRT for 1-4 years, which was statistically significant in the test for subgroup differences with other durations of use. They noted that the evidence was derived from the Women's International Study of long Duration Oestrogen after Menopause (WISDOM), which was underpowered and terminated early. Consequently, the committee felt that this finding should be interpreted cautiously. The committee discussed that most of the RCT evidence for combined HRT on coronary heart disease was derived from findings in older postmenopausal women (Women's Health Initiative [WHI] and the Heart and Estrogen Progestin Replacement Study [HERS] studies) with a mean age of 63.2 and 66.7 years respectively. Although both studies did include women aged 50-59 years (the group considered most likely to be taking HRT), the reported mean age of participants was higher than what may be considered the usual starting age for HRT treatment for symptoms associated with the menopause.

When discussing the evidence on the time of HRT initiation post menopause in current users of combined oestrogen and progestogen, the committee noted an increase in coronary heart disease risk for those taking HRT for 5-9 years when initiated 10 years or more after menopause but no difference in risk for those starting less than 10 years since the start of menopause. They looked at the test for subgroup differences that showed no significant difference between the subgroups, therefore they could not conclude that there was a difference in effect in different subgroups. All other RCT evidence showed no important difference between combined HRT and placebo for coronary heart disease and cardiac event composite scores.

Observational studies

The committee discussed the observational evidence for coronary heart disease and noted that for in some studies for current users with an unknown duration of use, the evidence showed a reduction in the risk of coronary heart disease among users of combined HRT. They discussed that this was not reflected in another observational study that showed no differences in risk of coronary heart disease in current and past users with different durations of use.

The committee also discussed the evidence for coronary heart disease risk by age at first use. They noted that one observational study showed a reduced risk when combined HRT was started at ages 45 to 64 years, but no difference when started over 65 years. However, the test for subgroup differences showed that the differences between the age groups was not significant, therefore they agreed that they could not conclude that there was a reduction in risk if HRT was started at a younger age.

Interpretation of both RCT and observational evidence

The committee discussed that overall, the RCT evidence showed that there were no differences in the risk of coronary heart disease between combined HRT users and placebo but noted that some of the observational studies showed an overall decrease in the risk of coronary heart disease. However, since the observational studies are limited by the high number of potential confounding factors, they felt less confident about the certainty of these findings as a basis for a recommendation. Given that there was uncertainty in the evidence, but that most of the evidence showed no important differences between people taking combined HRT, compared to placebo or no HRT, the committee concluded that on balance

people without pre-existing CHD should be advised that combined HRT has not been shown to increase the risk of coronary heart disease, so that this can be considered when undertaking shared decision-making for the use of HRT as a treatment for menopausal symptoms.

Oestrogen-only HRT

RCT

The committee noted that RCT evidence, on the whole, showed no difference in the risk of coronary heart disease and cardiac event composite scores between those who took oestrogen-only HRT and those who took placebo.

The committee discussed the subgroup analysis from the RCT evidence for time since menopause at first use, and also for age at first use, in current users with 5-9 years duration of oestrogen-only HRT. The evidence showed no difference in risk of coronary heart disease across all subgroups. They noted that a subgroup analysis for current and past users with 5-9 years duration of oestrogen-only HRT, at 13 years cumulative follow-up, showed that there was an isolated reduced risk when age at first use was 50-59. However, the committee looked at the test for subgroup differences which was not significant, therefore they agreed they could not conclude that there was a difference in risk between the different ages at first use.

Observational studies

The committee noted that the observational evidence showed an overall decrease in coronary heart disease risk in current users taking either oestrogen-only HRT for an unknown duration. They also discussed that one other observational study which stratified current and past users by duration of use did not show the same reduction in risk. The committee looked at the subgroup analysis from the observational evidence for time since menopause at first use, and also for age at first use, in current users with an unknown duration of use. For women currently taking oestrogen-only HRT, who had been taking it for an unknown duration, the 2 observational studies reported different conclusions on this. One study showed a reduced risk of coronary heart disease when HRT was started within 4 years of menopause, while the other study showed no difference in risk when HRT was started between the ages of 45 to 54 (which is likely to be within 4 years of menopause). One study showed no difference when HRT was started more than 10 years after menopause, while the other study showed a reduction in risk when HRT was started between the ages of 65 and 74 (which is likely to be 10 years or more after menopause).

Interpretation of both RCT and observational evidence

The committee had a discussion similar to that of the combined HRT and coronary heart disease risk. They discussed that since there were concerns regarding residual confounders in the observational studies, inconsistent results between observational studies, and no statistically significant subgroup differences from the RCT evidence and no clear age trend, they could not make any recommendations specific to coronary heart disease risk following oestrogen-only HRT use by age at first use, or time since menopause when HRT was started. They discussed that the studies were not powered to detect differences in the subgroups and agreed they would make a research recommendation for age at first use and time since menopause. They discussed that overall; they could not make a conclusion that oestrogen-only reduced the risk of coronary heart disease as seen in the observational evidence due to the same concerns regarding residual confounders and that the RCT evidence did not support this conclusion. However, they agreed that on balance, people without pre-existing CHD should be advised that oestrogen-only HRT has not been shown to increase the risk of coronary heart disease, so that this can be considered when undertaking shared decision-making for the use of HRT as a treatment for menopausal symptoms.

Although the review focussed on HRT when taken for menopausal symptoms and its impact on health outcomes, since HRT may be prescribed in clinical practice for the prevention of cardiovascular disease, the committee felt a statement should be made reflecting the evidence on the use of HRT for prevention. When assessing the evidence for the role of HRT in the prevention of cardiovascular disease, the committee was clear that neither combined nor oestrogen-only HRT should be offered to reduce the risk of coronary heart disease. This was based on the RCT evidence showing no clear benefit in the use of either combined (continuous and sequential) or oestrogen-only HRT for the reduction of coronary heart disease risk or cardiac event composite scores. Although the observational studies adjusted data for confounding, the committee felt there was potential for residual confounding (including systematic differences between HRT users and controls particularly in sociodemographic factors, education, smoking and BMI) and like the RCT evidence, concluded there was no clear benefit in the use of oestrogen-only or combined HRT, compared to no HRT. The committee weighed up differences between the RCT and observational evidence, the absence of a clear pattern of effect with age, and after balancing the risks and benefits of HRT use, agreed that there was insufficient evidence to support any role for HRT in primary or secondary cardiovascular disease prevention. They also noted that many other approaches to reduce the risks of cardiovascular disease, such as lifestyle changes (exercise, diet and not smoking) are effective. Therefore, the committee agreed that HRT should not be initiated for primary or secondary prevention of cardiovascular disease and that HRT was only indicated for troublesome menopausal symptoms.

The committee noted that in people with a history of cardiovascular disease taking either combined HRT (continuous and sequential) or oestrogen-only HRT, the RCT evidence did not suggest any difference in coronary heart disease risk and cardiac event composite scores, when compared to placebo. Observational evidence did not include people with a history of cardiovascular disease. The committee discussed how the evidence suggested that a history of coronary heart disease may not be a contraindication to combined or oestrogen-only HRT. However, they felt that for this group of people the use of HRT should be discussed with and, if appropriate, initiated by a healthcare professional with expertise in menopause. This would ensure that people with a history of coronary heart disease who commence HRT are advised in an individualised way that relates to their specific history of coronary heart disease.

Mortality related to cardiovascular disease

Combined or oestrogen-only HRT

The committee discussed the RCT evidence and agreed that there did not appear to be an increase in mortality in people taking either combined HRT (continuous or sequential) or oestrogen-only HRT, compared to placebo. However, the evidence was largely based on WHI findings where participants took HRT for an average of 5.6 years and the trial was stopped early due to the potential for harm. The observational evidence supported RCT evidence and showed no increase in mortality in people taking combined HRT compared to no HRT. Due to the limited evidence, the committee discussed findings from the Danish Osteoporosis Prevention Study (DOPS - Schierbeck 2012), (which was an excluded study as it did not separately report results for people who received combined HRT from those who received oestrogen-only HRT – see appendix J). The study concluded after 10 years that there was no increase in mortality with the use of HRT. The committee felt there was sufficient evidence that HRT did not increase mortality.

Stroke

Combined HRT

RCT

The committee discussed the RCT evidence on combined HRT (continuous and sequential) and noted that most of the evidence showed no differences between combined HRT and placebo on the risk of stroke, when taken for up to 4 years. They noted that some of the evidence showed an increase in the risk of stroke when combined HRT (continuous) was taken for 5 to 9 years, and that the risk was difference depending on the age at initiation of HRT. The evidence suggested an increased risk of stroke in current users of combined HRT (continuous), aged 60 to 79 years when starting HRT, compared to placebo, but no difference when started between 50 to 59. The committee discussed that this evidence was derived from the WHI study where participants were taking continuous combined HRT orally.

The committee noted a lack of RCT evidence on the effect of dosage of combined continuous HRT on stroke, however the RCT evidence did not show a difference on the risk of stroke in those who took sequential combined HRT when dosages were adjusted and those who took placebo.

The committee discussed the RCT evidence that was stratified according to ethnicity, an increased risk in stroke was shown in current continuous combined HRT users taking HRT for 5-9 years, in people of white and black ethnicity but not in people of Hispanic, Asian, pacific islander, American Indian or Alaskan native ethnicities. This was consistent with RCT evidence findings of an increased risk of stroke with continuous combined HRT use between 5-9 years. The committee noted the magnitude of effect was greater in people of black ethnicity which was analysed by the WHI study as a subgroup. Based on knowledge, the committee agreed that the baseline risk of stroke is higher in people with black ethnicity therefore the potential increased stroke risk associated with combined HRT should discussed.

The committee discussed how the route of HRT administration (oral or transdermal) may affect the risk of stroke and noted that all RCT evidence for continuous combined HRT was based on oral medication. RCT evidence from the WHI study showed an increased risk of stroke in current users taking continuous combined HRT (orally) for 5-9 years, compared to placebo. This was in line with the evidence from observational studies. For sequential combined HRT, there was RCT evidence for both oral and transdermal oestrogen. This showed no important difference in stroke when sequential combined HRT was given orally (both oestrogen and progesterone), and when the oestrogen component of HRT was given transdermal only (progesterone was given orally), compared to placebo.

Observational studies

The committee discussed the observational evidence, and noted that it supported RCT findings and showed an increased risk in stroke in people aged 60 years or above when starting combined HRT, compared to no HRT, however the duration of use was not reported. They discussed that the observational evidence also supported no difference in stroke risk for people starting combined HRT at age 50 to 59 years.

The committee discussed that the observational evidence showed an increased risk of stroke in people taking continuous combined HRT compared to no HRT when the oestrogen dose was described as high and no important difference between groups with a lower oestrogen dose. However, this observational study did not describe the dosage amounts that were considered low or high. This dose related finding aligned with the committee's collective clinical interpretation that the largest effect seen in combined HRT is from the oestrogen component and that the risk of stroke increases with increasing oestrogen dose.

The committee discussed the observational evidence for the route of administration. They noted that the evidence showed an increased risk of stroke with oral continuous combined HRT, but the evidence showed no important difference in the risk of stroke for people taking transdermal sequential combined HRT, compared to no HRT.

Interpretation of RCT and observational evidence

The committee discussed how the RCT and observational evidence could be used to inform recommendations. They first discussed that there was evidence from both RCT and observational studies that supported recommendations to highlight that combined HRT increases the risk of stroke, and that the risk increases with increasing age. The committee discussed that there were limitations of the observational studies that some of the important confounders such as smoking, and alcohol had not been adjusted for. However they discussed that since there was limited RCT evidence for transdermal route of administration, and that one of the observational studies contributing to the evidence was large, they felt confident from the evidence that HRT with transdermal oestrogen was unlikely to increase the risk of stroke. They agreed that these differences should be considered when discussing with people the route of HRT administration and made a recommendation. The committee also used the evidence on dosage to inform recommendations.

Oestrogen-only HRT

RCT

The committee discussed the RCT evidence on oral oestrogen-only HRT and noted an increased risk of stroke in current users taking this for 5-9 years, compared to placebo. The increased risk of stroke was also seen in current users taking oral oestrogen-only HRT for 5-9 years for people aged above 60 years at first use and in people starting HRT more than 10 years after menopause. The committee discussed the evidence for oestrogen-only HRT by route of administration and noted a lack of RCT evidence on transdermal medications for the outcome stroke.

Observational studies

The committee discussed the evidence from observational studies and noted that this evidence also showed an increased risk of stroke in current users of oestrogen-only HRT when compared to no HRT. The observational evidence also showed an increased risk for stroke when oestrogen-only HRT was given at a high dose, whilst at low and middle doses there were no differences between oestrogen-only HRT and no HRT. However, the evidence did not provide details on the low, middle, or high doses.

Interpretation of RCT and observational evidence

The committee considered the evidence from both RCT and observational studies to inform their recommendations that there was an increased risk of stroke in those who took oestrogen-only HRT. They agreed the evidence also supported recommendations informing people of other risk factors such as dosage and age at starting HRT. The committee discussed that since there was no RCT evidence on transdermal route of administration, they would draw on observational evidence which showed no important differences in the risk of stroke with transdermal oestrogen-only HRT, compared to no HRT, but an increased risk of stroke when given orally. They had a similar discussion regarding the limitations of the observational evidence regarding transdermal route of administration, however they were led by the large size of the observational data and believed the evidence showing no difference in risk in transdermal routes of administration. They agreed that this should be taken into consideration when discussing the choice of route of administration taking into consideration the person's preference.

The committee looked at the evidence to determine if there was an increased risk of stroke associated with combined or oestrogen-only HRT use in people with a previous history of stroke. However, there was a lack of RCT and observational evidence in people with menopausal symptoms and a history of stroke. Given the potential for risk of stroke recurrence, the committee agreed that people with a personal history of stroke wishing to

take either combined or oestrogen-only HRT should ensure that HRT is discussed with, and if appropriate initiated, by a healthcare professional with expertise in menopause. This is to ensure they can be individually advised in light of their personal circumstances that may relate to their history of stroke.

When discussing the evidence on HRT constituents (oestrogenic and progestogenic), the committee agreed that there was not enough evidence to recommend any specific type. They particularly noted a lack of evidence on how different types of progestogen/progesterone in HRT may affect the risk of developing cardiovascular disease and stroke. The committee decided to add a research recommendation in this area. However, because this was also a research recommendation related to breast and endometrial cancer this has been added to appendix K of evidence report D.

Trans-men and non-binary people registered female at birth

Despite a lack of evidence relating to transgender men and non-binary people registered female at birth, the committee agreed that the evidence was generalisable to those who have never taken gender affirming hormone therapy. The committee noted that there was uncertainty about transgender people who have taken gender affirming hormone therapy in the past. Given the lack of evidence, it is not known whether past hormone treatment could influence the choice of HRT, and whether giving HRT to someone who previously had hormone therapy would alter their cardiovascular or other health risks. The committee agreed that trans-men and non-binary people registered female at birth who have taken gender-affirming hormone therapy in the past should be able to discuss their troublesome menopause symptoms with a healthcare professional with expertise in menopause.

Research recommendations

The committee also discussed that the available evidence on the risk of coronary heart disease and the age and time from menopause when starting HRT was underpowered. They decided to make a research recommendation in this topic (see Appendix K).

The committee decided that it would be important to find out whether previous gender affirming hormone therapy would impact on health outcomes so that trans-men and non-binary people registered female at birth who have had such therapy could be appropriated counselled. They therefore prioritised this topic for a research recommendation (see Appendix K).

They also noted that there was little evidence for people from minority ethnic family backgrounds. They agreed to make research recommendations for these groups to fill this encourage further research. The descriptions of the research recommendations can be found in Appendix K.

The committee discussed that there was no evidence to inform recommendations regarding whether the risk of HRT on coronary heart disease differs depending on the type of progestogen or mode of administration. They decided to make research recommendations for these topics (see Appendix K in Evidence review D).

Cost effectiveness and resource use

No previous economic evidence was identified for this topic, and it was not prioritised for economic modelling.

The recommendations made for this review topic centre around the risk of HRT and cardiovascular disease and stroke. An increase in the use of HRT would likely lead to an increase in overall resource use. Whilst recommendations in this area will potentially lead to

people being better informed about treatment decisions, it is unclear how such information will change the overall use of HRT. It would however be unethical to prevent such information being discussed with people even if it did lead to an increase in resource use through changes in treatment decisions.

Recommendations identifying a decreased risk of stroke from transdermal HRT compared to oral HRT may encourage more people to opt for the transdermal administration. Transdermal administration is approximately double the cost of oral. This risk was highlighted in the previous guideline so people concerned about increased risk will likely already be taking HRT via transdermal patches. This recommendation is therefore unlikely to have a large resource impact.

Other factors the committee took into account

The committee were aware of the following systematic reviews Boardman 2015, Kim 2020 and Salpeter 2006 which did not meet the inclusion criteria of this evidence review due to combining data for participants who received combined HRT and oestrogen-only HRT (Boardman 2015) or the inclusion of studies that did not match the protocol and could therefore not be included as a whole review (Kim 2020 and Salpeter 2006 - the included studies lists of these were checked for any relevant studies and were included). However, the committee did comment on whether the conclusions made from the included evidence base aligned with the findings of these three systematic reviews. Although there were differences observed in certain areas, none of them challenged the overall conclusion that HRT does not increase coronary heart disease.

The committee discussed that in relation to any cardiovascular outcomes an individualised approach should be used and risk factors and approaches to reduce them should be discussed in line with the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.27, 1.5.32, 1.6.2 (except the first bullet point), 1.6.3 (except the first bullet point), 1.6.4 and statements in tables 1 and 2 related to coronary heart disease and stroke and research recommendations 6 (on impact of timing of HRT for menopause-associated symptoms on risk of coronary heart disease), 8 (on health outcomes of HRT for trans men and non-binary people registered female at birth [who are not taking cross-sex hormones as gender-affirming therapy at the time of taking HRT or in the follow-up period]) and 9 (on health outcomes of HRT for people from minority ethnic family backgrounds) in the NICE guideline. The details of the research recommendations are described in appendix K.1.1, K.1.2 and K.1.3.

Research recommendation 2 (on the type of progestogen in HRT and breast, endometrial cancer or cardiovascular disease) and research recommendation 3 (mode of administration) are also relevant to this evidence review. The details of this are described in appendix K of evidence review D.

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Appendices

Appendix A Review protocols

Review protocol for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022362148
1.	Review title	Cardiovascular disease
2.	Review question	What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?
3.	Objective	To update the recommendations in NG23
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE ePub Ahead-of-Print and MEDLINE-in-Process • Epistemonikos • HTA via CRD • INAHTA Searches will be restricted by: • English language • Human studies The full search strategies will be published in the final review.

5.	Condition or domain being studied	Menopause
6.	Population	Women, non-binary, and trans people with menopause (including perimenopause and post-menopause)

7.	Intervention/Exposure/Test	• HRT*
		  ○ Oestrogen-only
		  ○ Combined oestrogen and progestogen
		  - Sequential combined
		  - Continuous combined
		  - Any combined
		* Regulated bioidentical hormones are included but compounded bioidentical hormones are excluded.

8.	Comparator/Reference standard/Confounding factors	• Placebo treatment • No HRT
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs • Observational study designs where data on HRT use are collected before the outcome of interest is known such as prospective cohort studies, nested case-control studies within prospective cohorts, and record linkage studies. Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
10.	Other exclusion criteria	• People with premature ovarian insufficiency • People with early menopause (aged 40 to 44) If any study or systematic review includes <1/3 of women with the above characteristics/ who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness. Observational studies will need to adjust for confounders Relevant confounders may include BMI, family history, lifestyle factors (smoking or alcohol intake), socioeconomic status), previous cardiovascular disease, atrial fibrillation, diabetes, treatment for cardiovascular disease such as statins, stroke, TIA

11.	Context	This guideline will partly update the following: Menopause NG23
12.	Primary outcomes (critical outcomes)	• Coronary heart disease (including myocardial infarction) • Cardiac event composite scores • Mortality (cardiovascular disease related) • Stroke
13.	Secondary outcomes (important outcomes)	TIA
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomised trials • ROBINS-I for non-randomised, controlled/cohort studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software.

		A fixed effect meta-analysis will be conducted, and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: • Mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x control group SD for continuous outcomes How the evidence included in NG23 will be incorporated with the new evidence: Studies meeting the current protocol criteria and previously included in the NG23 will be included in this update. The methods for quantitative analysis (data extraction, risk of bias, strategy for data synthesis, and analysis of subgroups) will be the same as for the new evidence and as outlined in this protocol.
17.	Analysis of sub-groups	Evidence will be stratified (in 2 layers) by: • Recency of HRT use (current users, < 5 years, 5-9 years, ≥ 10 years since last use) by duration of HRT use (<1 year, 1-4 years, 5-9 years, 10-14 years, ≥ 15 years) Additional stratification will be done only for a single specified duration and recency of HRT use (for example: only current HRT users with 5 to 14 years of use) and will only be possible if evidence is reported in this way. Evidence will be stratified by: • Age at first use (45-50 years, 50-59 years, 60-69 years, >69 years) • Time since menopause at first use (<1 year, 1-4 years, 5-9 years, >10 years) • Constituent (equine oestrogen, oestradiol) • Mode of administration (oral, transdermal)

		• Progestogenic constituent (for combined HRT only: (Levo)norgestrel, Norethisterone acetate, Medroxyprogesterone acetate, Micronised progesterone, any synthetic progestin)
		• Length of cycle (for sequential combined HRT only: Sequential long cycle [3 monthly], Sequential 30 day cycle)
		• By surgical menopause (surgical menopause, no surgical menopause)
		• BMI (<18.5, 18.5 to 24.9, ≥25)
		• By factors identified in the equalities section of the scope:
		  ○ Ethnicity (White British, Asian/Asian British, Black/African/Caribbean/Black British, Mixed/Multiple ethnic groups)
		  ○ Disability (disability, no disability)
		  ○ Socioeconomic group (deprived, non-deprived)
		  ○ Non-binary and trans people
		Where evidence is stratified or sub-grouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			

18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	September 2022			
22.	Anticipated completion date	August 2023			
23.		Review stage		Started	Completed

	Stage of review at time of this submission	Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact Guideline development team NGA 5b Named contact e-mail menopause@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
25.	Review team members	• Senior Systematic Reviewer • Systematic Reviewer.		
26.	Funding sources/sponsor	This systematic review is being completed by NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [https://www.nice.org.uk/guidance/ng23].	
29.	Other registration details	None	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=362148	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Menopause, Cardiovascular	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation.

Appendix B Literature search strategies

Literature search strategies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

There was a combined literature search strategies for review questions:

C What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

D What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing breast cancer?

E What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing endometrial cancer?

F What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing ovarian cancer?

G What are the effects of hormone replacement therapy for menopausal symptoms on the risk of developing dementia?

H What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

I What are the effects of hormone replacement therapy taken by women, non-binary and trans people with early menopause (aged 40 to 44) on all-cause mortality and developing:

- **venous thromboembolism**
- **cardiovascular disease**
- **type 2 diabetes**
- **breast cancer**
- **endometrial cancer**
- **ovarian cancer**
- **osteoporosis**
- **dementia**
- **loss of muscle mass and strength?**

Clinical searches

Database: Ovid MEDLINE(R) ALL <1946 to September 30, 2022>

Date of last search: 03/10/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	56226
3	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
4	("change of life" or life change?).ti,ab.	3175
5	or/1-4	117224
6	exp Hormone Replacement Therapy/	26181

#	Searches	
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
9	exp *Estrogens/	97369
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
11	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	8328
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
14	or/6-13	300800
15	5 and 14	38439
16	exp Breast Neoplasms/	331829
17	exp "Neoplasms, Ductal, Lobular, and Medullary"/	45099
18	exp breast/ and exp neoplasms/	31705
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	412638
20	exp uterine neoplasms/	143954
21	Endometrial Hyperplasia/	3751
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	71639
23	exp Ovarian Neoplasms/	92941
24	Fallopian Tube Neoplasms/	3090
25	Peritoneal Neoplasms/	16848
26	Pelvic Neoplasms/	7356
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	134115
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	18696
29	exp Dementia/	195885
30	(amentia* or dementia* or lewy body).ti,ab.	131539
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	172723
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	212540
33	Death/ or exp Mortality/	438343
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	2676396
35	exp Cardiovascular Diseases/	2652417
36	exp Stroke/	164004
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	265024
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	391497
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	237740
40	(stroke or strokes).ti,ab.	293720
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	177232
42	TIA.ti,ab.	9584
43	(myocardial adj2 infarct*).ti,ab.	215115
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	85723
45	atrial flutter*.ti,ab.	6330
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	150990
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	23385

#	Searches	
48	pulmonary embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or upper extremity deep vein thrombosis/	98814
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	110885
50	exp osteoporosis/	61247
51	fractures, bone/ or osteoporotic fractures/	76201
52	exp Bone Remodeling/ or Bone Density/	118506
53	exp radius fractures/ or spinal fractures/ or hip fractures/	45889
54	(osteoporo* or osteop?en*).ti,ab.	91147
55	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	136427
56	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	76474
57	exp Muscle Strength/ or Muscle Contraction/ or Muscle, Skeletal/ or Muscle weakness/	275399
58	exp Muscular Atrophy/	20100
59	(sarcop?en* or dynap?eni*).ti,ab.	12753
60	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	89183
61	exp Diabetes Mellitus, Type 2/	162254
62	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	178683
63	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	3367
64	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1079
65	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	11970
66	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	52630
67	or/16-66	7071734
68	15 and 67	24780
69	animals/ not humans/	5018518
70	exp Animals, Laboratory/	944064
71	exp Animal Experimentation/	10221
72	exp Models, Animal/	633340
73	exp Rodentia/	3486788
74	(rat or rats or mouse or mice).ti.	1413148
75	or/69-74	6058843
76	68 not 75	22173
77	limit 76 to english language	19974
78	Climacteric/	4935
79	Menopause/ or Perimenopause/ or Postmenopause/	56226
80	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
81	("change of life" or life change?).ti,ab.	3175
82	or/78-81	117224
83	exp Hormone Replacement Therapy/	26181
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
86	exp *Estrogens/	97369
87	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
88	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
89	((combin* or sequen* or continu*) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	6337
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
91	or/83-90	300359
92	82 and 91	38419
93	animals/ not humans/	5018518

#	Searches	
94	exp Animals, Laboratory/	944064
95	exp Animal Experimentation/	10221
96	exp Models, Animal/	633340
97	exp Rodentia/	3486788
98	(rat or rats or mouse or mice).ti.	1413148
99	or/93-98	6058843
100	92 not 99	34708
101	limit 100 to english language	30818
102	randomized controlled trial.pt.	578276
103	controlled clinical trial.pt.	95066
104	pragmatic clinical trial.pt.	2153
105	randomi#ed.ab.	690521
106	placebo.ab.	232230
107	randomly.ab.	392671
108	Clinical Trials as topic.sh.	200427
109	trial.ti.	271569
110	or/102-109	1520899
111	COMPARATIVE STUDIES/	1911627
112	FOLLOW-UP STUDIES/	687669
113	TIME FACTORS/	1228326
114	reviewed.tw.	604810
115	prospective$.tw.	826138
116	retrospective$.tw.	951729
117	baseline.tw.	681295
118	cohort.tw.	716940
119	case series.tw.	96297
120	or/111-119	5840666
121	COHORT STUDIES/	319704
122	FOLLOW-UP STUDIES/	687669
123	LONGITUDINAL STUDIES/	160686
124	PROSPECTIVE STUDIES/	640096
125	RETROSPECTIVE STUDIES/	1062925
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	990520
127	(incidence? adj (stud* or research or analys*)).tw.	2167
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	8189
129	(prospective* adj method*).tw.	492
130	(retrospective* adj design*).tw.	2556
131	Case-Control Studies/	323880
132	"nested case control".ti,ab.	10276
133	or/121-132	2937576
134	110 or 120 or 133	7274173
135	101 and 134	16133
136	77 or 135	25292

Database: Embase <1974 to 2022 September 30>

Date of last search: 03/10/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8994

#	Searches	
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
4	("change of life" or life change?).tw.	4281
5	or/1-4	184584
6	exp hormone substitution/	61182
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
9	exp *estrogen/	126164
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
11	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
14	or/6-13	401114
15	5 and 14	58995
16	exp breast tumor/	610160
17	exp medullary carcinoma/	11738
18	exp breast/ and exp neoplasm/	81181
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	580028
20	exp uterus cancer/	178703
21	endometrium hyperplasia/	8475
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	94083
23	exp ovary tumor/	165879
24	uterine tube tumor/	1128
25	exp peritoneum tumor/	32297
26	exp pelvis tumor/	8687
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	189064
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	26375
29	exp dementia/	414481
30	(amentia* or dementia* or lewy body).ti,ab.	188972
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	233156
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	296024
33	death/ or fatality/ or exp mortality/	1565750
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	3638723
35	exp cardiovascular disease/	4653676
36	exp cerebrovascular accident/	278318
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	395575
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	582395
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	388936
40	(stroke or strokes).ti,ab.	467280
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	248980
42	TIA.ti,ab.	21167

#	Searches	
43	(myocardial adj2 infarct*).ti,ab.	308381
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	151993
45	atrial flutter*.ti,ab.	10322
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	225615
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	38407
48	pulmonary embolism/ or lung embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or vein thrombosis/ or upper extremity deep vein thrombosis/	238572
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	173070
50	exp osteoporosis/	144975
51	exp fracture/	333661
52	bone remodeling/ or bone density/	136963
53	(osteoporo* or osteop?en*).ti,ab.	139235
54	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	184524
55	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	105447
56	muscle strength/ or muscle contraction/ or skeletal muscle/ or muscle weakness/	298183
57	exp muscle atrophy/	53010
58	(sarcop?en* or dynap?eni*).ti,ab.	19831
59	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	123477
60	diabetes mellitus/ or non insulin dependent diabetes mellitus/	903538
61	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	274466
62	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	4587
63	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1729
64	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	13941
65	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	87957
66	or/16-65	10247056
67	15 and 66	41567
68	animal/ not human/	1164743
69	nonhuman/	7043049
70	exp Animal Experiment/	2901019
71	exp Experimental Animal/	776639
72	animal model/	1589792
73	exp Rodent/	3873528
74	(rat or rats or mouse or mice).ti.	1563613
75	or/68-74	9201242
76	67 not 75	35048
77	limit 76 to english language	30447
78	climacterium/ or "menopause and climacterium"/	8994
79	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
80	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
81	("change of life" or life change?).tw.	4281
82	or/78-81	184584
83	exp hormone substitution/	61182
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
86	exp *estrogen/	126164
87	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
88	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303

#	Searches	
89	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
91	or/83-90	401114
92	82 and 91	58995
93	animal/ not human/	1164743
94	nonhuman/	7043049
95	exp Animal Experiment/	2901019
96	exp Experimental Animal/	776639
97	animal model/	1589792
98	exp Rodent/	3873528
99	(rat or rats or mouse or mice).ti.	1563613
100	or/93-99	9201242
101	92 not 100	50424
102	limit 101 to english language	43215
103	random*.ti,ab.	1840480
104	factorial*.ti,ab.	44821
105	(crossover* or cross over*).ti,ab.	120165
106	((doubl* or singl*) adj blind*).ti,ab.	261774
107	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1196283
108	crossover procedure/	71600
109	single blind procedure/	47754
110	randomized controlled trial/	730322
111	double blind procedure/	199308
112	or/103-111	2737481
113	CONTROLLED STUDY/	9111478
114	TREATMENT OUTCOME/	935485
115	MAJOR CLINICAL STUDY/	4618747
116	CLINICAL TRIAL/	1046476
117	reviewed.tw.	873307
118	baseline.tw.	1157267
119	(compare$ or compara$).tw.	7021464
120	or/113-119	16140633
121	COHORT ANALYSIS/	901841
122	FOLLOW UP/	1902143
123	LONGITUDINAL STUDY/	179050
124	PROSPECTIVE STUDY/	798586
125	RETROSPECTIVE STUDIES/	1035839
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	1497898
127	(incidence? adj (stud* or research or analys*)).tw.	2924
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	10476
129	(prospective* adj method*).tw.	1417
130	(retrospective* adj design*).tw.	4171
131	case control study/	193429
132	"nested case control".ti,ab.	13700
133	or/121-132	4296161
134	112 or 120 or 133	17894341
135	102 and 134	30379
136	77 or 135	39104
137	(conference abstract or conference paper or conference proceeding or "conference review").pt.	5322870

#	Searches	
138	136 not 137	30760

Database: APA PsycInfo <1806 to September Week 4 2022>

Date of last search: 03/10/2022

#	Searches	
1	menopause/ or life changes/	9242
2	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
3	("change of life" or life change?).ti,ab.	2938
4	or/1-3	15066
5	hormone therapy/	2262
6	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
7	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
8	exp *estrogens/	5657
9	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
10	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
11	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
12	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
13	or/5-12	24383
14	4 and 13	2373
15	breast neoplasms/	11017
16	Breast/ and exp neoplasms/	300
17	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	15213
18	uterus/ and exp neoplasms/	43
19	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	457
20	ovaries/ and exp neoplasms/	444
21	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	1347
22	((epithelial or germ cell) adj5 ovar*).ti,ab.	58
23	exp dementia/ or exp alzheimer's disease/	87977
24	(amentia* or dementia* or lewy body).ti,ab.	72463
25	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	67104
26	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	120339
27	exp "death and dying"/	45080
28	(death or dying or die* or dead or mortality or fatal*).ti,ab.	218375
29	exp Cardiovascular Disorders/ or Cerebrovascular Accidents/	68930
30	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	14620
31	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	16319
32	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	6390
33	(stroke or strokes).ti,ab,mh.	38668
34	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or	14812

#	Searches	
	haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	
35	TIA.ti,ab.	993
36	(myocardial adj2 infarct*).ti,ab.	4538
37	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	1391
38	atrial flutter*.ti,ab.	27
39	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	4960
40	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).mp.	709
41	embolisms/ or thromboses/	1323
42	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	1179
43	osteoporosis/	1165
44	bones/ and (accidents/ or injuries/ or falls/)	117
45	(osteoporo* or osteop?en*).ti,ab.	2275
46	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab,mh.	2050
47	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab,mh.	1936
48	muscle contractions/	2056
49	muscular atrophy/	752
50	(sarcop?en* or dynap?eni*).ti,ab.	357
51	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	5464
52	exp type 2 diabetes/	5494
53	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	9348
54	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	75
55	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	28
56	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	265
57	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	2147
58	or/15-57	522743
59	14 and 58	1116
60	animal.po.	432218
61	(rat or rats or mouse or mice).ti.	123700
62	60 or 61	436853
63	59 not 62	872
64	limit 63 to english language	849
65	menopause/ or life changes/	9242
66	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
67	("change of life" or life change?).ti,ab.	2938
68	or/65-67	15066
69	hormone therapy/	2262
70	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
71	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
72	exp *estrogens/	5657
73	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
74	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
75	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
76	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
77	or/69-76	24383
78	68 and 77	2373
79	animal.po.	432218

#	Searches	
80	(rat or rats or mouse or mice).ti.	123700
81	79 or 80	436853
82	78 not 81	1974
83	limit 82 to english language	1898
84	clinical trial.md.	34832
85	clinical trial.md.	34832
86	Clinical trials/	12104
87	Randomized controlled trials/	913
88	Randomized clinical trials/	383
89	assign*.ti,ab.	106838
90	allocat*.ti,ab.	35101
91	crossover*.ti,ab.	8375
92	cross over*.ti,ab.	3251
93	((doubl* or singl*) adj blind*).ti,ab.	28070
94	factorial*.ti,ab.	21909
95	placebo*.ti,ab.	42984
96	random*.ti,ab.	229145
97	volunteer*.ti,ab.	41704
98	trial?.ti,ab.	203614
99	or/84-98	512268
100	FOLLOWUP STUDY/	0
101	followup study.md.	86839
102	TREATMENT OUTCOMES/	38539
103	treatment outcome.md.	22898
104	CLINICAL TRIALS/	12104
105	clinical trial.md.	34832
106	reviewed.tw.	93954
107	prospective$.tw.	78083
108	retrospective$.tw.	50502
109	baseline.tw.	133530
110	cohort.tw.	81269
111	case series.tw.	4679
112	(compare$ or compara$).tw.	719207
113	or/100-112	1088229
114	COHORT ANALYSIS/	1643
115	LONGITUDINAL STUDIES/ or longitudinal study.md.	188660
116	FOLLOWUP STUDIES/ or followup study.md.	87168
117	PROSPECTIVE STUDIES/ or prospective study.md.	49600
118	RETROSPECTIVE STUDIES/ or retrospective study.md.	34340
119	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	141639
120	(incidence? adj (stud* or research or analys*)).tw.	614
121	(longitudinal* adj1 (survey* or evaluat*)).tw.	5386
122	(prospective* adj method*).tw.	156
123	(retrospective* adj design*).tw.	489
124	or/114-123	307794
125	99 or 113 or 124	1485971
126	83 and 125	1056
127	64 or 126	1411

Database: Cochrane Database of Systematic Reviews (CDSR) Issue 10 of 12, October 2022

Date of last search: 03/10/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1625
3	MeSH descriptor: [Perimenopause] this term only	172
4	MeSH descriptor: [Postmenopause] this term only	4992
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	28112
6	("change of life" or "life change*"):ti,ab	175
7	{or #1-#6}	28696
8	MeSH descriptor: [Hormone Replacement Therapy] explode all trees	3018
9	(hormon* NEAR/2 (replac* or therap* or substitut*)):ti,ab	9032
10	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab	7486
11	MeSH descriptor: [Estrogens] explode all trees	1958
12	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ab	17513
14	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)):ti,ab	2443
15	(("body identical*" or bio-identical* or bioidentical*) NEAR/2 hormon*):ti,ab	29
16	{or #8-#15}	31472
17	#7 AND #16	11025
18	"conference":pt or (clinicaltrials or trialsearch):so	641065
19	#17 NOT #18	8124
20	#19 in Cochrane Reviews	56

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 10 of 12, October 2022

Date of last search: 03/10/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1625
3	MeSH descriptor: [Perimenopause] this term only	172
4	MeSH descriptor: [Postmenopause] this term only	4992
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	28112
6	("change of life" or "life change*"):ti,ab	175
7	{or #1-#6}	28696
8	MeSH descriptor: [Hormone Replacement Therapy] explode all trees	3018
9	(hormon* NEAR/2 (replac* or therap* or substitut*)):ti,ab	9032
10	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab	7486
11	MeSH descriptor: [Estrogens] explode all trees	1958
12	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138
13	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ab	17513
14	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)):ti,ab	2443
15	(("body identical*" or bio-identical* or bioidentical*) NEAR/2 hormon*):ti,ab	29
16	{or #8-#15}	31472
17	#7 AND #16	11025
18	"conference":pt or (clinicaltrials or trialsearch):so	641065
19	#17 NOT #18	8124
20	#19 in Cochrane Reviews	56

#	Searches	
21	#19 in Trials	8053

Database: Epistemonikos

Date of last search: 27/07/2022

#	Searches	
1	(menopau* OR postmenopau* OR perimenopau* OR climacteri* OR "change of life" OR "life change" OR "life changes")	
2	((hormone AND (replac* OR therap* OR substitut*)) OR HRT OR HT OR MHT OR ERT OR EPRT OR SEPRT OR oestrogen* OR estrogen* OR oestradiol* OR estradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR ((combin* OR sequen* OR continu* OR plus) AND (progest* OR gestagen* OR gestogen* OR medroxyprogesterone* OR norgestrel* OR drospirenone* OR norethisterone* OR dydrogesterone* OR levonorgestrel*)) OR (("body identical*" OR bio-identical* OR bioidentical*) AND hormon*))	
3	1 AND 2	7537

Database: HTA via CRD

Date of last search: 03/10/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR Postmenopause	209
5	((menopau* or postmenopau* or perimenopau* or climacteri*))	957
6	(("change of life" or "life change" or "life changes"))	38
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	994
8	MeSH DESCRIPTOR Hormone Replacement Therapy EXPLODE ALL TREES	191
9	((hormon* AND (replac* or therap* or substitut*)))	1577
10	((HRT or HT or MHT or ERT or EPRT or SEPRT))	435
11	MeSH DESCRIPTOR Estrogens EXPLODE ALL TREES	136
12	((oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*))	670
13	(((combin* or sequen* or continu* or plus) AND (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)))	291
14	((("body identical*" or bio-identical* or bioidentical*) AND hormon*))	3
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	2314
16	#7 AND #15	473
17	(#7 AND #15) IN HTA	71

Database: INAHTA

Date of last search: 03/10/2022

#	Searches	
1	"Climacteric"[mh] or "Menopause"[mh] or "Perimenopause"[mh] or "Postmenopause"[mh]	56
2	(menopau* or postmenopau* or perimenopau* or climacteri*)	158
3	("change of life" or "life change" or "life changes")	1
4	#3 OR #2 OR #1	162
5	"Hormone Replacement Therapy"[mhe]	31
6	(hormon* AND (replac* or therap* or substitut*))	161
7	(HRT or HT or MHT or ERT or EPRT or SEPRT)	33
8	"Estrogens"[mhe]	7

#	Searches	
9	(oestrogen* or estrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*)	83
10	((combin* or sequen* or continu* or plus) AND (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*))	16
11	(("body identical*" or bio-identical* or bioidentical*) AND hormon*)	1
12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5	232
13	#12 AND #4	73
14	Limit to English Language	57

Economic searches

Database: Ovid MEDLINE(R) ALL <1946 to July 27, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	55972
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102310
4	("change of life" or life change?).tw.	3141
5	or/1-4	116452
6	limit 5 to english language	103660
7	limit 6 to yr="2012 -Current"	41579
8	letter/	1188475
9	editorial/	613156
10	news/	213557
11	exp historical article/	408665
12	Anecdotes as Topic/	4746
13	comment/	973045
14	case report/	2282504
15	(letter or comment*).ti.	179095
16	or/8-15	4782431
17	randomized controlled trial/ or random*.ti,ab.	1466248
18	16 not 17	4751747
19	animals/ not humans/	4997958
20	exp Animals, Laboratory/	942090
21	exp Animal Experimentation/	10205
22	exp Models, Animal/	631246
23	exp Rodentia/	3472512
24	(rat or rats or mouse or mice).ti.	1407073
25	or/18-24	10620565
26	7 not 25	34368
27	Economics/	27455
28	Value of life/	5793
29	exp "Costs and Cost Analysis"/	259348
30	exp Economics, Hospital/	25612
31	exp Economics, Medical/	14359
32	Economics, Nursing/	4013
33	Economics, Pharmaceutical/	3074
34	exp "Fees and Charges"/	31172
35	exp Budgets/	14034
36	budget*.ti,ab.	33535

#	Searches	
37	cost*.ti.	136425
38	(economic* or pharmaco?economic*).ti.	56592
39	(price* or pricing*).ti,ab.	48567
40	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	191586
41	(financ* or fee or fees).ti,ab.	145674
42	(value adj2 (money or monetary)).ti,ab.	2817
43	or/27-42	689907
44	exp models, economic/	16130
45	*Models, Theoretical/	64214
46	*Models, Organizational/	6490
47	markov chains/	15758
48	monte carlo method/	31445
49	exp Decision Theory/	12940
50	(markov* or monte carlo).ti,ab.	79077
51	econom* model*.ti,ab.	4760
52	(decision* adj2 (tree* or analy* or model*)).ti,ab.	31806
53	or/44-52	210296
54	43 or 53	865352
55	26 and 54	849

Database: Embase <1974 to 2022 July 27>

Date of last search: 28/07/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8930
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	133601
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	147803
4	("change of life" or life change?).tw.	4239
5	or/1-4	183218
6	limit 5 to english language	163179
7	limit 6 to yr="2012 -Current"	81270
8	letter.pt. or letter/	1241876
9	note.pt.	901797
10	editorial.pt.	733613
11	case report/ or case study/	2836641
12	(letter or comment*).ti.	224206
13	or/8-12	5462442
14	randomized controlled trial/ or random*.ti,ab.	1928915
15	13 not 14	5407726
16	animal/ not human/	1159758
17	nonhuman/	6983755
18	exp Animal Experiment/	2874637
19	exp Experimental Animal/	770091
20	animal model/	1570755
21	exp Rodent/	3850325
22	(rat or rats or mouse or mice).ti.	1557060
23	or/15-22	14181910
24	7 not 23	61890
25	health economics/	34559
26	exp economic evaluation/	337213
27	exp health care cost/	322230
28	exp fee/	42496

#	Searches	
29	budget/	32003
30	funding/	67739
31	budget*.ti,ab.	44183
32	cost*.ti.	181970
33	(economic* or pharmaco?economic*).ti.	70774
34	(price* or pricing*).ti,ab.	67140
35	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	264737
36	(financ* or fee or fees).ti,ab.	200470
37	(value adj2 (money or monetary)).ti,ab.	3792
38	or/25-37	1085390
39	statistical model/	171255
40	exp economic aspect/	2251504
41	39 and 40	27469
42	*theoretical model/	30994
43	*nonbiological model/	5065
44	stochastic model/	19388
45	decision theory/	1802
46	decision tree/	18095
47	monte carlo method/	46995
48	(markov* or monte carlo).ti,ab.	87061
49	econom* model*.ti,ab.	7134
50	(decision* adj2 (tree* or analy* or model*)).ti,ab.	43807
51	or/41-50	225433
52	38 or 51	1266430
53	24 and 52	2248

Database: Cochrane Database of Systematic Reviews (CDSR) Issue 7 of 12, July 2022

Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347

#	Searches	
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	#7 and #37 with Cochrane Library publication date Between Jan 2012 and Aug 2022, in Cochrane Reviews	37

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7 of 12, July 2022

Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744

#	Searches	
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	"conference":pt or (clinicaltrials or trialsearch):so	608941
40	#38 not #39 with Publication Year from 2012 to 2022, in Trials	326

Database: EconLit <1886 to July 21, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	0
2	Menopause/ or Perimenopause/ or Postmenopause/ or exp Menopause Related Disorder/	0
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	70
4	("change of life" or life change?).tw.	92
5	or/1-4	162
6	limit 5 to yr="2012 -Current"	69

Database: CRD HTA

Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN HTA FROM 2012 TO 2022	42

Database: INAHTA

Date of last search: 28/07/2022

#	Searches	
1	"Climacteric"[mh]	2
2	"Menopause"[mh]	28
3	"Perimenopause"[mh]	1
4	"Postmenopause"[mh]	31
5	(menopau* or postmenopau* or perimenopau* or climacteri*)	159
6	("change of life" or "life change" or "life changes")	1
7	#6 OR #5 OR #4 OR #3 OR #2 OR #1	163
8	Limit to English Language	134

Database: EED

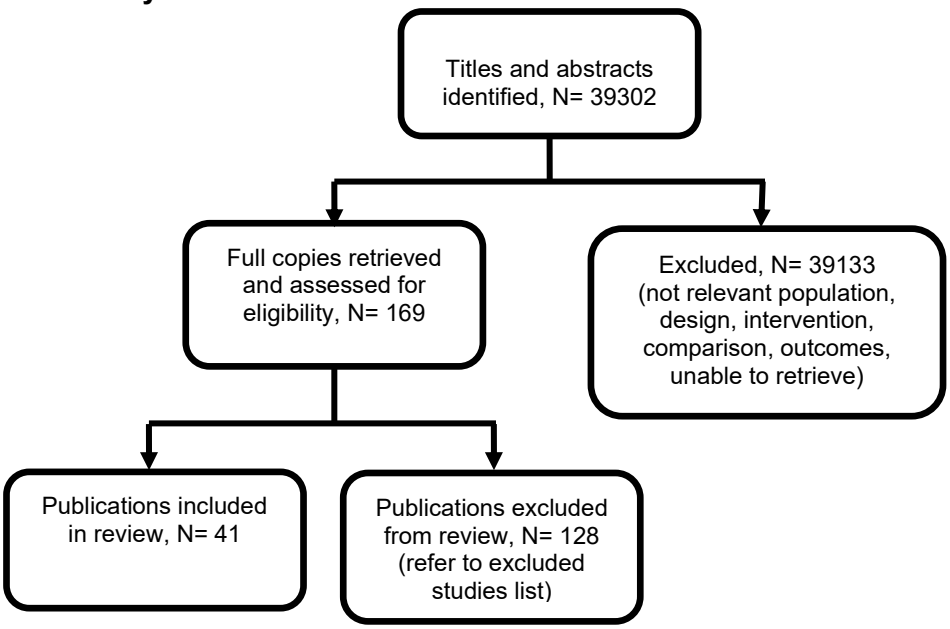
Date of last search: 28/07/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR postmenopause	209
5	(((menopau* or postmenopau* or perimenopau* or climacteri*)))	957
6	((("change of life" or "life change" or "life changes")))	38
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) IN NHSEED FROM 2012 TO 2022	33

Appendix C Effectiveness evidence study selection

Study selection for: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

Table 4: Evidence tables: See Supplement 17 for outcome data (RCTs) and Supplement 18 for outcome data (observational studies)

Anderson, 2004

Bibliographic Reference	Anderson, Garnet L; Limacher, Marian; Assaf, Annlouise R; Bassford, Tamsen; Beresford, Shirley A A; Black, Henry; Bonds, Denise; Brunner, Robert; Brzyski, Robert; Caan, Bette; Chlebowski, Rowan; Curb, David; Gass, Margery; Hays, Jennifer; Heiss, Gerardo; Hendrix, Susan; Howard, Barbara V; Hsia, Judith; Hubbell, Allan; Jackson, Rebecca; Johnson, Karen C; Judd, Howard; Kotchen, Jane Morley; Kuller, Lewis; LaCroix, Andrea Z; Lane, Dorothy; Langer, Robert D; Lasser, Norman; Lewis, Cora E; Manson, JoAnn; Margolis, Karen; Ockene, Judith; O'Sullivan, Mary Jo; Phillips, Lawrence; Prentice, Ross L; Ritenbaugh, Cheryl; Robbins, John; Rossouw, Jacques E; Sarto, Gloria; Stefanick, Marcia L; Van Horn, Linda; Wactawski-Wende, Jean; Wallace, Robert; Wassertheil-Smoller, Sylvia; Women's Health Initiative Steering, Committee; Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial.; JAMA; 2004; vol. 291 (no. 14); 1701-12

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 2004
Inclusion criteria	Women aged 50 to 79 years old at initial screening, had undergone hysterectomy (thereby considered postmenopausal for enrolment purposes), and were likely to reside in the area for 3 years
Exclusion criteria	Exclusions were related to competing risks (any medical condition likely to be associated with a predicted survival of <3 years), safety (e.g., prior breast cancer, other prior cancer within the last 10 years except nonmelanoma skin cancer), adherence and retention concerns (e.g., alcoholism, dementia, and transportation problems), or the clinical judgment of the participant's health care practitioner to continue hormone therapy in symptomatic or osteoporotic women.

Patient characteristics	**Age at screening, mean (SD), years** All participants: 63.6 (7.3) Oestrogen-only (CEE): 63.6 (7.3) Placebo: 63.6 (7.3) **Age group at screening, years, No (%)** **50-59 years** Oestrogen-only (CEE): 1637 (30.8) Placebo: 1673 (30.8) **60-59 years** Oestrogen-only (CEE): 2387 (45) Placebo: 2465 (45.4) **70-79 years** Oestrogen-only (CEE): 1286 (24.2) Placebo: 1291 (23.8) **Body mass index, mean (SD), years** Oestrogen-only (CEE): 30.1 (6.1) Placebo: 30.1 (6.2) **Body mass index, No (%)** **<25** Oestrogen-only (CEE): 1110 (21) Placebo: 1096 (20.3) **25-29 years**

	Oestrogen-only (CEE): 1795 (34) Placebo: 1912 (35.5) **≥30** Oestrogen-only (CEE): 2376 (45) Placebo: 2383 (44.2) **Race/ethnicity, No (%)** **White** Oestrogen-only (CEE): 4007 (75.5) Placebo: 4075 (75.1) **Black** Oestrogen-only (CEE): 782 (14.7) Placebo: 835 (15.4) **Hispanic** Oestrogen-only (CEE): 322 (6.1) Placebo: 333 (6.1) **American Indian** Oestrogen-only (CEE): 41 (0.8) Placebo: 34 (0.6) **Black Asian/Pacific Islander** Oestrogen-only (CEE): 86 (1.6) Placebo: 78 (1.4) **Unknown**

	Oestrogen-only (CEE): 72 (1.4) Placebo: 74 (1.4) **Age at menopause or last menstrual period** Not reported **Hormone use, No (%)** **Never** Oestrogen-only (CEE): 2769 (52.2) Placebo: 2770 (51.1) **Past** Oestrogen-only (CEE): 1871 (35.2) Placebo: 1948 (35.9) **Current** Oestrogen-only (CEE): 669 (12.6) Placebo: 708 (13.0) **Duration of prior hormone use, No (%)** **<5 years** Oestrogen-only (CEE): 1352 (53.2) Placebo: 1412 (53.1) **5-10 years** Oestrogen-only (CEE): 469 (18.5)

	Placebo: 515 (19.4) **≥10 years** Oestrogen-only (CEE): 720 (28.3) Placebo: 732 (27.5) **Medical history – number (%)** **Myocardial infarction** Oestrogen-only (CEE): 165 (3.1) Placebo: 172 (3.2) **Angina** Oestrogen-only (CEE): 308 (5.8) Placebo: 306 (5.7) **CABG/PTCA** Oestrogen-only (CEE): 120 (2.3) Placebo: 114 (2.1) **Stroke** Oestrogen-only (CEE): 76 (1.4) Placebo: 92 (1.7) **DVT or PE** Oestrogen-only (CEE): 87 (1.6) Placebo: 84 (1.5)
Intervention(s)/control	**Oestrogen-only (CEE)** Women received 0.625 mg/d of CEE (Premarin; Wyeth, St Davids, Pa) **Placebo**

	Women received matching placebo **Duration and recency of HRT use** Duration • 6.8 years (mean) Recency • Current users
Duration of follow-up	Study participants were contacted by telephone 6 weeks after randomization to assess symptoms and reinforce adherence. Follow-up contacts by telephone or clinic visit occurred every 6 months.
Sources of funding	The National Heart, Lung, and Blood Institute (NHLBI) funds the WHI program. The NHLBI participated in the design, conduct, and oversight of the trial and reviewed the data and this report. One NHLBI representative serves as a member of the WHI Steering Committee and writing group. Wyeth provided study pills (active and placebo) but had no other role in the study.
Sample size	n=10,739

Study arms

Oestrogen-only (N = 5310)

Placebo (N = 5429)
Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Anonymous, 1995

Bibliographic Reference	Anonymous; Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial.; JAMA; 1995; vol. 273 (no. 3); 199-208

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	December 1989 and February 1991
Inclusion criteria	Women aged 45 to 64 years, with or without a uterus; Women were required to be naturally or surgically menopausal: if naturally menopausal, at least 1 year, but not greater than 10 years, past their last menstrual period; if surgically menopausal, at least 2 months after hysterectomy and with a follicle stimulating hormone level greater than or equal to 40 IU/L. Normal baseline results of mammography and endometrial biopsy also were required.
Exclusion criteria	Women who: had severe menopausal symptoms (to minimize the potential for unblinding), who had used oestrogens or progestins within 3 months, those treated with thyroid hormone who had not been taking a stable dose for at least 3 months and who did not have a normal thyroid stimulating hormone level, women with serious illness (eg, myocardial infarction within 6 months, congestive heart failure, stroke, transient ischemic attack) or contraindications to oestrogen, including prior breast or endometrial cancer
Patient characteristics	**Mean age** (reported for all participants only) 56.1 years **Body size, weight (kg): Mean (SD)** Placebo: 70.2 (3.4) CEE only: 70.1 (1.0) Sequential CEE plus MPA: 69.0 (1.0) Continuous CEE plus MPA: 69.5 (0.9) Sequential CEE plus MP: 68.8 (1.0) **Body side, waist-hip ratio: Mean (SD)**

	Placebo: 0.793 (0.006) CEE only: 0.796(0.006) Sequential CEE plus MPA: 0.784 (0.005) Continuous CEE plus MPA: 0.794 (0.006) Sequential CEE plus MP: 0.786 (0.005) **Ethnicity** (reported for all participants combined only): 89% White, 5% Hispanic, 4% African American, 2% Asian, 0.5% Native American **Age at menopause or last menstrual period** Not reported **Previous use of hormone replacement therapy (HRT)** Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, Stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	All medications were taken orally. Placebo Placebo pills Sequential combined oestrogen and progestogen (CEE plus MPA) CEE, 0.625 mg/d, plus MPA, 10 mg/d for the first 12 days Oestrogen-only (CEE) CEE, 0.625 mg/d

	Sequential combined oestrogen and progestogen (CEE plus MP) CEE, 0.625 mg/d, plus MP, 200 mg/d for the first 12 days Continuous combined oestrogen and progestogen (CEE plus MPA) CEE, 0.625 mg/d, plus MPA 2.5 mg/d **Duration and recency of HRT use** Duration • 3 years Recency • Current users
Duration of follow-up	Women were scheduled to be seen at 3, 6, and 12 months the first year after randomization and thereafter every 6 months for a total of 3 years
Sources of funding	Not reported
Sample size	N=875

Study arms

Sequential CEE plus MPA (N = 174)

Oestrogen-only (CEE) (N = 175)

Placebo (N = 174)

Sequential CEE plus MP (N = 178)

CEE plus MPA (N = 174)

Outcomes. See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (treatment assignment was determined by a computer program that verified all eligibility criteria prior to blocked randomization) and any baseline differences observed between intervention groups appear to be compatible with chance)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate analysis was used to estimate the effect of assignment to intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the*

Section	Question	Answer
		measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data is likely analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis and the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain. Reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Arana, 2006

Bibliographic Reference	Arana, Alejandro; Varas, Cristina; Gonzalez-Perez, Antonio; Gutierrez, Lia; Bjerrum, Lars; Garcia Rodriguez, Luis A; Hormone therapy and cerebrovascular events: a population-based nested case-control study.; Menopause (New York, N.Y.); 2006; vol. 13 (no. 5); 730-6

Study details

Country where study was carried out	UK
Study type	Retrospective cohort study

	Case control study
Study dates	1991-1997
Inclusion criteria	• Women aged 50-69 registered on General Practice Research Database (GPRD)
Exclusion criteria	• History of cardiovascular diseases (coronary heart disease, cerebrovascular disease, and arrhythmias), • Neoplasms • Coagulopathies • Vasculitis • Alcohol-related diseases
Patient characteristics	**Mean age, years** 62 **Body size** Not reported **Body side, waist-hip ratio** Not reported **Ethnicity** Not reported **Age at menopause or last menstrual period** Not reported **Previous use of hormone replacement therapy (HRT)** Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, Stroke, DVT or pulmonary embolism or previous CHD** Not reported

Intervention(s)/control	Intervention • Oestrogen-only (unopposed or opposed) Low, medium, or high dose; low: less than 0.625mg for oral estrogens and 25µg for transdermal estradiol; medium: 0.625mg to 1.24mg for oral estrogens and 50µg for transdermal estradiol; high: 1.25mg or higher for oral estrogens and 100µg for transdermal estradiol Control • No HRT **Duration and recency of HRT use** Duration • Not reported Recency • Current users
Sources of funding	• Novartis
Sample size	N=10920

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal - CASP Critical appraisal checklist for case-control studies - 2.1 cardiovascular

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes

Section	Question	Answer
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age Past use of HT History of smoking Hypertension Diabetes Obesity Hypercholesterolemia Family history of cardiovascular disease Surgical menopause Lipid-lowering drug use Anticoagulant drug use Cardioprophylactic use of aspirin
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes

Section	Question	Answer
(B) What are the results?	7. What are the results of this study?	The study showed no important harms for using HRT (oestrogen alone and oestrogen combined with progestogen) compared to no HRT in the risk of TIAs. Although the estimates favoured no HRT the CI crossed the line of no effect.
(B) What are the results?	8. How precise are the results?	No concerns regarding imprecision.
(B) What are the results?	9. Do you believe the results?	No concerns regarding imprecision and results consistent with those of other studies.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

Bhupathiraju, 2017

Bibliographic Reference	Bhupathiraju, Shilpa N; Grodstein, Francine; Rosner, Bernard A; Stampfer, Meir J; Hu, Frank B; Willett, Walter C; Manson, JoAnn E; Hormone Therapy Use and Risk of Chronic Disease in the Nurses' Health Study: A Comparative Analysis With the Women's Health Initiative.; American journal of epidemiology; 2017; vol. 186 (no. 6); 696-708

Study details

Country where study was carried out	US
Study dates	1980-2002
Inclusion criteria	• Female registered nurses • Included in the analysis if postmenopausal and reached age of 50 years

Exclusion criteria	• Women with diagnosis of cancer • History of cardiovascular disease (for cardiovascular outcomes) • Women who initiated HRT use prior the age of 50 years and after 79 years at time of entry into analysis • Premenopausal women and women with uncertain postmenopausal status
Patient characteristics	**Age (mean, SD- years):** • No HRT and underwent hysterectomy: 55.2 (2.4) • No HRT and have intact uterus: 53.6 (2.6) • HRT (0.625mg/day) and underwent hysterectomy: 55.5 (2.4) • HRT (0.625mg/day + <10mg/day MPA) and intact uterus: 53.4 (2.6) **Body mass index (mean, SD - weight(kg)/height(m)2:** • No HRT and underwent hysterectomy: 26.5 (5.2) • No HRT and have intact uterus: 25.8 (5.1) • HRT (0.625mg/day) and underwent hysterectomy: 25.1 (4.4) • HRT (0.625mg/day + <10mg/day MPA) and intact uterus: 25.0 (4.4) **Ethnicity white, (%)** • No HRT and underwent hysterectomy: 96 • No HRT and have intact uterus: 97 • HRT (0.625mg/day) and underwent hysterectomy: 97 • HRT (0.625mg/day + <10mg/day MPA) and intact uterus: 98 **Age at menopause (mean, SD - years):** • No HRT and underwent hysterectomy: 49.7 (4.4) • No HRT and have intact uterus: 50.6 (3.3) • HRT (0.625mg/day) and underwent hysterectomy: 49.6 (3.9) • HRT (0.625mg/day + <10mg/day MPA) and intact uterus: 51.6 (2.7)

	Previous use of hormone replacement therapy (HRT) Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, Stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	• No HRT and underwent hysterectomy • No HRT and have intact uterus • HRT (0.625mg/day CEE) and underwent hysterectomy • HRT (0.625mg/day CEE + <10mg/day MPA) and intact uterus **Duration and recency of HRT use** Duration • Not reported Recency • Current users
Duration of follow-up	Not reported
Sources of funding	National Institutes of Health
Sample size	N=48385
Other information	NHS trial

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal – ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Authors controlled for confounding factors but not for time-varying confounding)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention groups were clearly defined.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(No deviations apparent, with participants adhering to interventions.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data were available for all participants.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Assessors were aware of intervention received but outcome measures could not have been influenced by knowledge of intervention received.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(No bias in reporting selected outcomes detected.)*
Overall bias	Risk of bias judgement	Moderate *(Moderate risk of bias due to concerns of moderate risk of bias due to confounding and selecting of participants.)*
Overall bias	Directness	Directly applicable

Canonico, 2016

Bibliographic Reference	Canonico, Marianne; Carcaillon, Laure; Plu-Bureau, Genevieve; Oger, Emmanuel; Singh-Manoux, Archana; Tubert-Bitter, Pascale; Elbaz, Alexis; Scarabin, Pierre-Yves; Postmenopausal Hormone Therapy and Risk of Stroke: Impact of the Route of Estrogen Administration and Type of Progestogen.; Stroke; 2016; vol. 47 (no. 7); 1734-41

Study details

Country where study was carried out	France
Study type	Retrospective cohort study
Study dates	January 1st 2009 - December 31st 2011
Inclusion criteria	• Women aged 51 to 62 years • First hospitalisation between January 1st 2009 and December 31st 2011 for a stroke
Exclusion criteria	• Cases identified in aftercare and rehabilitation • Contraindications to HRT • Antithrombotic therapy during 3 months before the event
Patient characteristics	**Age (mean, SD - years):** Cases: 56.7 (2.8) Control: 56.6 (2.7) **Body mass index** Not reported **Ethnicity** Not reported **Age at menopause or last menstrual period** Not reported **Current use of HRT (n, %):** Cases: 194 (6.2) Control: 827 (6.8) **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, Stroke, DVT or pulmonary embolism or previous CHD** Not reported

Intervention(s)/control	HRT: • low: ≤1 mg/d of oral estrogens or <50 µg/d of transdermal estrogens • intermediate: 1.5 mg/d of oral estrogens or 50 µg/d of transdermal estrogens • high: ≥2 mg/d of oral estrogens or >50 µg/d of transdermal estrogens Matched control: • No HRT **Duration and recency of HRT use** Duration • Not reported Recency • Current users
Duration of follow-up	Not reported
Sources of funding	• National Institute of Health and Medical Research (INSERM) • Institute of Research in Public Health (IReSP)
Sample size	N= 15302

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal - CASP Critical appraisal checklist for case-control studies - 2.1 cardiovascular

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age Antidiabetic medication Antihypertensive medication Antidyslipidemia medication Long-term chronic disease
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes

Section	Question	Answer
(B) What are the results?	7. What are the results of this study?	Overall, no important difference between combined HRT use and no HRT use and risk of stroke were found. Important harm was only found for when norpregnane derivatives were used as the progestogen.
(B) What are the results?	8. How precise are the results?	No concerns regarding imprecision.
(B) What are the results?	9. Do you believe the results?	No concerns regarding imprecision and overall results consistent with other studies.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

Cherry, 2002

Bibliographic Reference	Cherry, Nicola; Gilmour, Kyle; Hannaford, Philip; Heagerty, Anthony; Khan, Mohammed Amjed; Kitchener, Henry; McNamee, Roseanne; Elstein, Max; Kay, Clifford; Seif, Mourad; Buckley, Hilary; ESPRIT, team; Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo-controlled trial.; Lancet (London, England); 2002; vol. 360 (no. 9350); 2001-8

Study details

Country where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	1996 to 2000
Inclusion criteria	All women aged 50–69 years admitted to coronary care units or general medical wards in participating hospitals in England and Wales between July 1996, and February, 2000, were eligible for inclusion provided that they met the

	diagnostic criteria for myocardial infarction, they were discharged alive from hospital within 31 days of admission, and they had not had a previous documented myocardial infarction or any other exclusion condition. Myocardial infarction was defined as two or more of: typical chest pain; ST elevation of 0.1 mV or more in at least one standard, or two precordial, leads of a 12-lead ECG; or biochemical marker indicative of myocardial infarction (serum concentrations of creatinine kinase or aspartate transaminase greater than twice the normal laboratory value, or serum troponin concentration greater than the locally defined threshold for myocardial infarction)
Exclusion criteria	Use of HRT or vaginal bleeding in the 12 months before admission; history of breast, ovarian, or endometrial carcinoma; or active thrombophlebitis or a history of deep-vein thrombosis or pulmonary embolism, acute or chronic liver disease, Rotor syndrome, Dubin-Johnson syndrome, or severe renal disease.
Patient characteristics	**Age at admission to hospital (years): Mean (SD)** All participants: 62.6 (NR) Oestrogen-only (Oestradiol valerate): 62.3 (5.2) Placebo: 62.9 (4.9) **BMI (kg/m2): Mean (SD)** Oestrogen-only (Oestradiol valerate): 26.8 (5.1) Placebo: 26.7 (5.3) **Ethnicity (white): No (%)** Oestrogen-only (Oestradiol valerate): 496 (97) Placebo: 489 (97) **Age at last menstrual period (years): Mean (SD)** Oestrogen-only (Oestradiol valerate): 46.3 (5.8) Placebo: 46.6 (5.7)

	Used HRT >12 months before admission Oestrogen-only (Oestradiol valerate): 62 (12) Placebo: 51 (10) **Ever had (no, %)** Angina Oestrogen-only (Oestradiol valerate): 140 (27) Placebo: 136 (27) Stroke Oestrogen-only (Oestradiol valerate): 39 (8) Placebo: 36 (7)
Intervention(s)/control	**Oestrogen-only** Oestradiol valerate 2mg taken orally **Placebo** placebo pill taken orally **Duration and recency of HRT use** Duration • 2 years Recency • Current users
Duration of follow-up	3, 6, 12, and 18 months after study entry and at 24 months after finishing treatment
Sources of funding	The work was funded by the UK National Health Service Research and Development Programme on Cardiovascular Disease and Stroke, which provided funding for recruitment and the initial phases of follow-up. Follow-up was completed

	with funds from the University of Manchester, with additional input from Schering Health Care Limited. Schering AG also funded KG during the final 3 years of the project
Sample size	N=1,017
Other information	N=140 (27%) had hysterectomy in the oestrogen-only group, and N=105 (21%) had hysterectomy in the placebo group

Study arms

Oestrogen-only (Oestradiol) (N = 513)

Placebo (N = 504)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (the trial statistician used a restricted randomisation scheme based on a block size of four to generate a list of treatment allocations) and any baseline differences observed between intervention groups appear to be compatible with chance)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate analysis (intention to treat) was used to estimate the effect of assignment to intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants (no losses to follow-up))*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the*

Section	Question	Answer
		measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Cherry, 2014

Bibliographic Reference	Cherry, N; McNamee, R; Heagerty, A; Kitchener, H; Hannaford, P; Long-term safety of unopposed estrogen used by women surviving myocardial infarction: 14-year follow-up of the ESPRIT randomised controlled trial.; BJOG : an international journal of obstetrics and gynaecology; 2014; vol. 121 (no. 6); 700-705

Study details

Country where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	1996 to 2010

Inclusion criteria	Women aged 50-69 years who had survived a first Myocardial infarction
Exclusion criteria	Women who reported a history of cancer or use of hormone replacement therapy in the previous 12 months
Patient characteristics	Not reported
Intervention(s)/control	**Oestrogen-only** one tablet of oestradiol valerate (2mg; n=513) daily for 2 years **Placebo** placebo tablet (n=504), daily for 2 years **Duration and recency of HRT use** Duration • 2 years Recency • Past users of 14.1 years (mean)
Duration of follow-up	Each subject was followed up through their family physician at 3, 6, 12, 18 and 24 months from date of recruitment. Follow-up for this paper was to 30 June 2012 for mortality (mean follow-up 14.1 years range 12.4-16.0).
Sources of funding	The initial trial was funded by the UK National Health Services Research and Development Programme on Cardiovascular Disease and Stroke though a grant to the University of Manchester. Medication (active and placebo) used as the intervention was supplied without charge by Schering Ag. Additional support came from Schering Health Care Limited. Continued follow-up is supported by the University of Aberdeen. None of the funders have been involved with the collection, analysis and interpretation of data reported here.
Sample size	N=1,017

Study arms

Oestrogen-only (Oestradiol) (N = 513)

Placebo (N = 504)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB v2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (the trial statistician used a restricted randomisation scheme based on a block size of four to generate a list of treatment allocations) and any baseline differences observed between intervention groups appear to be compatible with chance)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate analysis (intention to treat) was used to estimate the effect of assignment to intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results,*

Section	Question	Answer
		from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Chilvers, 2003

Bibliographic Reference	Chilvers, Clair E D; Knibb, Rebecca C; Armstrong, Sarah J; Woods, Kent L; Logan, Richard F A; Post menopausal hormone replacement therapy and risk of acute myocardial infarction--a case control study of women in the East Midlands, UK.; European heart journal; 2003; vol. 24 (no. 24); 2197-205

Study details

Country where study was carried out	UK
Study type	Prospective cohort study
Study dates	April 1st 1995 – December 31st 1998
Inclusion criteria	• Cases of postmenopausal women of European ethnicity • Fatal and non-fatal acute myocardial infarction (AMI)
Exclusion criteria	• Patients with recurrent AMI • Not residential in the East Midlands area • Not European

Patient characteristics	**Age at MI - n (%):** • 35-39: Cases: 15 (3); Control: 30 (3) • 40-44: Cases: 28 (5); Control: 57 (5) • 45-49: Cases: 48 (8); Control: 88 (8) • 50-54: Cases: 77 (14); Control: 156 (14) • 55-59: Cases: 135 (24); Control: 268 (24) • 60-64: Cases: 207 (37); Control: 416 (37) • 65+: Cases: 52 (9); Control: 103 (9) **BMI - n (%):** • Normal weight - baseline: Cases 208 (37); Control: 554 (50) • Underweight: Cases: 20 (4); Control: 35 (3) • Overweight: Cases: 192 (34); Control: 343 (31) • Obese: Cases: 130 (23); Control: 171 (15) • Missing: Cases: 9(2); Control: 15 (1) **Ethnicity** Not reported **Age at menopause or last menstrual period** Not reported **Previous use of HRT** Not reported **Family history of MI in any family member before age 60 – n (%):** • No - baseline: Cases 289 (52); Control: 810 (73) • Yes: Cases: 251 (45); Control: 282 (25) • Missing: Cases: 19(3); Control: 26 (2)
Intervention(s)/control	**Intervention**

	• Oestrogen-only • Oestrogen + Progeston **Control** • No HRT **Duration and recency of HRT use** Duration • NR Recency • Current and past users
Duration of follow-up	Not reported
Sources of funding	NHS R&D Programme on Cardiovascular Disease and Stroke
Sample size	N= 1677

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal - CASP Critical appraisal checklist for case-control studies - 2.1 cardiovascular

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes

Section	Question	Answer
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	History of diabetes, history of hypertension, smoking (cigarette years of exposure), frequency of alcohol consumption, social class, health-conscious behaviour score, family history of heart disease/stroke in either a parent and/or a sibling before the age of 60, body mass index, cholesterol level, previous hysterectomy and amount of energetic activity per week.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	Important benefits were only found for combined HRT compared to no HRT in risk of developing coronary heart disease when treatment was over 5 years of duration. No other important differences were found.
(B) What are the results?	8. How precise are the results?	No concern regarding imprecision.
(B) What are the results?	9. Do you believe the results?	No concern regarding imprecision and results are consistent with previous results.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes

Section	Question	Answer
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

Collins, 2006

Bibliographic Reference	Collins, Peter; Flather, Marcus; Lees, Belinda; Mister, Rebecca; Proudler, Anthony J; Stevenson, John C; WHISP (Women's Hormone Intervention Secondary Prevention Study) Pilot Study, Investigators; Randomized trial of effects of continuous combined HRT on markers of lipids and coagulation in women with acute coronary syndromes: WHISP Pilot Study.; European heart journal; 2006; vol. 27 (no. 17); 2046-53

Study details

Country where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	October 1999 and October 2001
Inclusion criteria	Post-menopausal women (amenorrhoea for >12 months or women with hysterectomy >12 months oestrogen deficiency symptoms or aged >55 years) >48 h and <28 days after admission with ACS (MI or unstable angina), plus at least one of the following: Elevated cardiac enzymes (CK or AST twice upper limit or CKMB or troponin above the threshold considered diagnostic for myocardial damage in that centre); Changes on the electrocardiogram (ECG) supportive of a diagnosis of acute myocardial ischaemia; Prior history of CHD documented by history of prior MI or prior revascularization or angiography showing >50% stenosis in at least one major epicardial coronary artery; Provision of written informed consent
Exclusion criteria	Women for whom the diagnosis of ACS is not confirmed at the time they are considered for randomization, Use of HRT currently or within the previous 12 months (except for vaginal oestrogen use), Patients for whom there are clear indications for, or contraindications to, long-term HRT Increased risk of thrombo-embolism, Prior history of deep venous thrombosis or pulmonary embolus, BMI >32 kg/m2, Prolonged immobility or bed rest, Known breast or endometrial cancer, post-menopausal bleeding that has not been adequately investigated prior to the start of the study, Presence of non-cardiac condition influencing survival

Patient characteristics	**Age at randomisation (years): mean (SD)** Combined Oestrogen and progestogen (Oestradiol plus NETA): 69.4 (8.6) Placebo: 68.3 (9.0) **BMI (kg/m2): mean (SD)** Combined Oestrogen and progestogen (Oestradiol plus NETA): 26 (3.9) Placebo: 26.4 (4.7) **Ethnicity** Not reported **Time since menopause: years** Combined Oestrogen and progestogen (Oestradiol plus NETA): 21.6 Placebo: 23.9 **Time from onset of symptoms to randomization: days** Combined Oestrogen and progestogen (Oestradiol plus NETA): 4 Placebo: 4 **Previous use of hormone replacement therapy (HRT)** Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, Stroke, DVT or pulmonary embolism, or previous CHD** Not reported
Intervention(s)/control	**Combined Oestrogen and progestogen (Oestradiol plus NETA)** • continuous combined oral oestradiol-17b 1 mg and oral norethisterone acetate (NETA) 0.5 mg daily (KliovanceTM, Novo Nordisk) **Placebo** • Placebo pills **Duration and recency of HRT use**

	Duration • 1 year Recency • Current users
Duration of follow-up	12 months.
Sources of funding	The UK Medical Research Council provided a grant to support the study (Grant G9811667). Novo Nordisk provided funding for laboratory analyses and also provided the study drug.
Sample size	N=100
Other information	At the start of the study, eligibility criteria restricted enrolment to postmenopausal women with a confirmed myocardial infarction (MI) between 2 and 7 days of presentation, but after 34 patients had been enrolled, eligibility was extended to include patients with on-ST elevation acute coronary syndrome up to 28 days after presentation. The main reason for modifying eligibility part way through the study was to improve enrolment.

Study arms

Oestradiol plus NETA (N = 49)

Placebo (N = 51)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (telephone call to the co-ordinating centre, stratified by blocks of four) and any*

Section	Question	Answer
		baseline differences observed between intervention groups appear to be compatible with chance)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(It is unclear whether carers or people delivering the interventions were aware of intervention groups during the trial and there is no information on whether there were deviations from intended intervention because of the trial context. It is unclear whether an appropriate analysis was used to estimate the effect of assignment to intervention (although it appears as though this may be an intention to treat analysis) and the potential impact (on the estimated effect of intervention) of the failure to analyse participants in the group to which they were randomized was not substantial.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Outcome data were not available for all, or nearly all, randomized participants and there is a significant difference between the number of participants lost to follow-up between treatment groups (n=13 in HRT group, and n=6 in placebo group. There is no evidence that the result was not biased by missing outcome data. Missingness in the outcome could depend on its true value and it is likely that missingness in the outcome depended on its true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The method of measuring the outcome was not inappropriate and the measurement or ascertainment of the outcome did not appear to differ between intervention groups. The assessment of the outcome could have been influenced by knowledge of the intervention received however it is unlikely that assessment of the outcome was influenced by knowledge of intervention received)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were likely analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are*

Section	Question	Answer
		unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)
Overall bias and directness	Risk of bias judgement	High *(The study was judged to be at high risk of bias due to missing outcome data and had some concerns of bias due to deviations from the intended interventions (effect of assignment to intervention and effect of adhering to intervention), and in the measurement of the outcomes.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Ferrara, 2003

Bibliographic Reference	Ferrara A; Quesenberry CP; Karter AJ; Njoroge CW; Jacobson AS; Selby JV; ; Current use of unopposed estrogen and estrogen plus progestin and the risk of acute myocardial infarction among women with diabetes: the Northern California Kaiser Permanente Diabetes Registry, 1995-1998.; Circulation; 2003; vol. 107 (no. 1)

Study details

Country where study was carried out	US
Study type	Prospective cohort study
Study dates	1995-1998
Inclusion criteria	• Diabetic women aged 50 years and older
Patient characteristics	**Age - years (%):** • 50-59: No HRT: 28.1; Estrogen only: 42.2; Estrogen + Progestin: 57.5

	• 60-69: No HRT: 36.1; Estrogen only: 38.3; Estrogen + Progestin: 32.5 • >70: No HRT: 35.8; Estrogen only: 19.5; Estrogen + Progestin: 10.0 **BMI - kg/m2 (%):** • <27: No HRT: 29.6; Estrogen only: 26.0; Estrogen + Progestin: 30.4 • 27-31.9: No HRT: 26.0; Estrogen only: 28.8; Estrogen + Progestin: 24.9 • >32: No HRT: 29; Estrogen only: 32.5; Estrogen + Progestin: 32.6 • Unkown: No HRT: 15.4; Estrogen only: 12.7; Estrogen + Progestin: 12.1 **Ethnicity - (%):** • Non-Hispanic white: No HRT: 55.5; Estrogen only: 63.6; Estrogen + Progestin: 63.6 • African-American: No HRT: 14.2; Estrogen only: 11.3; Estrogen + Progestin: 6.8 • Hispanic: No HRT: 8.3; Estrogen only: 8.4; Estrogen + Progestin: 7.3 • Asian/Pacific Islander: No HRT: 11.2; Estrogen only: 6.3; Estrogen + Progestin: 11.5 • Other/unknown: No HRT: 10.8; Estrogen only: 10.4; Estrogen + Progestin: 10.8 **Age at menopause of last menstrual period** Not reported **Previous use of hormone replacement therapy (HRT)** Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, Stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	Intervention • Estrogen only (unopposed estrogen) • Estrogen + Progestin

	Current estrogen dose at a given point of time was classified as follows: low dose: <0.625 mg of oral estrogens or <0.02 mg of estradiol; medium dose: 0.625 mg of oral estrogens or 0.05 mg of estradiol; or high dose: >0.625 mg of oral estrogens or 0.1 mg of estradiol Control • No HRT **Duration and recency of HRT use** Duration • NR Recency • Current users
Duration of follow-up	Max 3 years
Sources of funding	• American Heart Association Western States Affiliate • Kaiser Foundation Research Institute
Sample size	N= 25000
Other information	

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal – ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Confounders were controlled for except time-varying confounders.)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Participants were not selected on characteristics observed after starting the intervention and start and follow-up times were similar across participants.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention groups clearly defined.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(No deviations apparent.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Outcomes available for all participants.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Assessors aware of intervention received however outcome measured could not have been influenced by knowledge of intervention received.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Low risk of bias detected in selection of the reported results.)*
Overall bias	Risk of bias judgement	Low *(Low risk of bias in all domains except for moderate risk of bias due to confounding as time-varying confounding not controlled for.)*
Overall bias	Risk of bias variation across outcomes	
Overall bias	Directness	Directly applicable

Grady, 2002

Bibliographic Reference	Grady, Deborah; Herrington, David; Bittner, Vera; Blumenthal, Roger; Davidson, Michael; Hlatky, Mark; Hsia, Judith; Hulley, Stephen; Herd, Alan; Khan, Steven; Newby, L Kristin; Waters, David; Vittinghoff, Eric; Wenger, Nanette; HERS Research,

Group; Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II).; JAMA; 2002; vol. 288 (no. 1); 49-57

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	End of trial, August 1998
Inclusion criteria	Postmenopausal women younger than 80 years with no prior hysterectomy and a history of at least one of the following: MI, coronary artery bypass graft surgery, percutaneous angioplasty, or more than 50% angiographic narrowing of a coronary artery
Exclusion criteria	Not reported
Patient characteristics	**Age, mean (SD), years** HERS CEE plus MPA: 67 (7) Placebo: 67 (7) HERS II CEE plus MPA: 67 (7) Placebo: 67 (7) **Body mass index, mean (SD), kg/m2** HERS CEE plus MPA: 29 (6) Placebo: 29 (6) HERS II CEE plus MPA: 29 (5) Placebo: 29 (5)

	Ethnicity White (%) HERS CEE plus MPA: 88 Placebo: 90 HERS II CEE plus MPA: 89 Placebo: 91 **Time since last menstrual period, mean (SD), years** HERS CEE plus MPA: 18 (8) Placebo: 18 (8) HERS II CEE plus MPA: 18 (8) Placebo: 18 (8) **Previous use of hormone replacement therapy** Not reported **Coronary heart disease manifestations, %** Myocardial infarction HERS CEE plus MPA: 50 Placebo: 52 HERS II CEE plus MPA: 50 Placebo: 51 **Percutaneous coronary revascularization** HERS

	CEE plus MPA: 43 Placebo: 43 HERS II CEE plus MPA: 45 Placebo: 42 **Coronary artery bypass graft surgery** HERS CEE plus MPA: 41 Placebo: 41 HERS II CEE plus MPA: 41 Placebo: 40 **Signs of congestive heart failure** HERS CEE plus MPA: 13 Placebo: 12 HERS II CEE plus MPA: 11 Placebo: 10
Intervention(s)/control	Combined oestrogen and progestogen (CEE plus MPA) • Continuous 0.625 mg/d of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate Placebo • Identical placebo

	Duration and recency of HRT use Duration • 4.1 years (HERS I) • 6.8 years (HERS I and II) Recency • Current users
Duration of follow-up	6.8 years
Sources of funding	This research was supported by the office of rural Health Policy of the US Public Health Service
Sample size	N=2,763

Study arms

CEE plus MPA (N = 1380)

Placebo (N = 1383)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computer generated random numbers were logged and assigned by each centre) and any baseline differences observed between intervention groups appear to be compatible with chance.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Grodstein, 2006

Bibliographic Reference	Grodstein, Francine; Manson, Joann E; Stampfer, Meir J; Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation.; Journal of women's health (2002); 2006; vol. 15 (no. 1); 35-44

Study details

Country where study was carried out	US
Study type	Retrospective cohort study
Study dates	1976-June 2000
Inclusion criteria	Postmenopausal women
Exclusion criteria	Women who reported: • stroke • myocardial infarction • angina • coronary revascularization • cancer (except nonmelanoma skin cancer)
Patient characteristics	Not reported
Intervention(s)/control	Intervention • Estrogen only • Estrogen + Progestin Control • No HRT **Duration and recency of HRT use** Duration • Not reported Recency • Current users

Duration of follow-up	24 years
Sources of funding	National Institute of Health
Sample size	N=754150
Other information	NHS study

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal – ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Some risk of bias due to lack of control of time varying confounding.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the intervention started. Follow-up and start time were similar for most participants.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention groups were clearly defined and recorded at start of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(No deviations detected.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Outcome data were available for all participants.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Assessors were aware of interventions received but outcome measures could not be influence by knowledge of intervention received.)*

Section	Question	Answer
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(No bias in selection of reported results detected.)*
Overall bias	Risk of bias judgement	Low *(Low risk of bias in all domains except bias due to confounding. Moderate bias due to confounding only detected as time-varying confounding were not controlled for.)*
Overall bias	Directness	Directly applicable

Grodstein, 2008

Bibliographic Reference	Grodstein, Francine; Manson, JoAnn E; Stampfer, Meir J; Rexrode, Kathryn; Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy.; Archives of internal medicine; 2008; vol. 168 (no. 8); 861-6

Study details

Country where study was carried out	US
Study type	Retrospective cohort study
Study dates	1976-2004
Inclusion criteria	• Women who began hormone use within 4 years of menopause
Exclusion criteria	Women who reported: • stroke • myocardial infarction • angina • coronary revascularization

	• cancer (except nonmelanoma skin cancer)
Patient characteristics	Not reported
Intervention(s)/control	Intervention • Estrogen only • Estrogen + Progestin Control • No HRT **Duration and recency of HRT use** Duration • Not reported Recency • Current users
Duration of follow-up	28 years
Sources of funding	• National Institute of Health • Manson and Rexrode
Sample size	N= 895616
Other information	NHS study

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal – ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Some risk of bias due to lack of control of time varying confounding.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Selection of participants was not based on characteristics observed after the intervention started. Follow-up and start time were similar for most participants.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention groups were clearly defined and recorded at start of intervention.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(No deviations detected.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Outcome data were available for all participants.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Assessors were aware of interventions received but outcome measures could not be influence by knowledge of intervention received.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(No bias in selection of reported results detected.)*
Overall bias	Risk of bias judgement	Low *(Low risk of bias in all domains except bias due to confounding. Moderate bias due to confounding only detected as time-varying confounding were not controlled for.)*
Overall bias	Directness	Directly applicable

Hall, 1998

Bibliographic Reference	Hall, G; Pripp, U; Schenck-Gustafsson, K; Landgren, B M; Long-term effects of hormone replacement therapy on symptoms of angina pectoris, quality of life and compliance in women with coronary artery disease.; Maturitas; 1998; vol. 28 (no. 3); 235-42

Study details

Country where study was carried out	Sweden
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Postmenopausal women with coronary artery disease aged 44–75 years
Exclusion criteria	Not reported
Patient characteristics	**Age (years): Mean (SD)** Transdermal: 58.6 (6.3) Placebo: 61.3 (7.0) Oral: 58.3 (6.5) All participants: 59.4 (6.7) **BMI: Mean (SD)** Transdermal: 26.8 (4.9) Placebo: 27.7 (5.2) Oral: 26.0 (4.6) Total: 25.9 (4.9) **Ethnicity** Not reported **Years after menopause: Mean (SD)** Transdermal: 9.3 (5.9)

	Placebo: 13.3 (7.8) Oral: 11.6 (6.7) Total: 11.4 (6.9) **Previous use of hormone replacement therapy** Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	Group one: Transdermal Transdermal 17b estradiol at a dose of 50 ug per 24 h alone, for 18 days (Estraderm®, Ciba– Geigy, Basel, Switzerland) followed by 10 days of combined treatment with transdermal estradiol and medroxy-progesterone acetate (MPA) (Provera®, Syntex US) 5 mg orally Group two: Placebo Transdermal placebo for 18 days followed by 10 days of combined placebo treatment with tablets. Group three: Oral Conjugated estrogens (CEE) orally for 18 days (Premarina®, Wyeth, Ayerst, Philadelphia) at a dose of 0.625 mg followed by a combined treatment with MPA at a dose of 5 mg daily for 10 days **Duration and recency of HRT use** Duration • 1 year Recency • Current users

Duration of follow-up	Clinical evaluations were performed at baseline and after 3, 6 and 12 months of treatment and 4–6 weeks after completion of treatment
Sources of funding	This study was performed with grants from the Swedish Heart and Lung Foundation, the Swedish Medical Research Council (grant No. 11654) and Ciba Geigy, Switzerland. Thanks are due to Ulrika Rosenberg.
Sample size	N=60

Study arms

Transdermal Oestradiol (N = 20)

Placebo (N = 20)

CEE plus MPA (N = 20)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(There is no information about concealment of the allocation sequence, or randomisation and baseline differences between intervention groups suggest a problem with the randomisation process)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	High *(it is unclear whether participants, carers and people delivering the interventions were unaware of intervention groups during the trial, nor whether study participants adhered to the assigned intervention regimen, and it is unclear whether an appropriate analysis was used to estimate the effect of adhering to intervention.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Outcome data were not available for all, or nearly all, randomized participants and there is no evidence that the result was not biased by missing outcome data. Missingness in the outcome could depend on its true value however it is not likely that missingness in the outcome depended on its true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The method of measuring the outcome was not inappropriate however there is no information on whether the measurement or ascertainment of the outcome could have differed between intervention groups. It is unlikely that the assessment of the outcome could have been influenced by knowledge of the intervention received.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(There is no information on whether the result being assessed is likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	High *(The study was judged to be at high risk of bias due to the randomisation process and deviations from the intended interventions (effect of assignment to intervention) and some concerns of bias due to deviations from the intended interventions (effect of adhering to intervention), missing outcome data, measurement of the outcomes and in the selection of the reported result.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Harman, 2014

Bibliographic Reference	Harman, S Mitchell; Black, Dennis M; Naftolin, Frederick; Brinton, Eliot A; Budoff, Matthew J; Cedars, Marcelle I; Hopkins, Paul N; Lobo, Rogerio A; Manson, JoAnn E; Merriam, George R; Miller, Virginia M; Neal-Perry, Genevieve; Santoro, Nanette; Taylor, Hugh S; Vittinghoff, Eric; Yan, Mingzhu; Hodis, Howard N; Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial.; Annals of internal medicine; 2014; vol. 161 (no. 4); 249-60

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	2005 to 2008
Inclusion criteria	women aged 42 to 58 years who were between 6 and 36 months from their last menses and had plasma follicle-stimulating hormone levels of 35 IU/L or greater, estradiol (E2) levels less than 147 pmol/L, or both were eligible
Exclusion criteria	Women with a history of clinical CVD, including myocardial infarction, angina, congestive heart failure, stroke, transient ischemic attack, or thromboembolic disease, were excluded
Patient characteristics	**Mean age (SD), years** Placebo: 52.5 (2.5) CEE plus MP: 52.8 (2.6) Transdermal Oestradiol plus MP: 52.7 (2.6) All participants: 52.7 (2.6) **Mean BMI (SD), kg/m2** Placebo: 26.4 (4.3) CEE plus MP: 26 (4.3) Transdermal Oestradiol plus MP: 26 (4.4) Total: 26.2 (4.3) **Ethnicity, n (%)** **White**

	Placebo: 211 (77) CEE plus MP: 177 (77) Transdermal Oestradiol plus MP: 169 (76) Total: 557 (77) **African American** Placebo: 23 (8) CEE plus MP: 17 (7) Transdermal Oestradiol plus MP: 14 (6) Total: 54 (7) **Asian or Hispanic** Placebo: 27 (10) CEE plus MP: 25 (11) Transdermal Oestradiol plus MP: 22 (10) Total: 74 (10) **Other** Placebo: 14 (5) CEE plus MP: 11 (5) Transdermal Oestradiol plus MP: 17 (8) Total: 42 (6) **Age at menopause or last menstrual period** Not reported **Hormone replacement status, n (%)** **Never** Placebo: 223 (81) CEE plus MP: 171 (74) Transdermal Oestradiol plus MP: 181 (82)

	Total: 575 (79) **Past/current** Placebo: 52 (19) CEE plus MP: 59 (26) Transdermal Oestradiol plus MP: 41 (18) Total: 152 (21) M**edical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, Stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	**CEE plus MP** o-CEE (Premarin, Pfizer Pharmaceuticals), 0.45 mg/d plus progesterone capsules (Prometrium, Abbott), 200 mg/d, on days 1 to 12 of each month. Women received placebo patches. **Transdermal Oestradiol plus MP** t-E2 (Climara, Bayer HealthCare), 50 mcg/d (patch replaced weekly) plus progesterone capsules (Prometrium, Abbott), 200 mg/d, on days 1 to 12 of each month. Women received placebo tablets **Placebo** Placebo tablets, patches, and capsules. **Duration and recency of HRT use** Duration • 4 years Recency • Current users
Duration of follow-up	4 years
Sources of funding	The Aurora Foundation provided funding for KEEPS through a grant to the Kronos Longevity Research Institute. Bayer HealthCare and Abbott Pharmaceuticals donated study drugs. Pfizer Pharmaceuticals provided a small grant for post

	hoc assessment of unexpected bleeding. The funding sources had no input into the design or conduct of the study or the writing, review, or approval of this manuscript.
Sample size	N=727

Study arms

CEE plus MP (N = 230)

Transdermal Oestradiol plus MP (N = 222)

Placebo (N = 275)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (KEEPS unblinded officer created the randomisation schema using a random-number generator to create randomly sequenced blocks of 13, stratified by study centre, in a ratio of 4:4:5) and any baseline differences observed between intervention groups appear to be compatible with chance)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Data was not available for all participants but there is evidence from sensitivity analysis that the results were not biased by missing outcome data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(The study has some concerns of bias due to missing outcome data)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Heiss, 2008

Bibliographic Reference	Heiss, G.; Wallace, R.; Anderson, G.L.; Aragaki, A.; Beresford, S.A.A.; Brzyski, R.; Chlebowski, R.T.; Gass, M.; LaCroix, A.; Manson, J.E.; Prentice, R.L.; Rossouw, J.; Stefanick, M.L.; Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin; JAMA; 2008; vol. 299 (no. 9); 1036-1045

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	2002 to 2005
Inclusion criteria	postmenopausal women aged 50 through 79 years with an intact uterus
Exclusion criteria	Not reported
Patient characteristics	**Age at baseline, mean (SD), years** CEE plus MPA: 63.1 (7.1) Placebo: 63.3 (7.1) **Body mass index, No (%)** **<25** CEE plus MPA: 2430 (30.3) Placebo: 2373 (31.1) **25-30** CEE plus MPA: 2826 (35.3) Placebo: 2689 (35.2) **≥30** CEE plus MPA: 2760 (34.4) Placebo: 2568 (33.7) **Race/ethnicity, No (%)** **White** CEE plus MPA: 6788 (84.3)

	Placebo: 6477 (84.4) **Black** CEE plus MPA: 517 (6.4) Placebo: 533 (6.9) **Hispanic** CEE plus MPA: 426 (5.3) Placebo: 385 (5.0) **American Indian** CEE plus MPA: 24 (0.3) Placebo: 27 (0.4) **Asian/Pacific Islander** CEE plus MPA: 180 (2.2) Placebo: 156 (2.0) **Unknown** CEE plus MPA: 117 (1.5) Placebo: 100 (1.3) **Years since menopause** **<5** CEE plus MPA: 1268 (17.4) Placebo: 1167 (16.4) **5-10** CEE plus MPA: 1405 (19.3) Placebo: 1432 (20.1) **10-15** CEE plus MPA: 1545 (21.1)

	Placebo: 1494 (21.0) **≥15** CEE plus MPA: 3066 (42.1) Placebo: 3027 (42.5) **Hormone usage status, No (%)** **Never** CEE plus MPA: 5929 (73.7) Placebo: 5710 (74.4) **Past** CEE plus MPA:1589 (19.7) Placebo: 1492 (19.4) **Current** CEE plus MPA: 530 (6.6) Placebo: 473 (6.2) **Duration of prior hormone use, No (%)** **<5 years** CEE plus MPA: 1468 (69.1) Placebo: 1394 (70.9) **5-10 years** CEE plus MPA: 405 (19.1) Placebo: 329 (16.7) **≥10 years** CEE plus MPA: 250 (11.8) Placebo: 244 (12.4)

	Medical history **Myocardial infarction** CEE plus MPA: 126 (1.6) Placebo: 136 (1.8) **Angina** CEE plus MPA: 290 (3.6) Placebo: 302 (4.0) **Coronary revascularization** CEE plus MPA: 88 (1.1) Placebo: 105 (1.4) **Stroke** CEE plus MPA: 55 (0.7) Placebo: 64 (0.8) **DVT or PE** CEE plus MPA: 74 (0.9) Placebo: 61 (0.8)
Intervention(s)/control	**CEE plus MPA** Continuous 0.625 mg of CEE, and 2.5 mg of MPA (Prempro, Wyeth Ayerst, Philadelphia, Pennsylvania) **Placebo** matching placebo **Duration and recency of HRT use** Duration

	• 5.6 years (mean) Recency • 2.4 years (mean)
Duration of follow-up	Follow-up during a mean of 2.4 years
Sources of funding	The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services
Sample size	N=15,730

Study arms

CEE plus MPA (N = 8052)

Placebo (N = 7678)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Hendrix, 2006

Bibliographic Reference	Hendrix, Susan L; Wassertheil-Smoller, Sylvia; Johnson, Karen C; Howard, Barbara V; Kooperberg, Charles; Rossouw, Jacques E; Trevisan, Maurizio; Aragaki, Aaron; Baird, Alison E; Bray, Paul F; Buring, Julie E; Criqui, Michael H; Herrington, David; Lynch, John K; Rapp, Stephen R; Torner, James; WHI, Investigators; Effects of conjugated equine estrogen on stroke in the Women's Health Initiative.; Circulation; 2006; vol. 113 (no. 20); 2425-34

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 2004
Inclusion criteria	Women aged 50 to 79 years were eligible for the WHI Estrogen Alone trial if they had a hysterectomy, with or without an oophorectomy, had no history of breast cancer ever or of other cancers within the past 10 years (except nonmelanoma skin cancer), had not had a heart attack or stroke within the past 6 months, had a predicted survival of 3 or more years, and planned to remain in the area for at least 3 years
Exclusion criteria	Women with systolic blood pressure (SBP) >200 mm Hg or diastolic blood pressure (DBP) >105 mm Hg were told to see their physician within a predefined period of time depending on level of blood pressure and were not eligible to participate in the study until their blood pressure was under control. Those women who were currently taking hormones were required to have a 3-month washout period before their baseline visit.
Patient characteristics	**Age group at screening, years: No (%)** **50-59 years** Oestrogen-only (CEE): 1637 (30.8) Placebo: 1673 (30.8) **60-69 years** Oestrogen-only (CEE): 2387 (45) Placebo: 2465 (45.4) **70-79 years** Oestrogen-only (CEE): 1286 (24.2) Placebo: 1291 (23.8)

	Mean age (years) for all participants: 63.6 **Body mass index, mean (SD), years** Oestrogen-only (CEE): 30.1 (6.1) Placebo: 30.1 (6.2) **Ethnicity, No (%)** **White** Oestrogen-only (CEE): 4007 (75.5) Placebo: 4075 (75.1) **Black** Oestrogen-only (CEE): 782 (14.7) Placebo: 835 (15.4) **Hispanic** Oestrogen-only (CEE): 322 (6.1) Placebo: 333 (6.1) **American indian** Oestrogen-only (CEE): 41 (0.8) Placebo: 34 (0.6)

	Black Asian/Pacific Islander Oestrogen-only (CEE): 86 (1.6) Placebo: 78 (1.4) **Unknown** Oestrogen-only (CEE): 72 (1.4) Placebo: 74 (1.4) **Age at menopause or last menstrual period** Not reported **Hormone use, No (%)** **Never** Oestrogen-only (CEE): 2769 (52.2) Placebo: 2770 (51.1) **Past** Oestrogen-only (CEE): 1871 (35.2) Placebo: 1948 (35.9) **Current** Oestrogen-only (CEE): 669 (12.6)

	Placebo: 708 (13.0) **Duration of prior hormone use, No (%)** **<5 years** Oestrogen-only (CEE): 1352 (53.2) Placebo: 1412 (53.1) **5-10 years** Oestrogen-only (CEE): 469 (18.5) Placebo: 515 (19.4) **≥10 years** Oestrogen-only (CEE): 720 (28.3) Placebo: 732 (27.5) **History of CVD** Oestrogen-only (CEE): 477 (9.1) Placebo: 469 (8.7) **History of MI** Oestrogen-only (CEE): 165 (3.1) Placebo: 172 (3.2)

	History of stroke Oestrogen-only (CEE): 76 (1.4) Placebo: 92 (1.7) **History of TIA** Oestrogen-only (CEE): 136 (2.6) Placebo: 125 (2.3) **ECG rhythm (atrial fibrillation)** Oestrogen-only (CEE): 5 (0.1) Placebo: 10 (0.2) **LVH (Minnesota code)** Oestrogen-only (CEE): 361 (6.9) Placebo: 371 (7.0) **History of carotid endarterectomy/angioplasty** Oestrogen-only (CEE): 20 (0.4) Placebo: 18 (0.3)
Intervention(s)/control	Oestrogen-only (CEE) • conjugated equine estrogen (CEE) 0.625 mg/d (Premarin) Placebo • matching placebo provided by Wyeth-Ayerst (St. Davids, Pa)

	Duration and recency of HRT use Duration • 7.1 years (mean) Recency • Current users
Duration of follow-up	average follow-up of 7.1 years
Sources of funding	The National Heart, Lung, and Blood Institute (NHLBI) funds the WHI program. The NHLBI participated in the design, conduct, and oversight of the trial and reviewed the data and this report. One NHLBI representative serves as a member of the WHI Steering Committee and writing group. Wyeth-Ayerst Research provided study pills (active and placebo) only and had no involvement in the design or conduct of the trial. The WHI Steering Committee gratefully acknowledges the dedicated efforts of investigators and staff at the WHI Clinical Centers, the WHI Clinical Coordinating Center, and the NHLBI program office (listing available at http:// www.whi.org). Most importantly, we want to recognize the WHI participants for their extraordinary commitment to the WHI program
Sample size	N=10,739

Study arms

Oestrogen-only (CEE) (N = 5310)

Placebo (N = 5429)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence for the WHI trial was adequately concealed and random (centrally computerized randomisation) and any baseline differences observed between intervention groups appear to be compatible with chance).)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias is low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Herrington, 2000

Bibliographic Reference	Herrington, D M; Reboussin, D M; Brosnihan, K B; Sharp, P C; Shumaker, S A; Snyder, T E; Furberg, C D; Kowalchuk, G J; Stuckey, T D; Rogers, W J; Givens, D H; Waters, D; Effects of estrogen replacement on the progression of coronary-artery atherosclerosis.; The New England journal of medicine; 2000; vol. 343 (no. 8); 522-9

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1995 to 1996
Inclusion criteria	postmenopausal women, not currently receiving estrogen-replacement treatment, and had one or more epicardial coronary stenoses of at least 30 percent of the luminal diameter, as measured by quantitative coronary angiography. Postmenopausal status was defined as the presence of one of the following conditions: an age of at least 55 years without natural menses for at least five years; no natural menses for at least one year and a serum follicle-stimulating hormone level of more than 40 IU per liter; documented bilateral oophorectomy; or self-reported bilateral oophorectomy, a follicle-stimulating hormone level of more than 40 IU per liter, and a serum estradiol level of less than 25 pg per milliliter (91.8 pmol per liter)
Exclusion criteria	Women with known or suspected breast or endometrial carcinoma, previous or planned coronary-artery bypass surgery, a history of deep-vein thrombosis or pulmonary embolism, symptomatic gallstones, a serum aspartate aminotransferase level more than 1.5 times the normal value, a triglyceride level of more than 400 mg per deciliter (4.52 mmol per liter) while fasting, a serum creatinine level of more than 2.0 mg per deciliter (176.8 µmol per liter), more than 70 percent stenosis of the left main coronary artery, uncontrolled hypertension, or uncontrolled diabetes.
Patient characteristics	**Age (years): Mean (SD)** CEE alone: 66.3 (7.6) CEE plus MPA: 65.5 (6.5) Placebo: 65.6 (7.3)

	All participants: 65.8 (range, 41.8 to 79.9)
	BMI >27.5 — no. (%)
	CEE alone: 64 (64)
	CEE plus MPA: 57 (56)
	Placebo: 56 (53)
	Ethnicity: No (%)
	White
	CEE alone: 81 (81)
	CEE plus MPA: 87 (84)
	Placebo: 85 (81)
	Black
	CEE alone: 14 (14)
	CEE plus MPA: 15 (14)
	Placebo: 14 (13)
	Other
	CEE alone: 5 (5)
	CEE plus MPA: 2 (2)
	Placebo: 6 (6)
	Years since menopause, Mean (SD)

	CEE alone: 23.2 (8.4) CEE plus MPA: 22.2 (9.4) Placebo: 24.0 (10.4) **Previous use of hormone replacement therapy** Not reported **Cardiac history — no. of subjects (%)** **MI** CEE alone: 48 (48) CEE plus MPA: 43 (41) Placebo: 58 (55) **PTCA** CEE alone: 51 (51) CEE plus MPA: 51 (49) Placebo: 44 (42)
Intervention(s)/control	CEE alone • one tablet containing 0.625 mg of conjugated equine estrogen (Premarin, Wyeth–Ayerst Research, Radnor, Pa.) and a placebo tablet CEE plus MPA • continuous; a tablet containing 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (Prempro, Wyeth–Ayerst) and a placebo tablet

	Placebo • two placebo tablets **Duration and recency of HRT use** Duration • 3.2 years (mean) Recency • Current users
Duration of follow-up	Participants were followed up in the clinic every six months and were contacted by telephone at three-month intervals between clinic visits. The women were followed for a mean (SD) of 3.2 (0.6) years.
Sources of funding	Supported by a grant from the National Heart, Lung, and Blood Institute (U01 HL-45488) and by a National Centre for Research Resources General Clinical Research Center grant (M01 RR07122). Study medications were provided by Wyeth–Ayerst Research
Sample size	N=309
Other information	The 28 women who were taking replacement estrogen at the screening visit were asked to stop for three months before being assigned to treatment

Study arms

CEE plus MPA (N = 104)

CEE alone (N = 100)

Placebo (N = 105)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computerised permuted block randomisation and computer displayed treatment assignment) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and it appears as though an appropriate analysis was used to estimate the effect of assignment to intervention (analyses are described as virtually identical to intention-to-treat analyses).)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was*

Section	Question	Answer
		finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Hodis, 2001

Bibliographic Reference	Hodis, H N; Mack, W J; Lobo, R A; Shoupe, D; Sevanian, A; Mahrer, P R; Selzer, R H; Liu Cr, C R; Liu Ch, C H; Azen, S P; Estrogen in the Prevention of Atherosclerosis Trial Research, Group; Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial.; Annals of internal medicine; 2001; vol. 135 (no. 11); 939-53

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Postmenopausal women (serum estradiol level <73.4 pmol/L [<20 pg/mL]), 45 years of age or older, and had a low-density lipoprotein (LDL) cholesterol level of 3.37 mmol/L or greater (≥130 mg/dL). All women, including those with diabetes mellitus, were included provided that their fasting blood glucose level was less than 11.1 mmol/L (<200 mg/dL).

Exclusion criteria	Women with breast or gynaecologic cancer diagnosed in the past 5 years or if these cancers were identified during screening; if they had previously used HRT for more than 10 years or had used HRT within 1 month of the first screening visit; if they had five or more hot flushes daily that interfered with daily activity and precluded randomisation, diastolic blood pressure greater than 110 mm Hg, untreated thyroid disease, life-threatening disease with a survival prognosis of less than 5 years, total triglyceride level of 4.52 mmol/L or greater ($400 mg/dL), high density lipoprotein (HDL) cholesterol level less than 0.78 mmol/L (,30 mg/dL), or serum creatinine concentration greater than 221 mmol/L (.2.5 mg/dL); or if they were current smokers
Patient characteristics	**Age, years: Mean (SD)** Placebo: 62.1 (7.1) Estradiol: 60.9 (6.7) All participants: 62.2 (range, 46 to 80) **Body mass index, kg/m2: mean (SD)** Placebo: 29 (5.3) Estradiol: 28.7 (5.5) **Ethnicity, n (%)** **White** Placebo: 63 (62) Estradiol: 55 (57) **Black** Placebo: 10 (10) Estradiol: 12 (12) **Hispanic**

	Placebo: 19 (18) Estradiol: 21 (22) **Asian** Placebo: 10 (10) Estradiol: 8 (8) **Other** Placebo: 0 (0) Estradiol: 1 (1) **Age at menopause or last menstrual period** Not reported **Previous use of hormone replacement therapy** Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	Micronized Oestradiol • Unopposed 1mg/d micronised oestradiol Placebo • Placebo

	Duration and recency of HRT use Duration • 2 years Recency • Current users
Duration of follow-up	Participants were followed every month for the first 6 months and every other month thereafter for a total of 2 years
Sources of funding	Mead Johnson Laboratories provided an investigator-initiated grant. Also supported in part by grant R01-AG-18798 from the National Institutes of Health. Mead Johnson Laboratories also supplied the micronized 17b-estradiol and placebo pills. Pharmacia & Upjohn Company provided the medroxyprogesterone acetate, Bristol-Myers Squibb Company provided the pravastatin, Merck & Co., Inc., provided the lovastatin and simvastatin, Parke-Davis provided the atorvastatin, and Novartis Pharmaceuticals Corp. provided the fluvastatin
Sample size	N=222

Study arms

Micronised Oestradiol (N = 111)

Placebo (N = 111)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computer-generated random numbers and sequential assignment of*

Section	Question	Answer
		medication packets) and any baseline differences observed between intervention groups appear to be compatible with chance.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participant)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Hoibraaten, 2000

Bibliographic Reference	Hoibraaten, E; Qvigstad, E; Arnesen, H; Larsen, S; Wickstrom, E; Sandset, P M; Increased risk of recurrent venous thromboembolism during hormone replacement therapy--results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET).; Thrombosis and haemostasis; 2000; vol. 84 (no. 6); 961-7

Study details

Country where study was carried out	Norway
Study type	Randomised controlled trial (RCT)
Study dates	1996 to 1998
Inclusion criteria	postmenopausal women younger than 70 years who had suffered previous DVT or PE. Previous VTE was verified by objective means, i.e., venography or ultrasound in cases of DVT, and lung-scan, helical computed tomography, or angiography in cases of PE. Women (n = 28) were also accepted for the study without objective testing if they had a typical history and had subsequently been treated for VTE. Postmenopausal was defined as no natural menstruation for at least one year
Exclusion criteria	current use or use of anticoagulants within the last three months; familial antithrombin deficiency; any type of malignant diseases including known, suspected or past history of carcinoma of the breast; acute or chronic liver disease or history of liver disease in which liver function tests had failed to return to normal; porphyria, known drug abuse or alcoholism; life expectancy less than two years; or women who had taken part in other clinical trials within 12 weeks before study entry
Patient characteristics	**Age, years: Mean (SD)** HRT: 55.8 (7.0) Placebo: 55.7 (5.9) All participants: 55.8 (NR) **Body mass index, kg/m2: Mean (SD)** HRT: 26.8 (4.3) Placebo: 27.4 (4.0)

	Ethnicity Not reported **Age at menopause or last menstrual period** Not reported **Previous use of hormone replacement therapy** Not reported **Previous/concomitant disease: Number** **Myocardial infarction** HRT: 0 Placebo: 1 **Angina pectoris** HRT: 2 Placebo: 2 **Thromboembolic stroke** HRT: 0 Placebo: 2 **Transient ischemic attack** HRT: 2 Placebo: 2
Intervention(s)/control	HRT • Continuous; 2 mg estradiol plus 1 mg norethisterone acetate (Kliogest®, Novo Nordisk, Gentofte, Denmark) , 1 tablet daily

	Placebo • equal looking placebo tablets **Duration and recency of HRT use** Duration • 1.3 years (mean) Recency • Current users
Duration of follow-up	Mean duration of follow-up in the study was 485 days and 483 days in HRT and placebo allocated women, respectively
Sources of funding	Supported by grants from Novo-Nordisk Pharma, Norway, and Research Forum, Ullevål University Hospital, Oslo, Norway
Sample size	N=140

Study arms

Estradiol plus NETA (N = 71)

Placebo (N = 69)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (participants were allocated to treatment by computer generated 1:1 block*

Section	Question	Answer
		randomization with fixed block sizes of 10) and any baseline differences observed between intervention groups appear to be compatible with chance)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial however it is unclear whether an appropriate analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(it is unclear whether outcome data were available for all, or nearly all, randomized participants, however this appears to be the case. There is no evidence that the result was not biased by missing outcome data, missingness in the outcome could depend on its true value however it is not likely that missingness in the outcome depended on its true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were likely analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data)*
Overall bias and directness	Risk of bias judgement	Some concerns *(The study has some concerns of bias due to deviations from the intended interventions (effect of assignment to intervention and effect of adhering to intervention) and missing outcome data.)*

Section	Question	Answer
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Hsia, 2006

Bibliographic Reference	Hsia, Judith; Langer, Robert D; Manson, Joann E; Kuller, Lewis; Johnson, Karen C; Hendrix, Susan L; Pettinger, Mary; Heckbert, Susan R; Greep, Nancy; Crawford, Sybil; Eaton, Charles B; Kostis, John B; Caralis, Pat; Prentice, Ross; Women's Health Initiative, Investigators; Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative.; Archives of internal medicine; 2006; vol. 166 (no. 3); 357-65

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 2004
Inclusion criteria	postmenopausal women 50 to 79 years of age who had undergone prior hysterectomy
Exclusion criteria	Not reported
Patient characteristics	**Mean (SD) age** – for all participants 63.6 years (7.3 years) **Body mass index** Not reported **Ethnicity** Not reported **Age at menopause or last menstrual period**

	Not reported **Previous use of hormone replacement therapy** Not reported **Medical history (%) – for all participants** Prior myocardial infarction: 3.1% Coronary revascularization: 2.2%
Intervention(s)/control	CEE alone • CEE, 0.625 mg/d (Premarin; Wyeth Pharmaceuticals, Madison, NJ), Placebo • matching placebo. **Duration and recency of HRT use** Duration • 7.1 years (mean) Recency • Current users
Duration of follow-up	Mean duration of follow-up was 7.1 years
Sources of funding	Wyeth Pharmaceuticals provided study pills (active and placebo) but had no other role in the study
Sample size	N=10,739
Other information	The National Institutes of Health decided to stop the trial in February 2004, deeming it unacceptable to subject healthy women in a prevention trial to increased risk of stroke with the possibility that no treatment effect on breast cancer risk would be demonstrated in the remaining intervention period; study participants were informed of this decision on March 1. The initial report of trial results was published 6 weeks later, based on outcomes for which adjudication, either local or central, had been completed as of February 29

Study arms

CEE alone (N = 5310)

Placebo (N = 5429)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Hulley, 1998

Bibliographic Reference	Hulley, S; Grady, D; Bush, T; Furberg, C; Herrington, D; Riggs, B; Vittinghoff, E; Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group.; JAMA; 1998; vol. 280 (no. 7); 605-13

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1998
Inclusion criteria	Postmenopausal women aged <80 years with established coronary disease who had not had a hysterectomy. Postmenopausal was defined as age ≥55 years and no natural menses for at least 5 years or no natural menses or at least 1 year and serum follicle stimulating hormone (FSH) level more than 40IU/L or documented bilateral oophorectomy with FSH level more than 40 IU/L and estradiol level less than 92pmol/L (25pg/mL). Established coronary disease was defined as evidence of 1 or more of the following: MI, coronary artery bypass graft surgery, percutaneous coronary revascularization, or angiographic evidence of at least a 50% occlusion of 1 or more major coronary arteries.
Exclusion criteria	CHD event within 6 months of randomization; serum triglyeride level higher than 3.39 mmol/L (300mg/dL); use of oral, parenteral, vaginal or transdermal sex hormones within 3 months of the screening visit; history of deep vein thrombosis

	of pulmonary embolism; history of breast cancer or breast examination or mammogram suggestive of breast cancer; history of endometrial cancer,; abnormal uterine bleeding, endometrial hyperplasia, or endometrium thickness greater than 5mm on baseline evaluation; abnormal or unobtainable papanicolaou test result; serum aspartate aminotransferese level more than 1.2 times normal; unlikely to remain geographically accessible for study visits for at least 4 years; disease (other than CHD) judged likely to be fatal within 4 years; New York Heart association class IV or severe class III congestive heart failure; alcoholism or other drug abuse; uncontrolled hypertension (diastolic blood pressure ≥105 mm Hg or systolic blood pressure ≥200 mm Hg); uncontrolled diabetes fasting blood glucose level ≥16.7 mmol/L (300 mg/dL); participation in another investigational drug or device study; less than 80% compliance with a placebo run-in prior to randomization; or history of intolerance to hormone therapy,
Patient characteristics	**Age, years: mean (SD)** CEE plus MPA: 67 (7) Placebo: 67 (7) All participants: 67 (7) **Body mass index >27 kg/m2: %** CEE plus MPA: 57 Placebo: 55 **Ethnicity, white: %** CEE plus MPA: 88 Placebo: 90 **Time since last menstrual period, years: mean (SD)** CEE plus MPA: 18 (8) Placebo: 18 (8) **Postmenopausal estrogen use: %** CEE plus MPA: 24 Placebo: 23 **CHD manifestations** **signs of congestive heart failure: %**

	CEE plus MPA: 10 Placebo: 9 **Q-wave myocardial infarction: %** CEE plus MPA: 17 Placebo: 17 **Percutaneous coronary revascularization: %** CEE plus MPA: 45 Placebo: 45 **Coronary artery bypass graft surgery: %** CEE plus MPA: 42 Placebo: 41
Intervention(s)/control	CEE plus MPA • Continuous; 1 tablet daily containing both conjugated equine estrogens, 0.625mg and medroxyprogesterone acetate, 2.5 mg (estrogen plus progestin), Prempro Placebo • 1 placebo tablet of identical appearance **Duration and recency of HRT use** Duration • 4.1 years Recency • Current users
Duration of follow-up	Follow-up every 4 months with a mean follow-up of 4.75 years
Sources of funding	Sponsored by Wyeth-Ayerst Research, Radnor
Sample size	N=2,763

Study arms

CEE plus MPA (N = 1380)

Placebo (N = 1383)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computer generated random numbers were logged and assigned by each centre) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Hulley, 2002

Bibliographic Reference	Hulley, Stephen; Furberg, Curt; Barrett-Connor, Elizabeth; Cauley, Jane; Grady, Deborah; Haskell, William; Knopp, Robert; Lowery, Maureen; Satterfield, Suzanne; Schrott, Helmut; Vittinghoff, Eric; Hunninghake, Donald; HERS Research, Group; Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II).; JAMA; 2002; vol. 288 (no. 1); 58-66

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 2000
Inclusion criteria	Postmenopausal women aged <80 years with established coronary disease who had not had a hysterectomy.

Exclusion criteria	history of deep vein thrombosis or pulmonary embolism, history of breast cancer, endometrial hyperplasia or caner, abnormal papanicolaou (pap) result, any hormone use within the past 3 months, and disease judged likely to be fatal within 4 years
Patient characteristics	**Age, mean (SD), years** All participants: 67 (7) **HERS** CEE plus MPA: 67 (7) Placebo: 67 (7) **HERS II** CEE plus MPA: 67 (7) Placebo: 67 (7) **Body mass index, mean (SD), kg/m2** **HERS** CEE plus MPA: 29 (6) Placebo: 29 (6) **HERS II** CEE plus MPA: 29 (5) Placebo: 29 (5) **Ethnicity White (%)** **HERS**

	CEE plus MPA: 88 Placebo: 90 **HERS II** CEE plus MPA: 89 Placebo: 91 **Age at last menstrual period, mean (SD), years** **HERS** CEE plus MPA: 49 (5) Placebo: 49 (5) **HERS II** CEE plus MPA: 49 (5) Placebo: 49 (5) **Previous use of hormone replacement therapy** Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	CEE plus MPA • Continuous; 0.625 mg/d of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate

	Placebo • Identical placebo **Duration and recency of HRT use** Duration • 4.1 years (HERS I) • 6.8 years (HERS I and II) Recency • Current users
Duration of follow-up	4.1 years duration (HERS) and subsequent open-label observational follow-up for 2.7 years (HERS II)
Sources of funding	Wyeth-Ayerst Research funded the study
Sample size	N=2,763

Study arms

CEE plus MPA (N = 1380)

Placebo (N = 1383)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computer generated random numbers were logged and assigned by each centre) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable

Section	Question	Answer
Overall bias and directness	Risk of bias variation across outcomes	None

Kim, 2006

Bibliographic Reference	Kim J; Evans S; Smeeth L; Pocock S; Hormone replacement therapy and acute myocardial infarction: a large observational study exploring the influence of age.; International journal of epidemiology; 2006; vol. 35 (no. 3)

Study details

Country where study was carried out	UK
Study type	Nested case-control study
Study dates	1987-2001
Inclusion criteria	• Women with a first diagnosis of MI which occurred during the study period • Women selected from the UK General Practice Research Database (GPRD)
Exclusion criteria	• Previous history of MI • History of tibolone use • Topical formulations of HRT use
Patient characteristics	**Age - range, n (for all participants)** • 45-54 years: 174447 • 65+ years: 295280 **Body mass index** Not reported **Ethnicity**

	Not reported **Age at menopause or last menstrual period** Not reported **Previous use of hormone replacement therapy** Not reported **Age at MI - mean (SD), years (for all participants)** • 73 (11)
Intervention(s)/control	Intervention • Estrogen only (unopposed therapy) • Estrogen + Progestin (opposed therapy) Control • No HRT **Duration and recency of HRT use** Duration • Not reported Recency • Current users
Duration of follow-up	14 years
Sources of funding	Not reported
Sample size	N=166 310

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal - CASP Critical appraisal checklist for case-control studies - 2.1 cardiovascular

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Hyperlipidaemia Hypertension Atheroma Diabetes History of angina Smoking Alcohol BMI Aspirin use Cardiovascular drug use

Section	Question	Answer
		Consultation rate Atrial fibrillation Peripheral vascular disease Stroke Heart failure
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	Important benefits for current users of estrogen only and estrogen combined with progestogen compared to no HRT in risk of developing coronary heart disease (including MI). Benefits were present for users where estrogen only was started at age 55-64 and 65-74. Benefits were also present for users where combined HRT was started at age 45-54 and 55-64.
(B) What are the results?	8. How precise are the results?	No concerns regarding imprecision.
(B) What are the results?	9. Do you believe the results?	No concerns regarding imprecision and large number of participants.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

LaCroix, 2011

Bibliographic Reference	LaCroix, Andrea Z; Chlebowski, Rowan T; Manson, JoAnn E; Aragaki, Aaron K; Johnson, Karen C; Martin, Lisa; Margolis, Karen L; Stefanick, Marcia L; Brzyski, Robert; Curb, J David; Howard, Barbara V; Lewis, Cora E; Wactawski-Wende, Jean; WHI, Investigators; Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial.; JAMA; 2011; vol. 305 (no. 13); 1305-14

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	2004 to 2009
Inclusion criteria	Postmenopausal women aged 50 to 79 years; eligible if they had a prior hysterectomy, were not taking hormone therapy, and had an anticipated 3-year survival
Exclusion criteria	prior breast cancer or other cancer within 10 years (except non–melanoma skin cancer), or prior venous thromboembolism (if screened after 1997)
Patient characteristics	**Age group at screening, years, No (%)** **50-59 years** CEE only: 1223 (32.4) Placebo: 1232 (31.9) **60-59 years** CEE only: 1740 (46.1) Placebo: 1799 (46.5) **70-79 years**

	CEE only: 815 (21.6) Placebo: 836 (21.6) **Body mass index, No (%)** **<25** Oestrogen-only (CEE): 785 (20.9) Placebo: 771 (20.1) **25-29 years** Oestrogen-only (CEE): 1289 (34.3) Placebo: 1391 (36.2) **≥30** Oestrogen-only (CEE): 1687 (44.9) Placebo: 1683 (43.8) **Ethnicity, No (%)** **White** Oestrogen-only (CEE): 2945 (78) Placebo: 3001 (77.6) **Black**

	Oestrogen-only (CEE): 514 (13.6) Placebo: 565 (14.6) **Hispanic** Oestrogen-only (CEE): 189 (5.0) Placebo: 181 (4.7) **American Indian** Oestrogen-only (CEE): 31 (0.8) Placebo: 18 (0.5) **Asian/Pacific Islander** Oestrogen-only (CEE): 54 (1.4) Placebo: 49 (1.3) **Unknown** Oestrogen-only (CEE): 45 (1.2) Placebo: 53 (1.4) **Age at menopause or last menstrual period** Not reported **Hormone use, No (%)**

	Never Oestrogen-only (CEE): 1929 (51.1) Placebo: 1916 (49.6) **Past** Oestrogen-only (CEE): 1304 (34.5) Placebo: 1373 (35.5) **Current** Oestrogen-only (CEE): 544 (14.4) Placebo: 575 (14.9) **Duration of hormone therapy use, No (%)** **<5 years** Oestrogen-only (CEE): 960 (51.9) Placebo: 1036 (53.1) **5-10 years** Oestrogen-only (CEE): 348 (18.8) Placebo: 377 (19.3) **≥10 years** Oestrogen-only (CEE): 541 (29.3)

	Placebo: 538 (27.6) **Medical history, No (%)** **Angina** Oestrogen-only (CEE): 243 (6.5) Placebo: 253 (6.6) **CABG or PTCA** Oestrogen-only (CEE): 69 (1.9) Placebo: 70 (1.8) **Stroke** Oestrogen-only (CEE): 51 (1.3) Placebo: 47 (1.2) **DVT or PE** Oestrogen-only (CEE): 65 (1.7) Placebo: 60 (1.6)
Intervention(s)/control	CEE alone • 0.625 mg/d of CEE (Premarin, Wyeth Ayerst, Philadelphia, Pennsylvania) Placebo • matching placebo

	Duration and recency of HRT use Duration • 5.9 years (median) Recency • Current and past users
Duration of follow-up	average follow-up period of 10.7 years
Sources of funding	Wyeth Ayerst donated the study drugs. The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, the National Institutes of Health, and the US Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221
Sample size	N=10,739

Study arms

CEE alone (N = 5310)

Placebo (N = 5429)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline*

Section	Question	Answer
		differences observed between intervention groups appear to be compatible with chance.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Lemaitre, 2006

Bibliographic Reference	Lemaitre, Rozenn N; Weiss, Noel S; Smith, Nicholas L; Psaty, Bruce M; Lumley, Thomas; Larson, Eric B; Heckbert, Susan R; Esterified estrogen and conjugated equine estrogen and the risk of incident myocardial infarction and stroke.; Archives of internal medicine; 2006; vol. 166 (no. 4); 399-404

Study details

Country where study was carried out	US
Study type	Case control study
Study dates	1986-2001
Inclusion criteria	• Postmenopausal female Group Health Cooperative members • Incident of MI between 1986-2001
Exclusion criteria	• MI or stroke a result of complication of a procedure or surgery • Fewer visits than 4 before the index date
Patient characteristics	**Age - mean, years** • EE only: 66.2 • EE + progestin: 62.1 • CEE only: 65.1 • CEE + progestin: 62.2 • Control: 68.6 **Body mass index** Not reported **Ethnicity white, %**

- EE only: 91.8
- EE + progestin: 93.7
- CEE only: 96
- CEE + progestin: 87.8
- Control: 90

Age at menopause or last menstrual period

Not reported

Previous use of hormone replacement therapy

Not reported

Medical history, %

Angina

- EE only: 4.9
- EE + progestin: 1.4
- CEE only: 3.2
- CEE + progestin: 2.5
- Control: 5.6

Congestive heart failure

- EE only: 4.6
- EE + progestin: 1.4
- CEE only: 2.1
- CEE + progestin: 1.5
- Control: 3.1

Intervention(s)/control	Intervention • Conjugated equine estrogen (CEE) either alone or plus progestin • Esterified estrogen (EE) either alone or plus progestin Control • No HRT **Duration and recency of HRT use** Duration • Not reported Recency • Current users
Duration of follow-up	Not reported
Sources of funding	• National Heart, Lung, and Blood Institute, Bethesda, Md • American Heart Association, Dallas, Tex
Sample size	N=4205
Other information	

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal - CASP Critical appraisal checklist for case-control studies - 2.1 cardiovascular

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes

Section	Question	Answer
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age Year Hypertension Diabetes mellitus Angina Current smoking Systolic blood pressure
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	Important benefits were only found for estrogen only HRT (with CEE) compared to no HRT in risk of developing coronary heart disease. No other important differences were found.
(B) What are the results?	8. How precise are the results?	No concerns regarding imprecision.
(B) What are the results?	9. Do you believe the results?	No concerns regarding imprecision and results consistent with other studies.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes

Section	Question	Answer
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

Lokkegaard, 2017

Bibliographic Reference	Lokkegaard, Ellen; Nielsen, Lars Hougaard; Keiding, Niels; Risk of Stroke With Various Types of Menopausal Hormone Therapies: A National Cohort Study.; Stroke; 2017; vol. 48 (no. 8); 2266-2269

Study details

Country where study was carried out	Denmark
Study type	Retrospective cohort study
Study dates	1995-2009
Inclusion criteria	• Women aged 51-70 years
Exclusion criteria	• Currently using oral contraceptives • Registered with a prior diagnosis of cardiovascular disease or cancer in the National Patient Register before inclusion
Patient characteristics	Not reported
Intervention(s)/control	Intervention • Oestrogen-only (oral or transdermal route) • Oestrogen and progesterone (continuous combined, cyclic combined or long-cycle combined by transdermal, oral or vaginal route)

	Squential; cyclic combined progestin type: medroxyprogesterone, norethisterone, cyproterone acetate or levinorgestrel - sequential Continuous; combined progestin type: norethisterone, dienogest, tibolone or raloxifene Long cycle progestin type: not reported Control • No HRT **Duration and recency of HRT use** Duration • Not reported Recency • Current users
Duration of follow-up	Mean 7.9 years
Sources of funding	Not reported
Sample size	N=980,003

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal – ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(All outcomes were adjusted for confounding.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Participants were not selected on characteristics observed following start of interventions and start and follow-up times were similar across participants.)*

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Intervention groups clearly defined.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(No deviations apparent.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(Data available for all participants.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Assessors aware of interventions received however outcome measured could not have been influenced by knowledge of intervention received.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Low risk of bias for selection of the reported results.)*
Overall bias	Risk of bias judgement	Low *(Study rated as low risk of bias in all domains.)*
Overall bias	Directness	Directly applicable

Manson, 2003

Bibliographic Reference	Manson, JoAnn E; Hsia, Judith; Johnson, Karen C; Rossouw, Jacques E; Assaf, Annlouise R; Lasser, Norman L; Trevisan, Maurizio; Black, Henry R; Heckbert, Susan R; Detrano, Robert; Strickland, Ora L; Wong, Nathan D; Crouse, John R; Stein, Evan; Cushman, Mary; Women's Health Initiative, Investigators; Estrogen plus progestin and the risk of coronary heart disease.; The New England journal of medicine; 2003; vol. 349 (no. 6); 523-34

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)

Study dates	Not reported
Inclusion criteria	women were 50 to 79 years of age at the time of initial screening, were postmenopausal, and were likely to be residing in the same geographic area for at least three years. Postmenopausal women with an intact uterus at screening were eligible for the trial of combined estrogen and progestin; women who had undergone hysterectomy were eligible for the trial of estrogen alone.
Exclusion criteria	Not reported
Patient characteristics	**Mean age (SD):** All participants combined: 63.3 (7.1) years **Body mass index** Not reported **Ethnicity** All participants combined: Minority groups: 16% **Age at menopause or last menstrual period** Not reported **Previously used postmenopausal hormone therapy** All participants combined**:** 25% **Previous CHD (myocardial infarction, a coronary revascularization procedure, or both:** All participants combined: 2.4% **Previous CHD, stroke, or transient cerebral ischemia:** All participants combined: 4.4%
Intervention(s)/control	Combined estrogen and progestin • Continuous; one daily tablet containing 0.625 mg of oral conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate (Prempro, Wyeth) Placebo

	• matching placebo **Duration and recency of HRT use** Duration • 5.6 years (mean) Recency • Current users
Duration of follow-up	Follow-up of 5.2 years (planned duration, 8.5 years)
Sources of funding	Supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services
Sample size	N=16,608

Study arms

CEE plus MPA (N = 8506)

Placebo (N = 8102)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Manson, 2013

Bibliographic Reference	Manson, JoAnn E; Chlebowski, Rowan T; Stefanick, Marcia L; Aragaki, Aaron K; Rossouw, Jacques E; Prentice, Ross L; Anderson, Garnet; Howard, Barbara V; Thomson, Cynthia A; LaCroix, Andrea Z; Wactawski-Wende, Jean; Jackson, Rebecca D; Limacher, Marian; Margolis, Karen L; Wassertheil-Smoller, Sylvia; Beresford, Shirley A; Cauley, Jane A; Eaton, Charles B; Gass, Margery; Hsia, Judith; Johnson, Karen C; Kooperberg, Charles; Kuller, Lewis H; Lewis, Cora E; Liu, Simin; Martin, Lisa W; Ockene, Judith K; O'Sullivan, Mary Jo; Powell, Lynda H; Simon, Michael S; Van Horn, Linda; Vitolins, Mara Z; Wallace, Robert B.; Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials; JAMA; 2013; vol. 310 (no. 13); 1353-68

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1998
Inclusion criteria	postmenopausal women aged 50 to 79 years
Exclusion criteria	Not reported
Patient characteristics	**Age at screening, mean (SD), years** CEE plus MPA: 63.2 (7.1) CEE alone: 63.6 (7.3) Placebo: 63.3 (7.1) and 63.6 (7.3) **Body mass index, Median (IQR)** CEE plus MPA: 27.5 (24.2-31.7) Placebo: 27.5 (24.3-31.7) and 29.2 (25.7-33.5) CEE alone: 29.2 (25.7-33.7)

	Ethnicity, No (%)
	White
	CEE plus MPA: 7141 (84)
	Placebo: 6805 (84.0) and 4075 (75.1)
	CEE alone: 4009 (75.5)
	Black
	CEE plus MPA: 548 (6.4)
	Placebo: 574 (7.1) and 835 (15.4)
	CEE alone: 781 (14.7)
	Hispanic
	CEE plus MPA: 471 (5.5)
	Placebo: 415 (5.1) and 332 (6.1)
	CEE alone: 319 (6.0)
	American Indian
	CEE plus MPA: 25 (0.3)
	Placebo: 30 (0.4) and 34 (0.6)
	CEE alone: 41 (0.8)
	Asian/Pacific Islander

	CEE plus MPA: 194 (2.3) Placebo: 169 (2.1) and 78 (1.4) CEE alone: 86 (1.6) **Unknown** CEE plus MPA: 127 (1.5) Placebo: 109 (1.3) and 75 (1.4) CEE alone: 74 (1.4) **Years since menopause, years, No (%)** **<10** CEE plus MPA: 2780 (36.2) Placebo: 2711 (36.1) and 817 (17.6) CEE alone: 827 (18.4) **10-<20** CEE plus MPA:3049 (39.7) Placebo: 2992 (39.9) and 1500 (32.4) CEE alone: 1438 (32.0) **≥20** CEE plus MPA: 1850 (24.1)

	Placebo: 1805 (24.0) and 2319 (50.0) CEE alone: 2230 (49.6) **Hormone use, no (%)** **Never** CEE plus MPA: 6277 (73.8) Placebo: 6022 (74.4) and 2769 (51.0) CEE alone: 2769 (52.2) **Past** CEE plus MPA: 1671 (19.7) Placebo: 1587 (19.6) and 1947 (35.9) CEE alone: 1871 (35.2) **Current** CEE plus MPA: 554 (6.5) Placebo: 490 (6.1) and 709 (13.1) CEE alone: 669 (12.6) **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, stroke, DVT or pulmonary embolism or previous CHD** Not reported

Intervention(s)/control	CEE plus MPA • Continuous; oral CEE (0.625mg/d) plus MPA (2.5 mg/d) (Prempro) CEE alone • oral CEE (0.625 mg/d) alone (Premarin) Placebo • placebo **Duration and recency of HRT use** Duration • 5.6 years (median: combined HRT) and 7.2 years (median: oestrogen-only HRT) Recency • Current and past users
Duration of follow-up	CEE plus MPA trial The cumulative results include a median postintervention follow-up of 8.2 years (IQR, 6.6-8.2 years) and a median cumulative follow-up of 13.2 years (IQR, 10.5-14.2 years) CEE alone trial The cumulative results include a median postintervention follow-up was 6.6 years (IQR, 3.8-6.6 years) and the median cumulative follow-up of13.0 years (IQR, 9.1-14.1 years)
Sources of funding	The Women's Health Initiative is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 321115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. Wyeth-Ayerst donated the study drugs
Sample size	N=27,347

Other information	16,608 women with a uterus were randomized to oral CEE (0.625mg/d) plus MPA (2.5 mg/d) (Prempro) or placebo and 10,739 women with prior hysterectomy were randomized to oral CEE (0.625 mg/d) alone (Premarin) or placebo.

Study arms

CEE plus MPA (N = 8506)

CEE alone (N = 5310)

Placebo (N = 13531)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between*

Section	Question	Answer
		intervention groups and the outcome assessors were unaware of the intervention received by study participants.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Manson, 2017

Bibliographic Reference	Manson, JoAnn E; Aragaki, Aaron K; Rossouw, Jacques E; Anderson, Garnet L; Prentice, Ross L; LaCroix, Andrea Z; Chlebowski, Rowan T; Howard, Barbara V; Thomson, Cynthia A; Margolis, Karen L; Lewis, Cora E; Stefanick, Marcia L; Jackson, Rebecca D; Johnson, Karen C; Martin, Lisa W; Shumaker, Sally A; Espeland, Mark A; Wactawski-Wende, Jean; WHI, Investigators; Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials.; JAMA; 2017; vol. 318 (no. 10); 927-938

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)

Study dates	1993 to 1998
Inclusion criteria	postmenopausal women ages 50 to 79 years
Exclusion criteria	Not reported
Patient characteristics	**Age at screening, mean (SD), years** CEE plus MPA: 63.2 (7.1) CEE alone: 63.6 (7.3) Placebo: 63.3 (7.1) and 63.6 (7.3) **Age group at screening, years, no (%)** **50-59** CEE plus MPA: 2837 (33.4) Placebo: 2683 (33.1) CEE alone: 1639 (30.9) Placebo: 1674 (30.8) **60-69** CEE plus MPA: 3854 (45.3) Placebo: 3655 (45.1) CEE alone: 2386 (44.9) Placebo: 2465 (45.4)

	70-79 CEE plus MPA: 1815 (21.3) Placebo: 1764 (21.8) CEE alone: 1285 (24.2) Placebo: 1290 (23.8) **Body mass index, Median (IQR)** CEE plus MPA: 27.5 (24.2-31.7) Placebo: 27.5 (24.3-31.7) and 29.2 (25.7-33.5) CEE alone: 29.2 (25.7-33.7) **Ethnicity, No (%)** **White** CEE plus MPA: 7141 (84.0) Placebo: 6805 (84.0) CEE alone: 4009 (75.5) Placebo: 4075 (75.1) **Black** CEE plus MPA: 548 (6.4)

	Placebo: 574 (7.1) CEE alone: 781 (14.7) Placebo: 835 (15.4) **Hispanic** CEE plus MPA: 471 (5.5) Placebo: 415 (5.1) CEE alone: 319 (6.0) Placebo: 332 (6.1) **American Indian** CEE plus MPA: 25 (0.3) Placebo: 30 (0.4) CEE alone: 41 (0.8) Placebo: 34 (0.6) **Asian/Pacific Islander** CEE plus MPA: 194 (2.3) Placebo: 169 (2.1) CEE alone: 86 (1.6) Placebo: 78 (1.4) **Unknown**

	CEE plus MPA: 127 (1.5) Placebo: 109 (1.3) CEE alone: 74 (1.4) Placebo: 75 (1.4) **Age at menopause or last menstrual period** Not reported **Hormone use, no (%)** **Never** CEE plus MPA: 6277 (73.8) Placebo: 6022 (74.4) and 2769 (51.0) CEE alone: 2769 (52.2) **Past** CEE plus MPA: 1671 (19.7) Placebo: 1587 (19.6) and 1947 (35.9) CEE alone: 1871 (35.2) **Current** CEE plus MPA: 554 (6.5)

	Placebo: 490 (6.1) and 709 (13.1) CEE alone: 669 (12.6) **Medical history** **Myocardial infarction** CEE plus MPA: 139 (1.6) Placebo: 157 (1.9) CEE alone: 165 (3.1) Placebo: 173 (3.2) **Angina** CEE plus MPA: 318 (3.8) Placebo: 331 (4.1) CEE alone: 402 (7.6) Placebo: 388 (7.2) **CABG or PCI** CEE plus MPA: 95 (1.1) Placebo: 120 (1.5) CEE alone: 120 (2.3)

	Placebo: 114 (2.1) **Stroke** CEE plus MPA: 61 (0.7) Placebo: 77 (1.0) CEE alone: 76 (1.4) Placebo: 92 (1.7) **DVT or pulmonary embolism** CEE plus MPA: 79 (0.9) Placebo: 62 (0.8) CEE alone: 87 (1.6) Placebo: 84 (1.5)
Intervention(s)/control	CEE plus MPA • Continuous; daily oral CEE (0.625 mg) plus MPA (2.5 mg, Prempro) CEE only • daily oral CEE (0.625 mg, Premarin) alone Placebo • placebo **Duration and recency of HRT use** Duration • 5.6 years (median: combined HRT) and 7.2 years (median: oestrogen-only HRT)

	Recency • Current and past users
Duration of follow-up	Postintervention follow-up included deaths through December 31, 2014 (median, 18 years cumulatively)
Sources of funding	The Women's Health Initiative is funded by the NHLBI, NIH, and the US Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. Wyeth Ayerst donated the study drugs.
Sample size	N=27,347
Other information	The CEE plus MPA trial was stopped early (after 5.6 years) due to an increased risk of breast cancer and overall risks exceeding benefits; the CEE-alone trial was stopped after 7.2 years due to an increased risk of stroke. 16,608 women with a uterus were randomized to receive daily oral CEE (0.625 mg) plus MPA (2.5 mg, Prempro) or placebo and 10,739 women with hysterectomy were randomized to receive daily oral CEE (0.625 mg, Premarin) alone or placebo.

Study arms

CEE plus MPA (N = 8506)

CEE alone (N = 5310)

Placebo (N = 13531)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally*

Section	Question	Answer
		computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Nachtigall, 1979

Bibliographic Reference	Nachtigall, L E; Nachtigall, R H; Nachtigall, R D; Beckman, E M; Estrogen replacement therapy II: a prospective study in the relationship to carcinoma and cardiovascular and metabolic problems.; Obstetrics and gynecology; 1979; vol. 54 (no. 1); 74-9

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1956 to 1976 (thereabouts)
Inclusion criteria	female hospitalized patients, patients had to have has their last menstrual period 2 or more years previously, to have never undertaken hormone replacements, to have elevated follicle-stimulating hormone levels >105.5mU by biological assay and to have total urinary oestrogen levels <10ug/dl as measured by the Smith modification of the Brown method
Exclusion criteria	Patients with acute heart disease, hypertension with blood pressure recording of 160/94, any apparent malignancy or a prior hysterectomy.
Patient characteristics	**Mean age, years** Treated group: 55.3 Control group: 54.9 **Weight (in pounds)** Treated group: 132.1 Control group: 134.1 **Ethnicity** **%white** Treated group: 70

	Control group: 69 **%black** Treated group: 30 Control group: 31 **Years since last menstrual period** Treated group: 4.7 Control group: 4.5 **Previous use of hormone replacement therapy** Not reported **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	Treatment group • Conjugated estrogen (Premarin), 2.5mg daily and medroxyprogesterone acetate (provera), 10mg daily for 7 days in each month Control group • Placebo matching the active medications in appearance **Duration and recency of HRT use** Duration • 10 years Recency • Current users

Duration of follow-up	10 years
Sources of funding	Not reported
Sample size	N=168

Study arms

CEE plus MPA (N = 84)

Placebo (N = 84)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(The allocation sequence was not adequately concealed (the research nurse randomly elected which member of each pair would be assigned to treatment or control group).)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(The code was broken 13 times in the treatment group and 17 times in the control group (which was unbalanced between the groups) and meant that participants, carers or people delivering the interventions were likely aware of intervention groups during the trial. These deviations from intended interventions likely arose because of the trial context and were likely to have affected the outcome.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The method of measuring the outcome was not inappropriate and the measurement or ascertainment of the outcome did not appear to differ between intervention groups. It is unlikely that the assessment of the outcome could have been influenced by knowledge of the intervention received and it is unlikely that assessment of the outcome was influenced by knowledge of intervention received.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(There is no information on whether the result being assessed is likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	High *(The study has high risk of bias due to the randomisation process, deviations from the intended interventions (effect of assignment to intervention and effect of adhering to intervention) and some concerns of bias due to measurement of the outcomes and in the selection of the reported result.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Prentice, 2020

Bibliographic Reference	Prentice, Ross L; Aragaki, Aaron K; Chlebowski, Rowan T; Zhao, Shanshan; Anderson, Garnet L; Rossouw, Jacques E; Wallace, Robert; Banack, Hailey; Shadyab, Aladdin H; Qi, Lihong; Snively, Beverly M; Gass, Margery; Manson, JoAnn E; Dual-Outcome Intention-to-Treat Analyses in the Women's Health Initiative Randomized Controlled Hormone Therapy Trials.; American journal of epidemiology; 2020; vol. 189 (no. 9); 972-981

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 2005
Inclusion criteria	postmenopausal women aged 50–79 years
Exclusion criteria	Not reported
Patient characteristics	**Age at screening, mean (SD), years** CEE plus MPA: 63.2 (7.1) CEE alone: 63.6 (7.3) Placebo: 63.3 (7.1) and 63.6 (7.3) **Age group at screening, years, no (%)** **50-59** Continuous; CEE plus MPA: 2837 (33.4) Placebo: 2683 (33.1) CEE alone: 1639 (30.9) Placebo: 1674 (30.8) **60-69** CEE plus MPA: 3854 (45.3)

	Placebo: 3655 (45.1) CEE alone: 2386 (44.9) Placebo: 2465 (45.4) **70-79** CEE plus MPA: 1815 (21.3) Placebo: 1764 (21.8) CEE alone: 1285 (24.2) Placebo: 1290 (23.8) **Body mass index, Median (IQR)** CEE plus MPA: 27.5 (24.2-31.7) Placebo: 27.5 (24.3-31.7) and 29.2 (25.7-33.5) CEE alone: 29.2 (25.7-33.7) **Ethnicity, No (%)** **White** CEE plus MPA: 7141 (84.0) Placebo: 6805 (84.0) CEE alone: 4009 (75.5)

	Placebo: 4075 (75.1) **Black** CEE plus MPA: 548 (6.4) Placebo: 574 (7.1) CEE alone: 781 (14.7) Placebo: 835 (15.4) **Hispanic** CEE plus MPA: 471 (5.5) Placebo: 415 (5.1) CEE alone: 319 (6.0) Placebo: 332 (6.1) **American Indian** CEE plus MPA: 25 (0.3) Placebo: 30 (0.4) CEE alone: 41 (0.8) Placebo: 34 (0.6) **Asian/Pacific Islander** CEE plus MPA: 194 (2.3) Placebo: 169 (2.1)

	CEE alone: 86 (1.6) Placebo: 78 (1.4) **Unknown** CEE plus MPA: 127 (1.5) Placebo: 109 (1.3) CEE alone: 74 (1.4) Placebo: 75 (1.4) **Age at menopause or last menstrual period** Not reported **Hormone use, no (%)** **Never** CEE plus MPA: 6277 (73.8) Placebo: 6022 (74.4) and 2769 (51.0) CEE alone: 2769 (52.2) **Past** CEE plus MPA: 1671 (19.7) Placebo: 1587 (19.6) and 1947 (35.9)

	CEE alone: 1871 (35.2) **Current** CEE plus MPA: 554 (6.5) Placebo: 490 (6.1) and 709 (13.1) CEE alone: 669 (12.6) **Medical history** **Myocardial infarction** CEE plus MPA: 139 (1.6) Placebo: 157 (1.9) and 173 (3.2) CEE alone: 165 (3.1) **Angina** CEE plus MPA: 318 (3.8) Placebo: 331 (4.1) and 388 (7.2) CEE alone: 402 (7.6) **CABG or PCI** CEE plus MPA: 95 (1.1) Placebo: 120 (1.5) and 114 (2.1) CEE alone: 120 (2.3)

	Stroke CEE plus MPA: 61 (0.7) Placebo: 77 (1.0) and 92 (1.7) CEE alone: 76 (1.4) **DVT or pulmonary embolism** CEE plus MPA: 79 (0.9) Placebo: 62 (0.8) and 84 (1.5) CEE alone: 87 (1.6)
Intervention(s)/control	CEE only • CEE at 0.625 mg/day CEE plus MPA • CEE + MPA at 2.5 mg/day Placebo • Placebo **Duration and recency of HRT use** Duration • 5.6 years (median: combined HRT) and 7.2 years (median: oestrogen-only HRT) Recency • Current and past users
Duration of follow-up	Nonfatal and fatal outcomes (the latter including periodic National Death Index matching) occurring through December 31, 2016, are included, resulting in a median of 19.4 years of cumulative follow-up in each trial. Cumulative follow-up is defined as time from randomization to the end of the follow-up period for each participant.

Sources of funding	This work was supported by the National Cancer Institute (grants R01 CA119171 and R01 CA210921) and by the National Heart, Lung and Blood Institute, which supports the infrastructure of the Women's Health Initiative (WHI) (contracts HHSN268201100046C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, HHSN268201600004C, and HHSN271201600004C).
Sample size	N=27,347
Other information	10,739 women with prior hysterectomy were randomized to receive oral CEE at 0.625 mg/day (n = 5,310) or placebo (n = 5,429), and 16,608 women with a uterus were randomized to receive CEE + MPA at 2.5 mg/day (n = 8,506) or placebo (n = 8,102)

Study arms

CEE plus MPA (N = 8506)

Placebo (N = 5310)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Renoux, 2010

Bibliographic Reference	Renoux, Christel; Dell'aniello, Sophie; Garbe, Edeltraut; Suissa, Samy; Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study.; BMJ (Clinical research ed.); 2010; vol. 340; c2519

Study details

Country where study was carried out	Canada
Study type	Case control study
Study dates	January 1987 and 31 October 2006
Inclusion criteria	• Women aged 50-79 years registered with the General Practice Research Database (GPRD)
Exclusion criteria	• Stroke diagnosis before entering the study
Patient characteristics	**Age - mean (SD), years** • Cases: 70.3(7.3) • Controls: 70.3 (7.4) The mean age of cases and controls at the index date was 70 years Body weight status - n: • Obese: Cases - 2434; Control -8113 • Not obese: Cases - 8546; Control - 34143 • Unknown: Cases - 4730; Control - 17702 **Ethnicity** Not reported **Age at menopause or last menstrual period** Not reported **Previous use of hormone replacement therapy** Not reported **Medical history** • Atrial fibrillation: Cases – 10.2; Control -3.5 • Cardiovascular disease: Cases – 23.5; Control – 13.7

	• History of transient ischaemic attack: Cases – 15.2; Control – 2.7
Intervention(s)/control	Intervention: • Estrogen only (oral or transdermal route) • Estrogen + Progestin (oral or transdermal route) Oral route, low or high dose: low dose defined by ≤0.625 mg of equine oestrogen or ≤2 mg of estradiol and high dose defined by >0.625 mg of equine oestrogen or >2 mg of estradiol Transdermal route, low or high dose: low dose defined as ≤50µg and high dose defined as >50µg Control • No HRT **Duration and recency of HRT use** Duration • Not reported Recency • Current users
Duration of follow-up	• Cases, mean (SD): 6.68 • Controls, mean (SD): 6.68 (4.44)
Sources of funding	• Canadian Institutes of Health Research (CIHR) • Canadian Foundation for Innovation
Sample size	N=75668

Outcomes: See Supplement 18 for outcome data (Observational studies)

Critical appraisal - CASP Critical appraisal checklist for case-control studies - 2.1 cardiovascular

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age Body mass index Smoking status Alcohol misuse Diabetes Hyperlipidaemia Hypertension Atrial fibrillation Cardiovascular disease Transient ischaemic attack Aspirin or other NSAID use History of hysterectomy or oophorectomy
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes

Section	Question	Answer
(B) What are the results?	7. What are the results of this study?	Important harms were found for using estrogen only compared to no HRT in the risk of developing stroke only when taking orally (no important differences were found when taken transdermally)
(B) What are the results?	8. How precise are the results?	No concerns regarding imprecision.
(B) What are the results?	9. Do you believe the results?	No concerns regarding imprecision and results consistent with other evidence.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

Rossouw, 2002

Bibliographic Reference	Rossouw, Jacques E; Anderson, Garnet L; Prentice, Ross L; LaCroix, Andrea Z; Kooperberg, Charles; Stefanick, Marcia L; Jackson, Rebecca D; Beresford, Shirley A A; Howard, Barbara V; Johnson, Karen C; Kotchen, Jane Morley; Ockene, Judith; 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; vol. 288 (no. 3); 321-33

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1998

Inclusion criteria	Postmenopausal women aged 50 to 79 years without hysterectomy, likely to reside in the area for 3 years. Women were considered postmenopausal of she has experienced no vaginal bleeding for 6 months (12 months for 50–54-year-olds), had a hysterectomy, or had ever used postmenopausal hormones
Exclusion criteria	any medical conditions likely to be associated with a predicted survival <3 years, safety (e.g. prior breast cancer, other prior cancer within the last 10 years except nonmelanoma skin cancer, low haematocrit or platelet counts), and adherence and retention concerns (e.g. alcoholism, dementia)
Patient characteristics	**Age group at screening, years, mean (SD)** CEE plus MPA: 63.2 (7.1) Placebo: 63.3 (7.1) **Age group at screening, years, No (%)** **50-59 years** CEE plus MPA: 2839 (33.4) Placebo: 2683 (33.1) **60-59 years** CEE plus MPA: 3853 (45.3) Placebo: 3657 (45.1) **70-79 years** CEE plus MPA: 1814 (21.3) Placebo: 1762 (21.7) **Body mass index, mean (SD), kg/m2** CEE plus MPA: 28.5 (5.8)

	Placebo: 28.5 (5.9) **Body mass index, kg/m2, No (%)** **<25** CEE plus MPA: 2579 (30.4) Placebo: 2479 (30.8) **25-29** CEE plus MPA: 2992 (35.3) Placebo: 2834 (35.2) **≥30** CEE plus MPA: 2899 (34.2) Placebo: 2737 (34.0) **Ethnicity, No (%)** **White** CEE plus MPA: 7140 (83.9) Placebo: 6805 (84) **Black** CEE plus MPA: 549 (6.5) Placebo: 575 (7.1)

	Hispanic CEE plus MPA: 427 (5.5) Placebo: 416 (5.1) **American Indian** CEE plus MPA: 26 (0.3) Placebo: 30 (0.4) **Asian/Pacific Islander** CEE plus MPA: 194 (2.3) Placebo: 169 (2.1) **Unknown** CEE plus MPA: 124 (1.5) Placebo: 107 (1.3)
	Age at menopause or last menstrual period Not reported
	Hormone use, No (%) **Never** CEE plus MPA: 6280 (73.9)

	Placebo: 6024 (74.4) **Past** CEE plus MPA: 1674 (19.7) Placebo: 1588 (19.6) **Current** CEE plus MPA: 548 (6.4) Placebo: 487 (6.0) **Duration of prior hormone use, No (%)** **<5 years** CEE plus MPA: 1538 (69.1) Placebo: 1467 (70.6) **5-10 years** CEE plus MPA: 426 (19.1) Placebo: 357 (17.2) **≥10 years** CEE plus MPA: 262 (11.8) Placebo: 253 (12.2) **Medical history**

	Myocardial infarction CEE plus MPA: 139 (1.6) Placebo: 157 (1.9) **Angina** CEE plus MPA: 238 (2.8) Placebo: 234 (2.9) **CABG or PCI** CEE plus MPA: 95 (1.1) Placebo: 120 (1.5) **Stroke** CEE plus MPA: 61 (0.7) Placebo: 77 (1.0) **DVT or pulmonary embolism** CEE plus MPA: 79 (0.9) Placebo: 62 (0.8)
Intervention(s)/control	CEE plus MPA • Continuous; 1 daily tablet containing conjugated equine estrogen (CEE) 0.625mg and medroxyprogesterone acetate (MPA) 2.5 mg (Prempro, Wyeth Ayerst, philadelphia, pa) Placebo • Matching placebo

	Duration and recency of HRT use Duration • 5.2 years (mean) Recency • Current users
Duration of follow-up	Mean 5.2 years
Sources of funding	The National Heart, Lung, and Blood Institute (NHLBI) funds the WHI program. Wyeth Ayerst Research provided the study medication (active and placebo)
Sample size	N=16,608

Study arms

CEE plus MPA (N = 8506)

Placebo (N = 8102)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Rossouw, 2007

Bibliographic Reference	Rossouw, Jacques E; Prentice, Ross L; Manson, JoAnn E; Wu, Lieling; Barad, David; Barnabei, Vanessa M; Ko, Marcia; LaCroix, Andrea Z; Margolis, Karen L; Stefanick, Marcia L; Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause.; JAMA; 2007; vol. 297 (no. 13); 1465-77

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1998
Inclusion criteria	healthy postmenopausal women aged 50 to 79 years
Exclusion criteria	Not reported
Patient characteristics	**Age group at screening, years, No (%)** **50-59 years** <u><10 years since menopause</u> CEE and placebo: 1237 (75.3) CEE plus MPA and placebo: 4092 (74.5) <u>10-19 years since menopause</u> CEE and placebo: 1030 (35.1) CEE plus MPA and placebo: 831 (13.8) <u>≥20 years since menopause</u> CEE and placebo: 524 (11.5)

	CEE plus MPA and placebo: 55 (1.5) **60-59 years** <u><10 years since menopause</u> CEE and placebo: 406 (24.7) CEE plus MPA and placebo: 1402 (25.5) <u>10-19 years since menopause</u> CEE and placebo: 1564 (53.3) CEE plus MPA and placebo: 4320 (71.5) <u>≥20 years since menopause</u> CEE and placebo: 2150 (47.3) CEE plus MPA and placebo: 1145 (31.3) **70-79 years** <u><10 years since menopause</u> CEE and placebo: 0 CEE plus MPA and placebo: 0 <u>10-19 years since menopause</u> CEE and placebo: 342 (11.6) CEE plus MPA and placebo: 890 (14.7) <u>≥20 years since menopause</u>

	CEE and placebo: 1876 (41.2) CEE plus MPA and placebo: 2453 (76.2) **Body mass index** Not reported **Ethnicity** Not reported **Hormone use, No (%)** **Never** Oestrogen-only (CEE): 2769 (52.2) Placebo: 2770 (51.1) and 6020 (74.3) CEE plus MPA: 6277 (73.8) **Past** Oestrogen-only (CEE): 1871 (35.2) Placebo: 1948 (35.9) and 1588 (19.6) CEE plus MPA: 1671 (19.6) **Current** Oestrogen-only (CEE): 669 (12.6) Placebo: 708 (13.0) and 491 (6.1)

	CEE plus MPA: 554 (6.5) **Duration of prior hormone use, No (%)** **<5 years** Oestrogen-only (CEE): 1352 (53.2) Placebo: 1412 (53.1) and 1470 (18.1) CEE plus MPA: 1539 (18.1) **5-9 years** Oestrogen-only (CEE): 469 (18.5) Placebo: 515 (19.4) and 356 (4.4) CEE plus MPA: 427 (5) **≥10 years** Oestrogen-only (CEE): 720 (28.3) Placebo: 732 (27.5) and 255 (93.1) CEE plus MPA: 263 (3.1) **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, stroke, DVT or pulmonary embolism or previous CHD** Not reported
Intervention(s)/control	CEE only • 0.625 mg/d of CEE

	CEE plus MPA • 0.625 mg/d of CEE plus 2.5 mg/d of MPA Placebo • Placebo **Duration and recency of HRT use** Duration • 5.2 years (mean) Recency • Current users
Duration of follow-up	Mean 5.2 years
Sources of funding	The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services. The study drugs were supplied by Wyeth Research (St Davids, Pa).
Sample size	N=27,347
Other information	women who had undergone a hysterectomy and were randomized to 0.625 mg/d of CEE or placebo and women who had not had a hysterectomy and were randomized to 0.625 mg/d of CEE plus 2.5 mg/d of MPA or placebo

Study arms

CEE alone (N = 5310)

CEE plus MPA (N = 8506)

Placebo (N = 13531)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable

Section	Question	Answer
Overall bias and directness	Risk of bias variation across outcomes	None

Simon, 2001

Bibliographic Reference	Simon, J A; Hsia, J; Cauley, J A; Richards, C; Harris, F; Fong, J; Barrett-Connor, E; Hulley, S B; Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-progestin Replacement Study (HERS).; Circulation; 2001; vol. 103 (no. 5); 638-42

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1994
Inclusion criteria	postmenopausal women with CHD
Exclusion criteria	Not reported
Patient characteristics	**Age, years: mean (SD)** Estrogen-progestin therapy: 67 (7) Placebo: 67 (7) All participants: 67 (7) **Body mass index, kg/m2: mean (SD)** Estrogen-progestin therapy: 29 (6) Placebo: 29 (6)

	Ethnicity **White (%)** Estrogen-progestin therapy: 88 Placebo: 90 **Black (%)** Estrogen-progestin therapy: 8 Placebo: 7 **Other (%)** Estrogen-progestin therapy: 4 Placebo: 3 **Age at menopause or last menstrual period** Not reported **Past estrogen replacement therapy (%)** Estrogen-progestin therapy: 24 Placebo: 23 **Medical history including coronary heart disease manifestation, myocardial infarction, angina, CABG/PCI, Stroke, DVT or pulmonary embolism or previous CHD**

	Not reported
Intervention(s)/control	Hormone treatment, CEE plus MPA • Continuous; conjugated equine estrogen (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d) Placebo • placebo **Duration and recency of HRT use** Duration • 4.1 years Recency • Current users
Duration of follow-up	Participants were monitored by phone interview 3 times per year and were seen in clinic yearly for a physical examination and for evaluation of interval events Mean follow-up 4.1 years
Sources of funding	HERS was supported by a grant from Wyeth-Ayerst Research
Sample size	N=2,763

Study arms

CEE plus MPA (N = 1380)

Placebo (N = 1383)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (computer generated random numbers were logged and assigned by each centre) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable

Section	Question	Answer
Overall bias and directness	Risk of bias variation across outcomes	None

Tierney, 2009

Bibliographic Reference	Tierney, Mary C; Oh, Paul; Moineddin, Rahim; Greenblatt, Ellen M; Snow, W Gary; Fisher, Rory H; Iazzetta, John; Hyslop, Peter St George; MacLusky, Neil J; A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women.; Psychoneuroendocrinology; 2009; vol. 34 (no. 7); 1065-74

Study details

Country where study was carried out	Canada
Study type	Randomised controlled trial (RCT)
Study dates	April 2000 and January 2004 and follow-up was completed August 2006
Inclusion criteria	Women were ≥60 years of age with last menstrual cycle ≥12 months before screening and women with normal to below normal scores on our screening instrument, the short delay recall trial of the Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1982), i.e., ≤10 words for women 75 years or younger or ≤9 words for women 76 years or older.
Exclusion criteria	Women who met criteria for dementia or had a clinical history of a neurological, systemic or psychiatric condition that would affect cognition; women with conditions that were considered at the time of enrolment to be exacerbated by estrogen, including history of breast or endometrial cancer; history of myocardial infarction (MI), coronary artery bypass graft (CABG), angioplasty or unstable angina within the past year; history of congestive heart failure (CHF) (NYHA Class III or IV); or history of thromboembolic event within the past 6 months. Women with remote histories of any of these cardiac conditions were admitted to the study only after approval from their family physicians or cardiologists; women who were taking donepezil, galantamine, rivastigmine, hydergine, tamoxifen, or raloxifene, or had used any mode or dose of HT within the past 2 years. Women were fluent in English and could read normal print and hear normal speech
Patient characteristics	**Age at entry to study, years: mean (SD)**

	HRT: 75 (6.4) Placebo: 74.5 (7.4) All participants ranged between 61-87 years **Body mass index, kg/m2: mean (SD)** HRT: 27 (5.2) Placebo: 26.6 (5.4) **Ethnicity: N (%)** **White** HRT: 67 (95.7) Placebo: 65 (90.3) **Black** HRT: 2 (2.9) Placebo: 4 (5.6) **Asian** HRT: 1 (1.4) Placebo: 3 (4.2) **Age at menopause, years: mean (SD)**

	with a uterus, and at least one ovary HRT: 50.4 (3.8) Placebo: 49.1 (4.5) **Bilateral oophorectomy** HRT: 40.3 (8.3) Placebo: 43.5 (4.8) **Prior HRT use: N (%)** HRT: 22 (31.4) Placebo: 17 (23.6) **Prior HRT use, years: mean (SD)** HRT: 0.8 (2.6) Placebo: 0.9 (2.6) **Medical history** **Deep vein thrombosis or pulmonary embolism: N (%)** HRT: 1 (1.4) Placebo: 1 (1.4) **Atrial fibrillation: N (%)** HRT: 3 (4.3) Placebo: 6 (8.3)

	Myocardial infarction: N (%) HRT: 4 (5.7) Placebo: 3 (4.2) **Coronary artery bypass graft: N (%)** HRT: 1 (1.4) Placebo: 2 (2.8)
Intervention(s)/control	HRT (Sequential Oestradiol plus norethindrone) • one estrogen capsule (1 mg 17-b estradiol micronized) per day for 4 days followed by one combined estrogen and progestin capsule (1 mg 17-b estradiol and 0.35 mg norethindrone) per day for 3 days. Placebo • placebo capsules identical in appearance to the active capsule **Duration and recency of HRT use** Duration • 2 years Recency • Current users
Duration of follow-up	2 years
Sources of funding	This study was primarily funded by the Canadian Institutes of Health Research (CIHR) (Grant 15222). The Institute of Neurosciences, Mental Health and Addiction (CIHR), and Shire Biochem provided additional funding. Estrace (17-b estradiol) was provided by Shire Biochem and norethindrone was provided by Janssen-Ortho. The funding organizations had no role in the design and conduction of the study; nor in the collection, management, analysis and interpretation of the data; nor in the preparation, review, or approval of the manuscript
Sample size	N=142

Study arms

Sequential Oestradiol plus norethindrone (N = 70)

Placebo (N = 72)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (participants were randomised by the study biostatistician using computer generated permutated blocks of 4 and 6 and the treatment allocation list was provided to the study pharmacist) and any baseline differences observed between intervention groups appear to be compatible with chance)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Outcome data were not available for all, or nearly all, randomized participants and there is no evidence that the result was not biased by missing outcome data (although this appears unlikely). Missingness in the outcome could depend on its true value however it is not likely that missingness in the outcome depended on its true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(The method of measuring the outcome was not inappropriate and it is unlikely*

Section	Question	Answer
		that the measurement or ascertainment of the outcome differed between intervention groups. The assessment of the outcome could have been influenced by knowledge of the intervention received however it is unlikely that assessment of the outcome was influenced by knowledge of intervention received.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(It is likely that the data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Some concerns *(The study has some concerns due to missing outcome data, and measurement of the outcome.)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Veerus, 2006

Bibliographic Reference	Veerus, Piret; Hovi, Sirpa-Liisa; Fischer, Krista; Rahu, Mati; Hakama, Matti; Hemminki, Elina; Results from the Estonian postmenopausal hormone therapy trial [ISRCTN35338757].; Maturitas; 2006; vol. 55 (no. 2); 162-73

Study details

Country where study was carried out	Estonia

Study type	Randomised controlled trial (RCT)
Study dates	1999 to 2004
Inclusion criteria	Postmenopausal women aged 50–64 years within 3 years of their last period
Exclusion criteria	Not reported
Patient characteristics	**Age, years: mean (SD)** HT: 58.5 (3.9) Placebo: 59 (3.9) **Age at recruitment, years: mean (SD)** **50–54** HT: 95 (23.5) Placebo: 74 (19.8) **55–59** HT: 158 (39.1) Placebo: 128 (34.3) **60–64** HT: 138 (34.2) Placebo: 154 (41.3) **65–70** HT: 13 (3.2) Placebo: 17 (4.6) **BMI, mean (S.D.) (kg/m2)** HT: 27.0 (4.8) Placebo: 26.9 (4.2)

	Ethnicity Not reported **Age at menopause, mean (S.D.)** HT: 50.4 (3.8) Placebo: 50.3 (3.9) **Previous use of hormone replacement therapy** Not reported **Medical history** **Angina** HT: 6 (1.5) Placebo: 4 (1.1) **Myocardial infarction** HT: 2 (0.5) Placebo: 1 (0.3)
Intervention(s)/control	Hormone therapy • Continuous; 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 Placebo • matched placebo **Duration and recency of HRT use**

	Duration • 3.4 years (mean) Recency • Current users
Duration of follow-up	the mean follow-up time from recruitment was 3.43 years; the potential follow-up time was from 2.00 to 4.97 years
Sources of funding	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).
Sample size	N=777
Other information	Only blind study data has been extracted and utilised in the analysis

Study arms

CEE plus MPA (N = 404)

Placebo (N = 373)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (permuted block randomisation, each of a size 16 and each block of the three clinics separately and treatment allocation was enclosed in a non-transparent sealed envelope and sent to trial clinics) and any baseline differences observed between intervention groups appear to be compatible with chance.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The study is judged to have low risk of bias in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Vickers, 2007

Bibliographic Reference	Vickers, Madge R; MacLennan, Alastair H; Lawton, Beverley; Ford, Deborah; Martin, Jeannett; Meredith, Sarah K; DeStavola, Bianca L; Rose, Sally; Dowell, Anthony; Wilkes, Helen C; Darbyshire, Janet H; Meade, Tom W; WISDOM, group; Main

morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women.; BMJ (Clinical research ed.); 2007; vol. 335 (no. 7613); 239

Study details

Countries where study was carried out	UK, NZ and Australia
Study type	Randomised controlled trial (RCT)
Study dates	1999 to 2002
Inclusion criteria	Postmenopausal women (no menstrual period in the past 12 months or had undergone hysterectomy)
Exclusion criteria	Main exclusion criteria were a history of breast cancer; any other cancer in the past 10 years except basal and squamous cell skin cancer; endometriosis or endometrial hyperplasia; venous thromboembolism; gall bladder disease in women who had not had a cholecystectomy; and myocardial infarction, unstable angina, cerebrovascular accident, subarachnoid haemorrhage, transient ischaemic attack, or use of hormone replacement therapy within the past six months. Women taking hormone replacement therapy at screening who were prepared to enter the placebo controlled strata of the study agreed to stop the therapy for three months before the run-in phase. Women who were, in the opinion of their general practitioner, unlikely to be able to give informed consent or successfully complete trial procedures were also excluded.
Patient characteristics	**Age at randomisation (years): Mean (SD)** Combined therapy: 63.3 (4.7) Placebo: 63.3 (4.6) All participants: 62.8 (4.8) **Age at randomisation (years): N (%)** **50-54 years** Combined therapy: 145 (7)

	Placebo: 131 (6) **55-59 years** Combined therapy: 395 (18) Placebo: 419 (19) **60-64 years** Combined therapy: 716 (33) Placebo: 732 (33) **≥65 years** Combined therapy: 938 (43) Placebo: 906 (41) **Mean (SD) body mass index: N (%)** Combined therapy: 27.9 (4.9) Placebo: 28.0 (5.2) **Body mass index: N (%)** **<25** Combined therapy: 629 (29) Placebo: 659 (30) **25-29**

	Combined therapy: 934 (43) Placebo: 848 (39) **≥30** Combined therapy: 623 (28) Placebo: 675 (31) **Ethnicity: N (%)** **Non-white ethnic status** Combined therapy: 23 (1) Placebo: 30 (51) **Mean (SD) years since menopause (last menstruation)** Combined therapy: 14.8 (7.2) Placebo: 14.7 (7.1) **Using HRT at screening: N (%)** Combined therapy: 167 (8) Placebo: 184 (8) **Ever used HRT at screening: N (%)** Combined therapy: 1041 (47) Placebo: 1005 (46)

	Previous myocardial infarction: N (%) Combined therapy: 40 (2) Placebo: 26 (1) **Previous stroke** Combined therapy:30 (1) Placebo: 38 (2)
Intervention(s)/control	Combined therapy • Continuous; conjugated equine oestrogens 0.625mg orally plus medroxyprogesterone acetate 2.5 mg orally daily (Prempro, Wyeth Ayerst US) Placebo • placebo **Duration and recency of HRT use** Duration • 12.8 months (median) Recency • Current users
Duration of follow-up	Women were to be seen at 4, 14, 27, 40, and 52 weeks after start of treatment and then at six-month intervals. Median follow-up 12.8 months
Sources of funding	UK Medical Research Council, British Heart Foundation, Department of Health for England, Scottish Office, Welsh Office, Department of Health and Social Services for Northern Ireland, Royal Australian and New Zealand College of Obstetricians and Gynaecologists, Australasian Menopause Society, National Health and Medical Research Council (NHMRC), National Heart Foundation of Australia, The Cancer Council of South Australia, The Cancer Society of New Zealand (Wellington Branch), NHS R&D Executive (service support and excess treatment costs). MRC, in collaboration

	with the other UK funders, established a Trial Steering Committee (which reported annually to the MRC) with an independent chairman and independent Data Monitoring and Ethics Committee (which considered unblinded group data, took account of external developments relevant to the progress of the trial, and made recommendations to the steering committee). The funders in Australia and New Zealand monitored local progress and received reports on progress from the UK steering committee. The principal investigators from Australia and New Zealand were non-voting members of the UK steering committee
Sample size	N=4,385
Other information	Only the combined therapy group versus placebo were included in the review. The other comparison oestrogen-only group versus combined therapy were not included as the comparison did not match the inclusion criteria specified in the protocol. The age at randomisation was extended to include participants aged 50-69 years

Study arms

CEE plus MPA (N = 2196)

Placebo (N = 2189)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(randomly allocated centrally with a computer based, stratified block randomisation program)*
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended	High *(As far as possible participants, carers and people delivering the interventions were unaware of intervention groups during the trial (full blindness could not be*

Section	Question	Answer
interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	*maintained when vaginal bleeding triggered a code break and investigation for possible pathology). However there were deviations from the intended interventions that arose because of the trial context, these deviations were likely to have affected the outcome and were unbalanced between the intervention groups (whilst the treatment code was unblinded in only two of the 1971 women who had undergone hysterectomy, in women with a uterus the proportion unblinded was high, mostly as a result of vaginal bleeding in those randomised to combined therapy, where 712/ 1862 (38%) were unblinded, compared with 66/1859 (4%) of those randomised to placebo (hazard ratio 13.4 (95% confidence interval 10.4 to 17.3), P<0.001).) An appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Outcome data were not available for all, or nearly all, randomized participants, there is no evidence that the result was not biased by missing outcome data, missingness in the outcome could depend on its true value and it is likely that missingness in the outcome depended on its true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcomes were not inappropriate, and the measurement or ascertainment of the outcome did not appear to differ between intervention groups. As much as possible, for most participants the outcome assessors were unaware of the intervention received by study participants, and it is unlikely that the assessment of the outcome could have been influenced by knowledge of the intervention received.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to*

Section	Question	Answer
		have been selected, on the basis of the results, from multiple eligible analyses of the data.)
Overall bias and directness	Risk of bias judgement	High *(The study was at high risk of bias due to deviations from the intended interventions (effect of assignment to intervention) and missing outcome data, and some concerns of bias due to deviations from the intended interventions (effect of adhering to intervention).)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Viscoli, 2001

Bibliographic Reference	Viscoli, C M; Brass, L M; Kernan, W N; Sarrel, P M; Suissa, S; Horwitz, R I; A clinical trial of estrogen-replacement therapy after ischemic stroke.; The New England journal of medicine; 2001; vol. 345 (no. 17); 1243-9

Study details

Country where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	1993 to 1998
Inclusion criteria	Postmenopausal women older than 44 years of age within 90 days after a qualifying ischemic stroke or transient ischemic attack. Women were considered postmenopausal if they had had amenorrhea for at least 12 months or if they had undergone hysterectomy and were older than 55 years of age
Exclusion criteria	Women were excluded if their index event was disabling (had a severity score greater than 5 on the scale used in the North American Symptomatic Carotid Endarterectomy Trial) or if it occurred while the woman was taking estrogen. Women were not eligible if they had a history of breast or endometrial cancer, had had a venous thromboembolic event

	while receiving estrogen-replacement therapy, had a neurologic or psychiatric disease that could complicate the evaluation of end points, or had a coexisting condition that limited their life expectancy
Patient characteristics	**Age, years: mean (SD)** Estradiol: 72 (10) Placebo: 71 (10) All participants: 71 (range, 46 to 91) **Body-mass index: mean (SD)** Estradiol: 28 (7) Placebo: 28 (5) **Ethnicity: (%)** **White** Estradiol: 84 Placebo: 83 **Black** Estradiol: 13 Placebo: 13 **Other** Estradiol: 3 Placebo: 4 **Age at menopause or last menstrual period** Not reported **Previous estrogen-replacement therapy (%)**

	Estradiol: 28 Placebo: 31 **Myocardial infarction (%)** Estradiol: 25 Placebo: 23 **Congestive heart failure (%)** Estradiol: 13 Placebo: 16 **Atrial fibrillation (%)** Estradiol: 7 Placebo: 7 **Hypertension (%)** Estradiol: 75 Placebo: 72
Intervention(s)/control	Estradiol • Estradiol-17b (Estrace, Mead Johnson, Evansville, Ind.) at the standard replacement dose of 1 mg daily Placebo • matching placebo. **Duration and recency of HRT use** Duration • 2.8 years (mean) Recency • Current users

Duration of follow-up	Mean 2.8 years
Sources of funding	Supported by a grant (1-RO1-N531251) from the National Institute of Neurological Disorders and Stroke and by Mead Johnson Laboratories, which also provided the study drug
Sample size	N=664
Other information	44% had hysterectomy in the Oestrogen-only group and 45% had hysterectomy in the placebo group

Study arms

Oestradiol (N = 337)

Placebo (N = 327)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and randomised (a master list of computer-generated random treatment assignments was stored at the investigational pharmacy) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate (intention to treat) analysis was used to estimate the effect of assignment to intervention.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Wassertheil-Smoller, 2003

Bibliographic Reference	Wassertheil-Smoller, Sylvia; Hendrix, Susan L; Limacher, Marian; Heiss, Gerardo; Kooperberg, Charles; Baird, Alison; Kotchen, Theodore; Curb, J David; Black, Henry; Rossouw, Jacques E; Aragaki, Aaron; Safford, Monika; Stein, Evan; Laowattana, Somchai; Mysiw, W Jerry; WHI, Investigators; Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial.; JAMA; 2003; vol. 289 (no. 20); 2673-84

Study details

Country where study was carried out	US

Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Postmenopausal women aged 50 to 79 years old. Women were considered postmenopausal if she has experienced no vaginal bleeding for 6 months (12 months for 50–54-year-olds), had a hysterectomy, or had ever used postmenopausal hormones To be eligible for the trial of oestrogen plus progestin, women had to have an intact uterus
Exclusion criteria	any medical conditions likely to be associated with a predicted survival <3 years, alcoholism, drug dependency, diagnosed mental illness, dementia or other conditions suggesting that a women would not be adherent to study medications or other procedures
Patient characteristics	**Age group at screening, years, No (%)** **50-59 years** CEE plus MPA: 2839 (33.4) Placebo: 2683 (33.1) **60-59 years** CEE plus MPA: 3853 (45.3) Placebo: 3657 (45.1) **70-79 years** CEE plus MPA: 1814 (21.3) Placebo: 1762 (21.7) **Body mass index, mean (SD)**

	CEE plus MPA: 28.5 (5.8) Placebo: 28.5 (5.9) **Ethnicity, No (%)** **White** CEE plus MPA: 7140 (83.9) Placebo: 6805 (84) **Black** CEE plus MPA: 549 (6.5) Placebo: 575 (7.1) **Hispanic** CEE plus MPA: 472 (5.5) Placebo: 416 (5.1) **American Indian** CEE plus MPA: 26 (0.3) Placebo: 30 (0.4) **Asian/Pacific Islander** CEE plus MPA: 194 (2.3) Placebo: 169 (2.1)

	Unknown CEE plus MPA: 125 (1.5) Placebo: 107 (1.3) **Age at menopause or last menstrual period** Not reported **Hormone use, No (%)** **Never** CEE plus MPA: 6277 (73.8) Placebo: 6020 (74.3) **Past** CEE plus MPA: 1671 (19.6) Placebo: 1588 (19.6) **Current** CEE plus MPA: 554 (6.5) Placebo: 491 (6.1) **Duration of prior hormone use, No (%)**

	<5 years CEE plus MPA: 1539 (18.1) Placebo: 1470 (18.1) **5-10 years** CEE plus MPA: 427 (5.0) Placebo: 356 (4.4) **≥10 years** CEE plus MPA: 263 (3.1) Placebo: 255 (3.2) **Medical history, No (%)** **History of CVD** CEE plus MPA: 406 (4.8) Placebo: 419 (5.2) **Myocardial infarction ever** CEE plus MPA: 139 (1.6) Placebo: 157 (1.9) **Stroke ever** CEE plus MPA: 61 (0.7)

	Placebo: 77 (1.0) **History of transient ischemic attack** CEE plus MPA: 115 (1.4) Placebo: 143 (1.8) **ECG atrial fibrillation** CEE plus MPA: 7 (0.1) Placebo: 15 (0.2) **LVH, Minnesota code** CEE plus MPA: 402 (4.7) Placebo: 432 (5.3) C**arotid endarterectomy/angioplasty ever** CEE plus MPA: 15 (0.2) Placebo: 19 (0.2)
Intervention(s)/control	CEE plus MPA • Continuous; 1 daily tablet containing conjugated equine estrogen (CEE) 0.625mg and medroxyprogesterone acetate (MPA) 2.5 mg (Prempro, Wyeth Ayerst, Philadelphia, pa) Placebo • Matching placebo **Duration and recency of HRT use** Duration

	• 5.6 years (mean) Recency • Current users
Duration of follow-up	Mean 5.6 years
Sources of funding	The National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, Department of Health and Human Services. The active study drug and placebo were supplied by Wyeth Ayerst Research laboratories, Philadelphia, pa
Sample size	N=16,608

Study arms

CEE plus MPA (N = 8506)

Placebo (N = 8102)

Outcomes: See Supplement 17 for outcome data (RCTs)

Critical appraisal – Cochrane RoB 2.0

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(The allocation sequence was adequately concealed and random (centrally computerized randomisation with permuted block algorithm) and any baseline differences observed between intervention groups appear to be compatible with chance.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, carers and people delivering the interventions were unaware of intervention groups during the trial and an appropriate intention to treat analysis was used to estimate the effect of assignment to intervention.)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate, the measurement or ascertainment of the outcome did not differ between intervention groups and the outcome assessors were unaware of the intervention received by study participants.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis, the result being assessed is unlikely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain and reported outcome data are unlikely to have been selected, on the basis of the results, from multiple eligible analyses of the data.)*
Overall bias and directness	Risk of bias judgement	Low *(The risk of bias was low in all domains)*
Overall bias and directness	Overall directness	Directly applicable
Overall bias and directness	Risk of bias variation across outcomes	None

Appendix E Forest plots

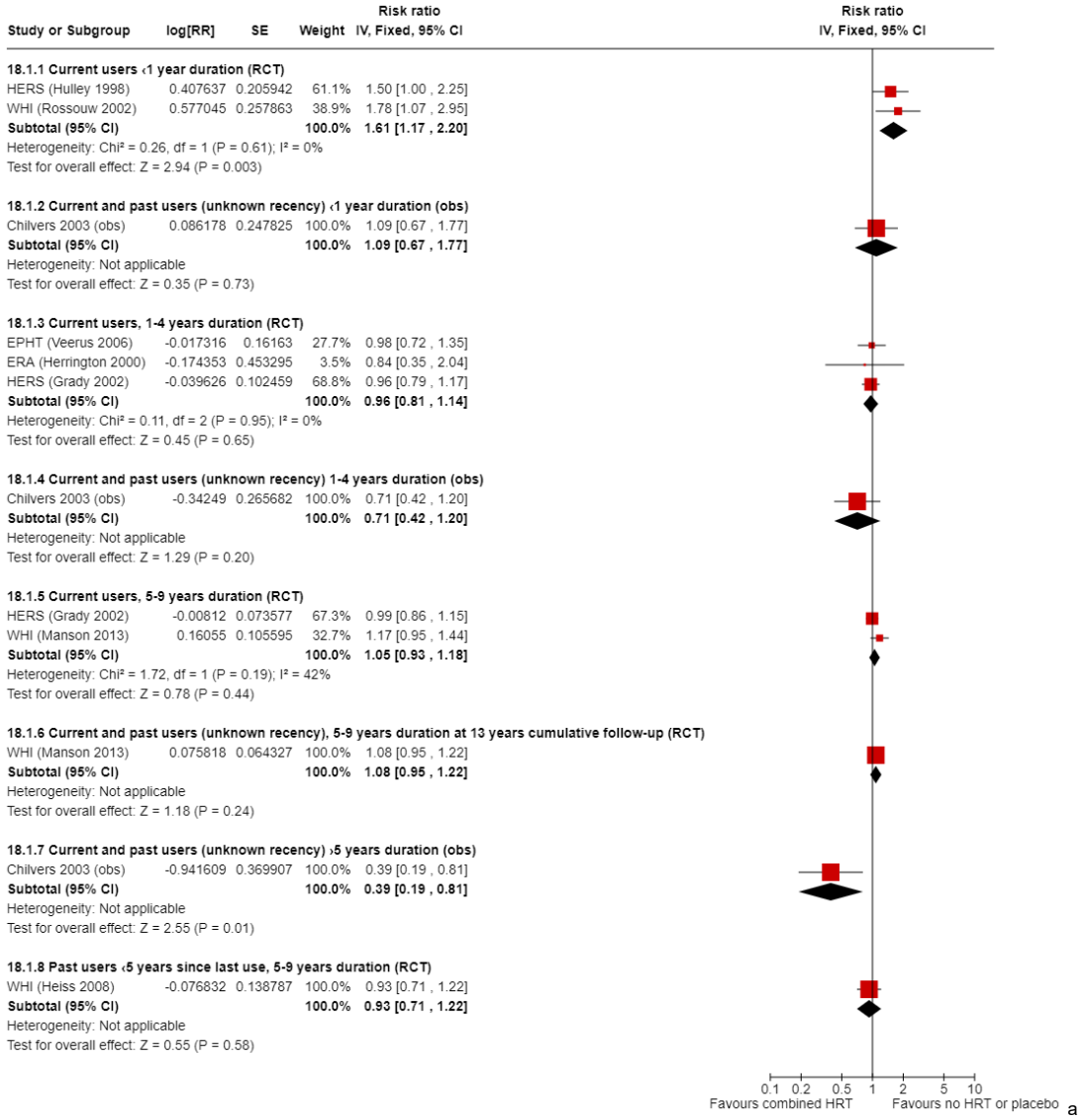
Forest plots for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here unless they provide information on subgroups; the quality assessment for such outcomes is provided in the GRADE profiles in Appendix F.

RCT evidence is presented first followed by observational evidence. In some instances, where possible due to similarity of outcomes and stratifications, observational evidence has been presented on the same forest plot as RCT evidence so that they can be compared visually, or consecutively if not on the same plot. Analyses remains separate for RCT evidence and observational evidence. Different summary measures are analysed separately, but where it was deemed necessary for visualisation purposes they have been presented on the same plot, but specifics of each provided in the footnotes where applicable. Please refer to the footnotes of relevant forest plots for more information where this is the case.

Combined HRT versus no HRT or placebo

Figure 2: Combined oestrogen and progestogen (continuous) versus placebo or no HRT, by recency and duration of HRT use: coronary heart disease (including MI) – RCT and observational studies


Risk ratio
Study or Subgroup log[RR] SE Weight IV, Fixed, 95% CI
Risk ratio
IV, Fixed, 95% CI
18.1.1 Current users ‹1 year duration (RCT)
HERS (Hulley 1998) 0.407637 0.205942 61.1% 1.50 [1.00 , 2.25]
WHI (Rossouw 2002) 0.577045 0.257863 38.9% 1.78 [1.07 , 2.95]
Subtotal (95% CI) 100.0% 1.61 [1.17 , 2.20]
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.94 (P = 0.003)
18.1.2 Current and past users (unknown recency) ‹1 year duration (obs)
Chilvers 2003 (obs) 0.086178 0.247825 100.0% 1.09 [0.67 , 1.77]
Subtotal (95% CI) 100.0% 1.09 [0.67 , 1.77]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)
18.1.3 Current users, 1-4 years duration (RCT)
EPHT (Veerus 2006) -0.017316 0.16163 27.7% 0.98 [0.72 , 1.35]
ERA (Herrington 2000) -0.174353 0.453295 3.5% 0.84 [0.35 , 2.04]
HERS (Grady 2002) -0.039626 0.102459 68.8% 0.96 [0.79 , 1.17]
Subtotal (95% CI) 100.0% 0.96 [0.81 , 1.14]
Heterogeneity: Chi² = 0.11, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
18.1.4 Current and past users (unknown recency) 1-4 years duration (obs)
Chilvers 2003 (obs) -0.34249 0.265682 100.0% 0.71 [0.42 , 1.20]
Subtotal (95% CI) 100.0% 0.71 [0.42 , 1.20]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
18.1.5 Current users, 5-9 years duration (RCT)
HERS (Grady 2002) -0.00812 0.073577 67.3% 0.99 [0.86 , 1.15]
WHI (Manson 2013) 0.16055 0.105595 32.7% 1.17 [0.95 , 1.44]
Subtotal (95% CI) 100.0% 1.05 [0.93 , 1.18]
Heterogeneity: Chi² = 1.72, df = 1 (P = 0.19); I² = 42%
Test for overall effect: Z = 0.78 (P = 0.44)
18.1.6 Current and past users (unknown recency), 5-9 years duration at 13 years cumulative follow-up (RCT)
WHI (Manson 2013) 0.075818 0.064327 100.0% 1.08 [0.95 , 1.22]
Subtotal (95% CI) 100.0% 1.08 [0.95 , 1.22]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)
18.1.7 Current and past users (unknown recency) ›5 years duration (obs)
Chilvers 2003 (obs) -0.941609 0.369907 100.0% 0.39 [0.19 , 0.81]
Subtotal (95% CI) 100.0% 0.39 [0.19 , 0.81]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.55 (P = 0.01)
18.1.8 Past users ‹5 years since last use, 5-9 years duration (RCT)
WHI (Heiss 2008) -0.076832 0.138787 100.0% 0.93 [0.71 , 1.22]
Subtotal (95% CI) 100.0% 0.93 [0.71 , 1.22]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
0.1 0.2 0.5 1 2 5 10
Favours combined HRT
Favours no HRT or placebo

a

Figure 3: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported): coronary heart disease (including MI) – HR – observational studies

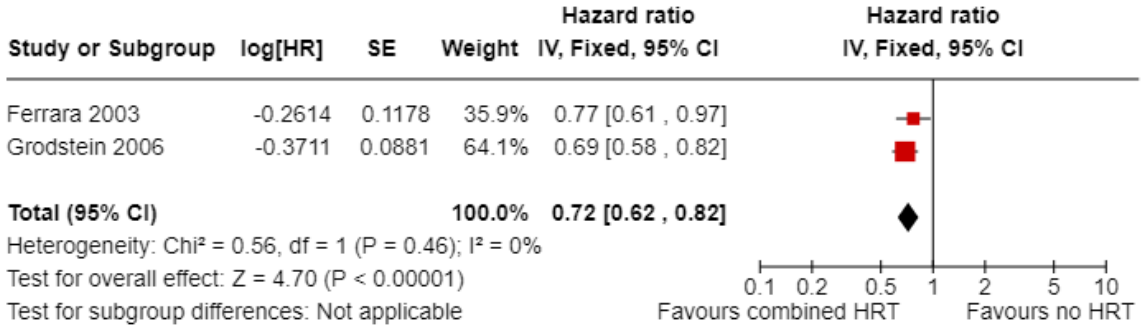
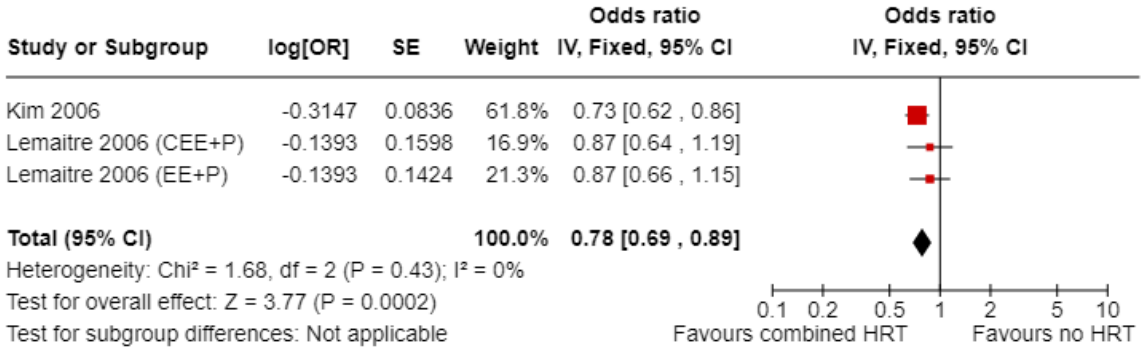


Figure 4: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported): coronary heart disease (including MI) – OR – observational studies



[a] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for observational evidence are odds ratios, but presented under risk ratio labels for presentational purposes. See table 5 for full GRADE profile for RCT evidence, and table 21 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 9.07$, df=4 (P=0.06), $I^2 = 55.9\%$. Test for subgroup differences for observational evidence: $Chi^2 = 5.39$, df=2 (P=0.07), $I^2 = 62.9\%$.

Figure 5: Combined oestrogen and progestogen (continuous) versus placebo, by recency and duration of HRT use: nonfatal MI - RCT

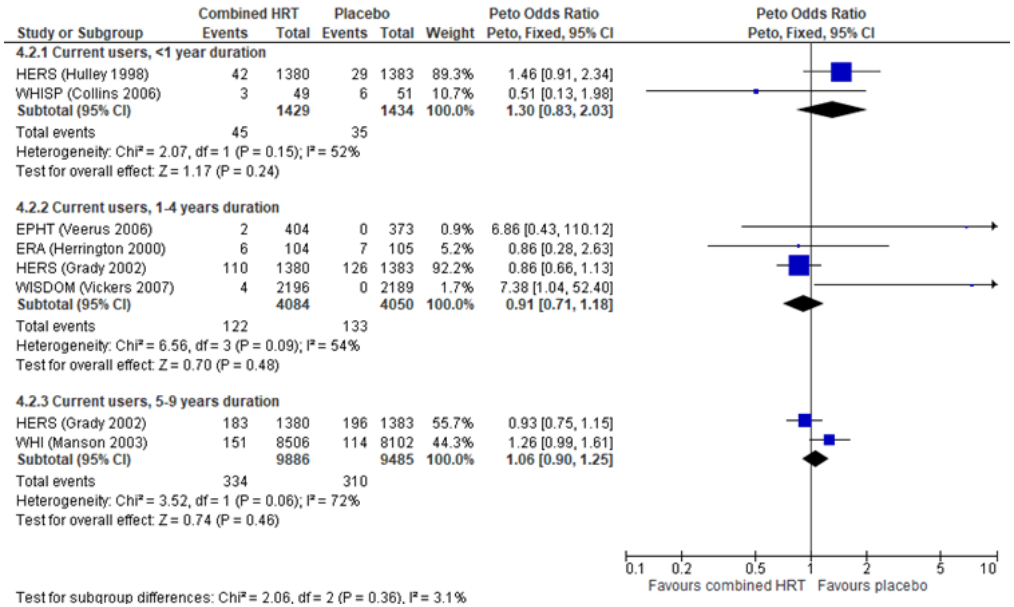


Figure 6: Combined oestrogen and progestogen (continuous) versus placebo, by recency and duration of HRT use: cardiac event composite score - RCT

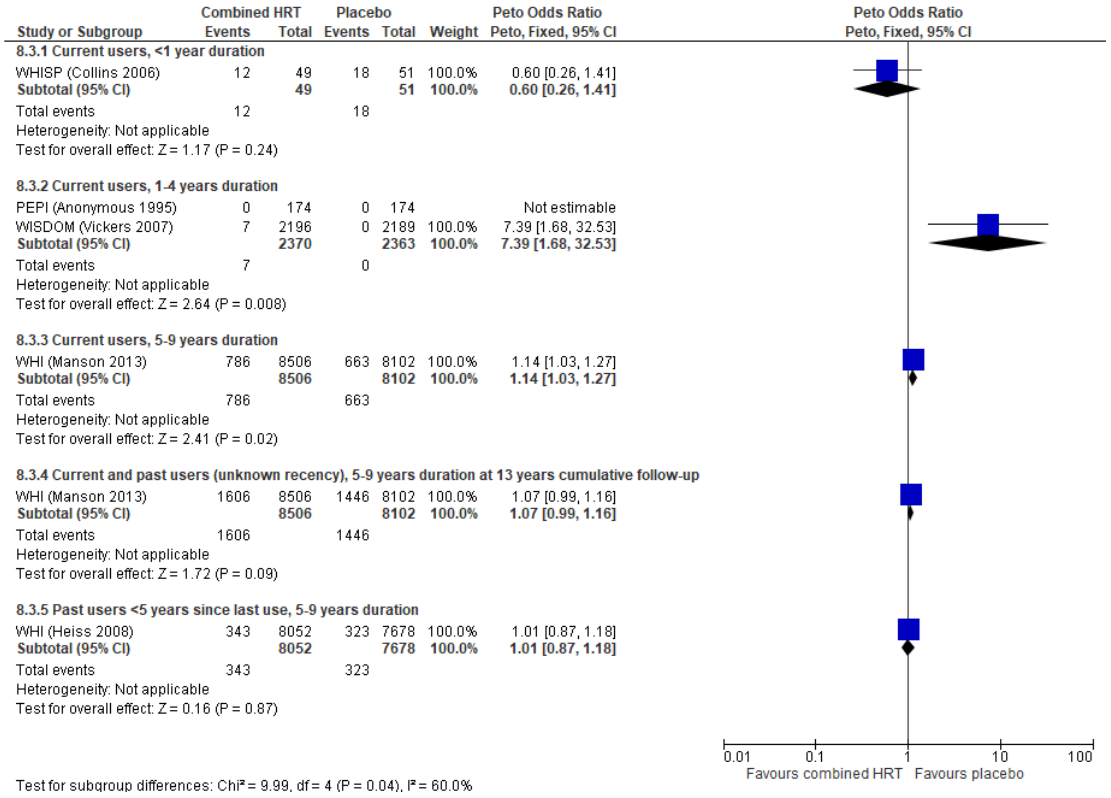

Combined HRT
Placebo
Peto Odds Ratio
Peto Odds Ratio
Study or Subgroup Events Total Events Total Weight Peto, Fixed, 95% CI
Peto, Fixed, 95% CI
8.3.1 Current users, <1 year duration
WHISP (Collins 2006) 12 49 18 51 100.0% 0.60 [0.26, 1.41]
Subtotal (95% CI) 49 51 100.0% 0.60 [0.26, 1.41]
Total events 12 18
Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)
8.3.2 Current users, 1-4 years duration
PEPI (Anonymous 1995) 0 174 0 174 Not estimable
WISDOM (Vickers 2007) 7 2196 0 2189 100.0% 7.39 [1.68, 32.53]
Subtotal (95% CI) 2370 2363 100.0% 7.39 [1.68, 32.53]
Total events 7 0
Heterogeneity: Not applicable
Test for overall effect: Z = 2.64 (P = 0.008)
8.3.3 Current users, 5-9 years duration
WHI (Manson 2013) 786 8506 663 8102 100.0% 1.14 [1.03, 1.27]
Subtotal (95% CI) 8506 8102 100.0% 1.14 [1.03, 1.27]
Total events 786 663
Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)
8.3.4 Current and past users (unknown recency), 5-9 years duration at 13 years cumulative follow-up
WHI (Manson 2013) 1606 8506 1446 8102 100.0% 1.07 [0.99, 1.16]
Subtotal (95% CI) 8506 8102 100.0% 1.07 [0.99, 1.16]
Total events 1606 1446
Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)
8.3.5 Past users <5 years since last use, 5-9 years duration
WHI (Heiss 2008) 343 8052 323 7678 100.0% 1.01 [0.87, 1.18]
Subtotal (95% CI) 8052 7678 100.0% 1.01 [0.87, 1.18]
Total events 343 323
Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)
0.01
0.1
1
10
100
Favours combined HRT
Favours placebo
Test for subgroup differences: Chi² = 9.99, df = 4 (P = 0.04), I² = 60.0%

Figure 7: Combined oestrogen and progestogen (continuous) versus placebo, by recency and duration of HRT use: mortality (cardiovascular disease related) - RCT

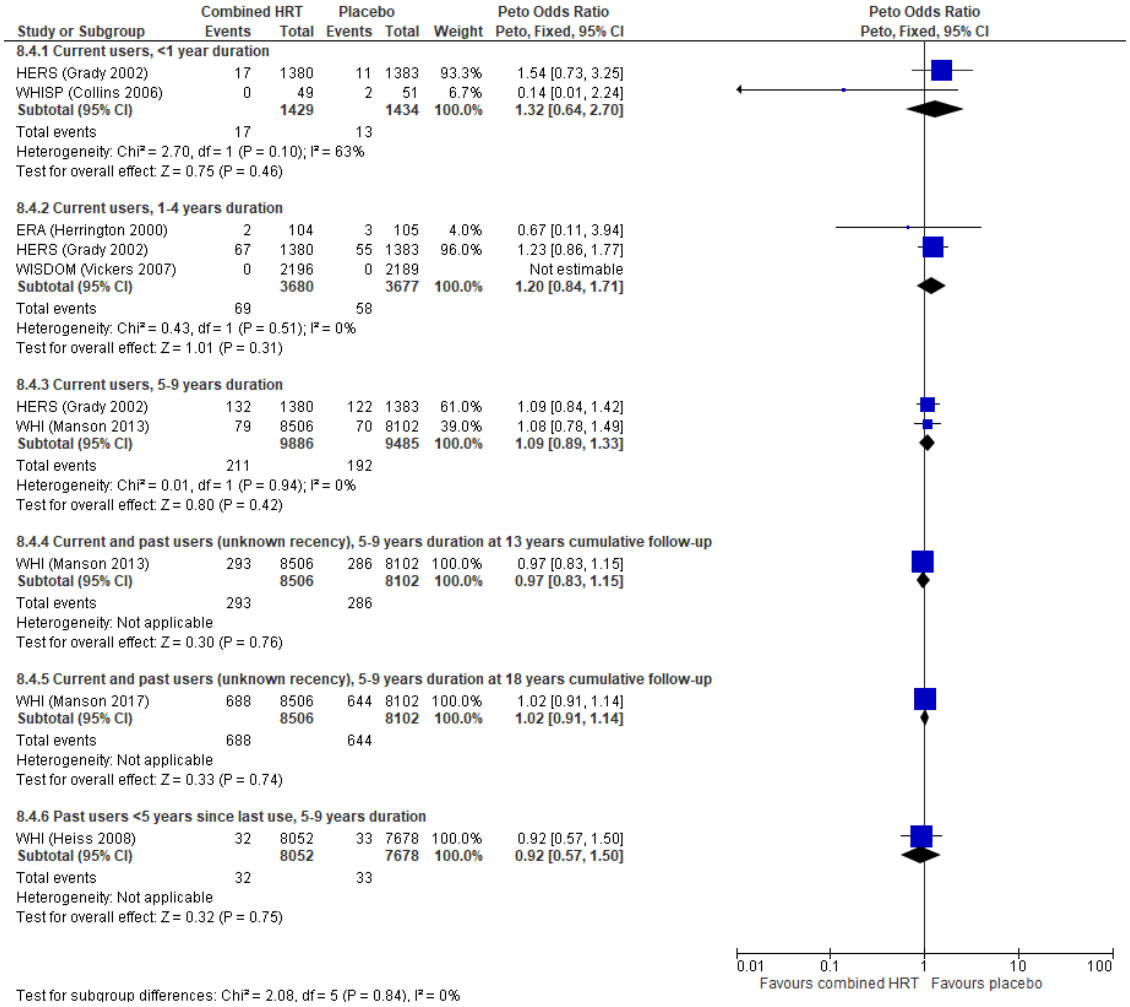


Figure 8: Combined oestrogen and progestogen (continuous) versus placebo, by recency and duration of HRT use: stroke - RCT

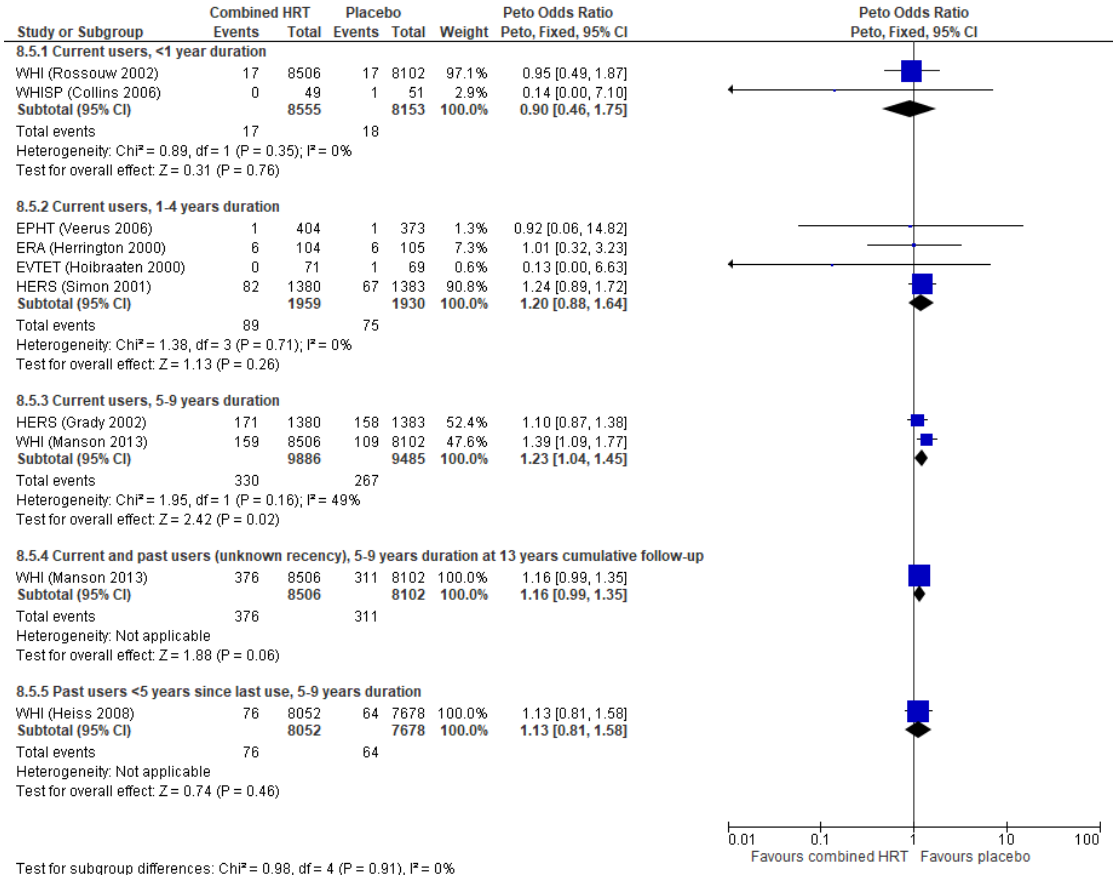


Figure 9: Combined oestrogen and progestogen (continuous) versus placebo in current users with <1 year duration of HRT use, by oestrogenic constituent: nonfatal MI - RCT

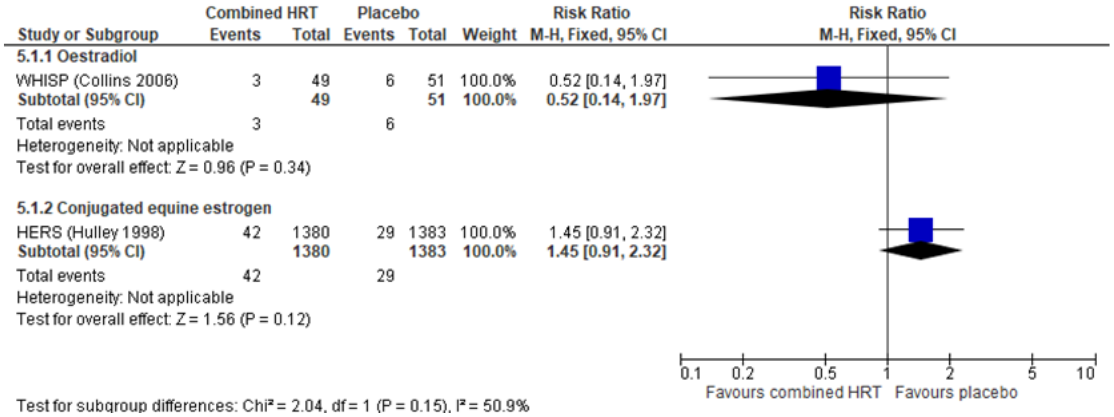


Figure 10: Combined oestrogen and progestogen (continuous) versus placebo in current users with <1 year duration of HRT use, by oestrogenic constituent: mortality (cardiovascular disease related) - RCT

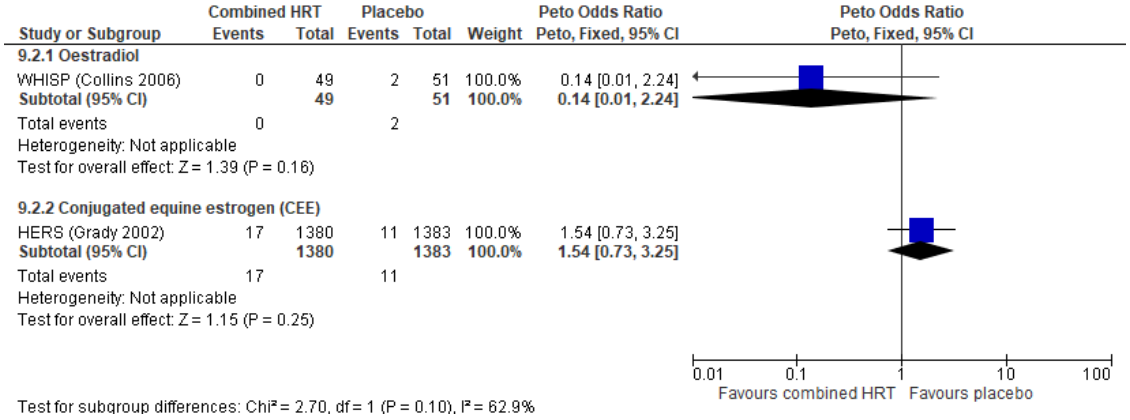


Figure 11: Combined oestrogen and progestogen (continuous) versus placebo in current users with <1 year duration of HRT use, by oestrogenic constituent: stroke - RCT

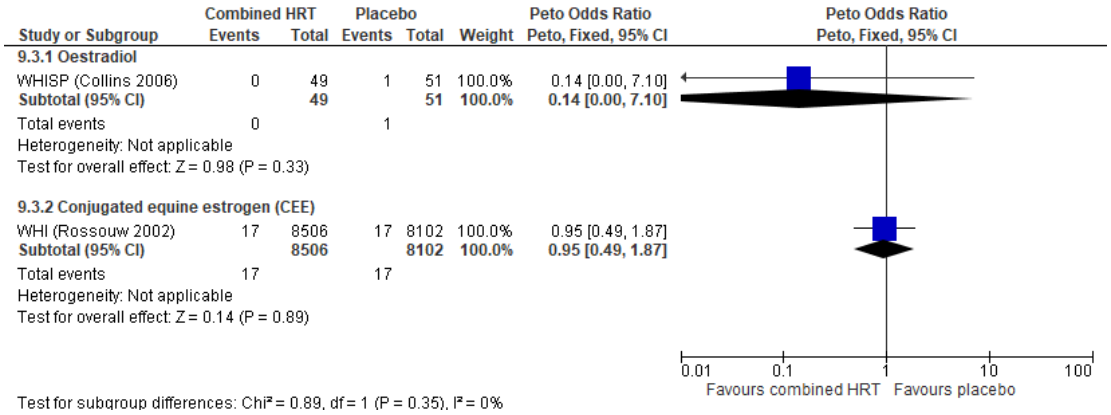


Figure 12: Combined oestrogen and progestogen (continuous) versus placebo in current users with <1 year duration of HRT use, by progestogenic constituent: nonfatal MI - RCT

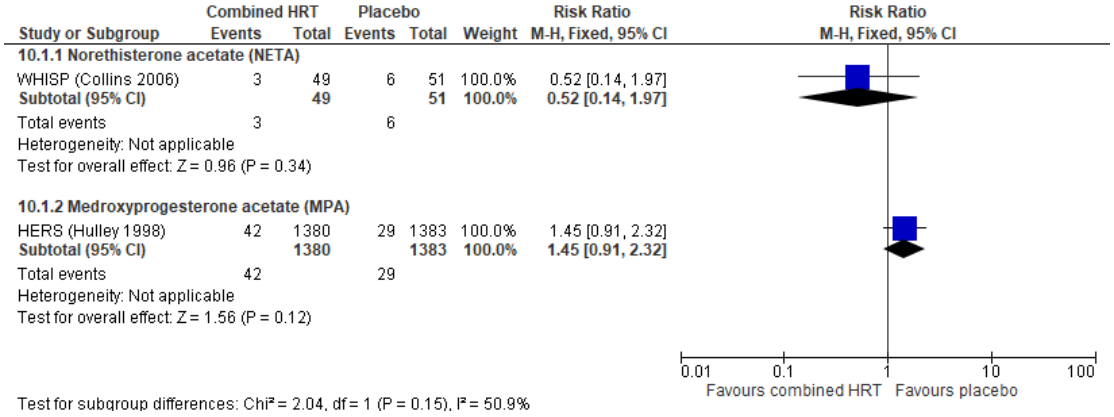


Figure 13: Combined oestrogen and progestogen (continuous) versus placebo in current users with <1 year duration of HRT use, by progestogenic constituent: mortality (cardiovascular disease related) - RCT

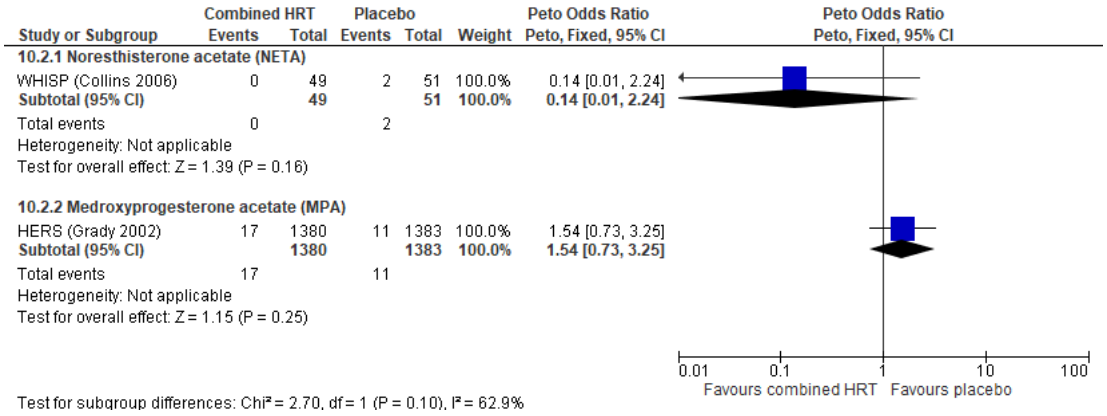


Figure 14: Combined oestrogen and progestogen (continuous) versus placebo in current users with <1 year duration of HRT use, by progestogenic constituent: stroke - RCT

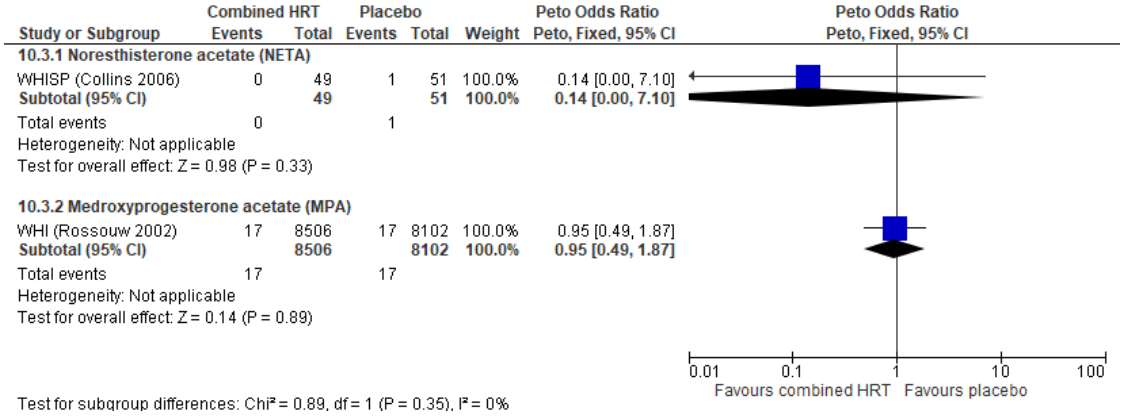


Figure 15: Combined oestrogen and progestogen (continuous) versus placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: stroke - RCT

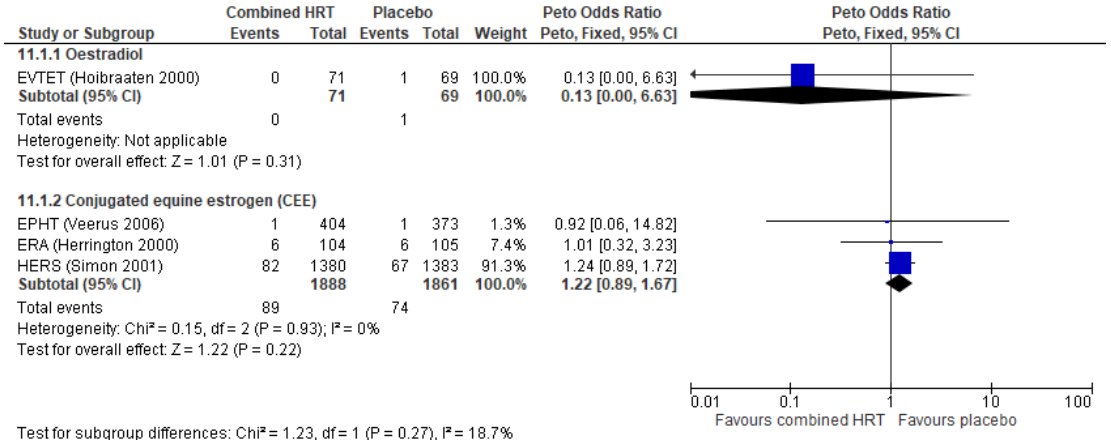


Figure 16: Combined oestrogen and progestogen (continuous) versus placebo in current users with 1-4 years duration of HRT use, by progestogenic constituent: stroke - RCT

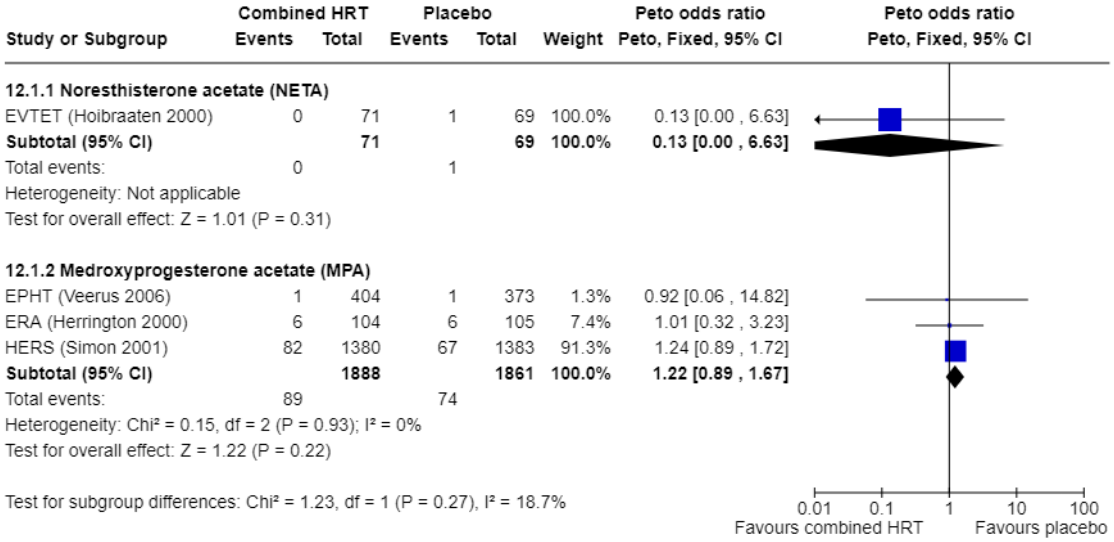
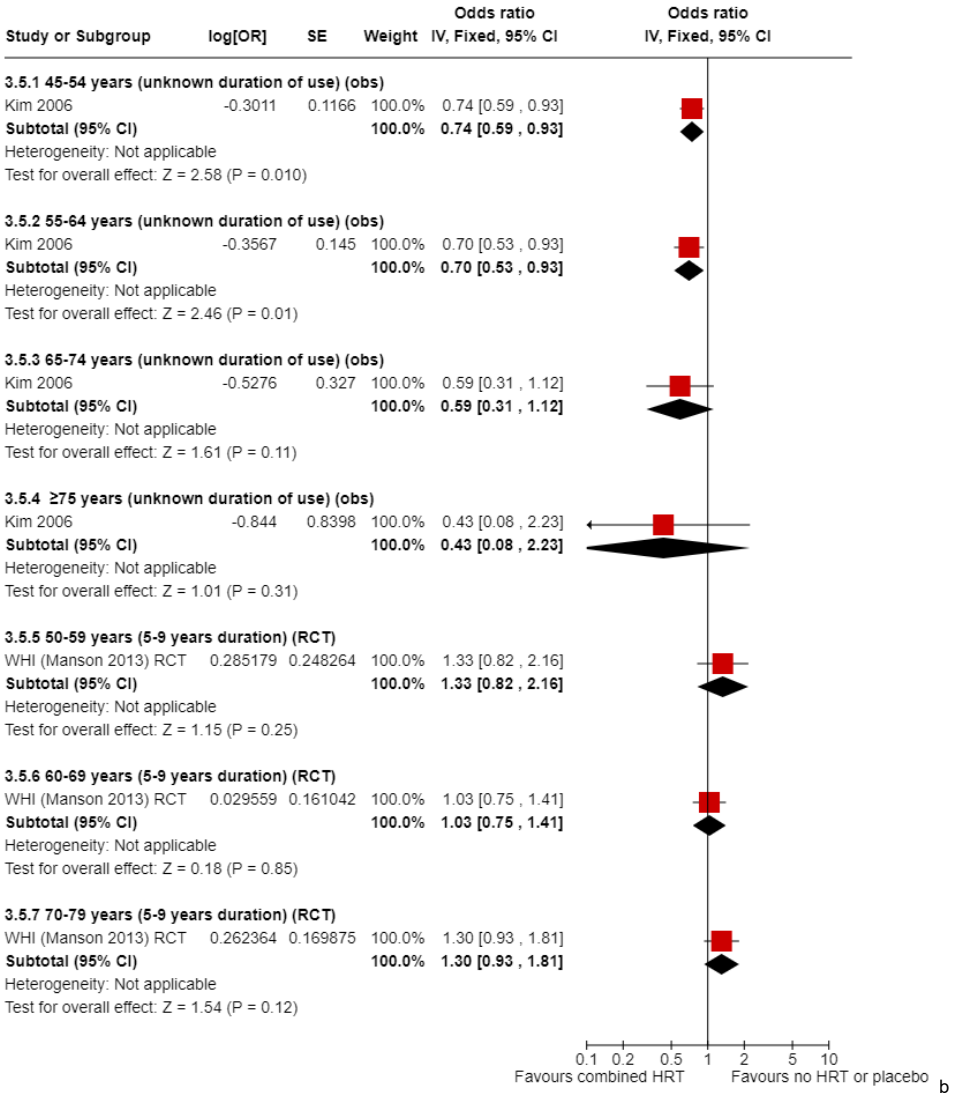
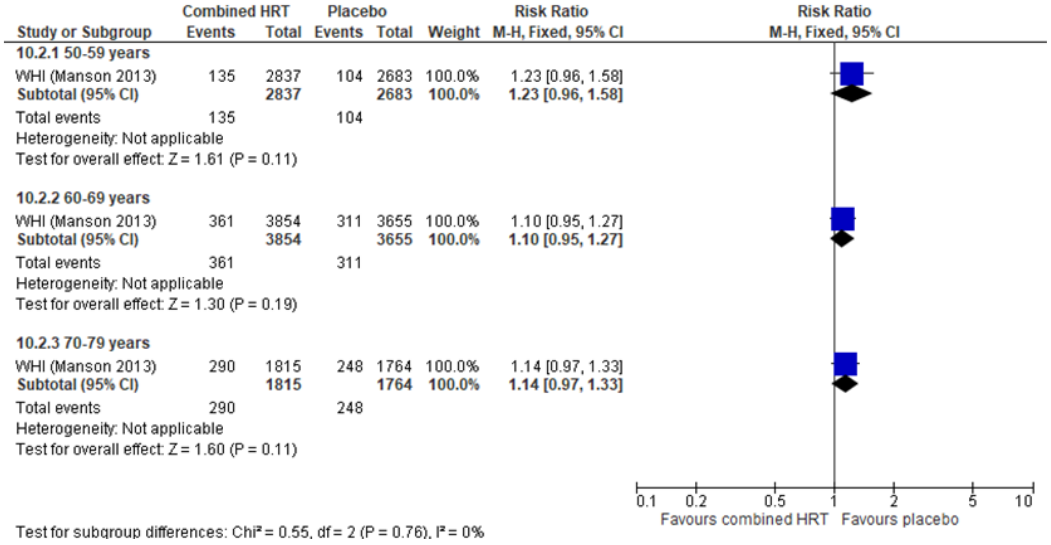


Figure 17: Combined oestrogen and progestogen (continuous) versus placebo or no HRT in current users by duration of HRT use, by age at first use: coronary heart disease (including MI) – RCT and observational studies


Study or Subgroup
log[OR]
SE
Weight
Odds ratio IV, Fixed, 95% CI
Odds ratio IV, Fixed, 95% CI
3.5.1 45-54 years (unknown duration of use) (obs)
Kim 2006 -0.3011 0.1166 100.0% 0.74 [0.59 , 0.93]
Subtotal (95% CI) 100.0% 0.74 [0.59 , 0.93]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.58 (P = 0.010)
3.5.2 55-64 years (unknown duration of use) (obs)
Kim 2006 -0.3567 0.145 100.0% 0.70 [0.53 , 0.93]
Subtotal (95% CI) 100.0% 0.70 [0.53 , 0.93]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.46 (P = 0.01)
3.5.3 65-74 years (unknown duration of use) (obs)
Kim 2006 -0.5276 0.327 100.0% 0.59 [0.31 , 1.12]
Subtotal (95% CI) 100.0% 0.59 [0.31 , 1.12]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)
3.5.4 ≥75 years (unknown duration of use) (obs)
Kim 2006 -0.844 0.8398 100.0% 0.43 [0.08 , 2.23]
Subtotal (95% CI) 100.0% 0.43 [0.08 , 2.23]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
3.5.5 50-59 years (5-9 years duration) (RCT)
WHI (Manson 2013) RCT 0.285179 0.248264 100.0% 1.33 [0.82 , 2.16]
Subtotal (95% CI) 100.0% 1.33 [0.82 , 2.16]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)
3.5.6 60-69 years (5-9 years duration) (RCT)
WHI (Manson 2013) RCT 0.029559 0.161042 100.0% 1.03 [0.75 , 1.41]
Subtotal (95% CI) 100.0% 1.03 [0.75 , 1.41]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.85)
3.5.7 70-79 years (5-9 years duration) (RCT)
WHI (Manson 2013) RCT 0.262364 0.169875 100.0% 1.30 [0.93 , 1.81]
Subtotal (95% CI) 100.0% 1.30 [0.93 , 1.81]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)
0.1 0.2 0.5 1 2 5 10
Favours combined HRT
Favours no HRT or placebo

b

Figure 18: Combined oestrogen and progestogen (continuous) versus placebo in current users with 5-9 years duration of HRT use, by age at first use: cardiovascular event composite score - RCT



[b] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for RCT evidence are risk ratios, but presented under odds ratio labels for presentational purposes. See table 10 for full GRADE profile for RCT evidence, and table 21 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 1.32$, df=2 (P=0.52), $I^2 = 0\%$. Test for subgroup differences for observational evidence: $Chi^2 = 0.81$, df=3 (P=0.85), $I^2 = 0\%$.

Figure 19: Combined oestrogen and progestogen (continuous) versus placebo in current users with 5-9 years duration of HRT use, by age at first use: mortality (cardiovascular disease related) - RCT

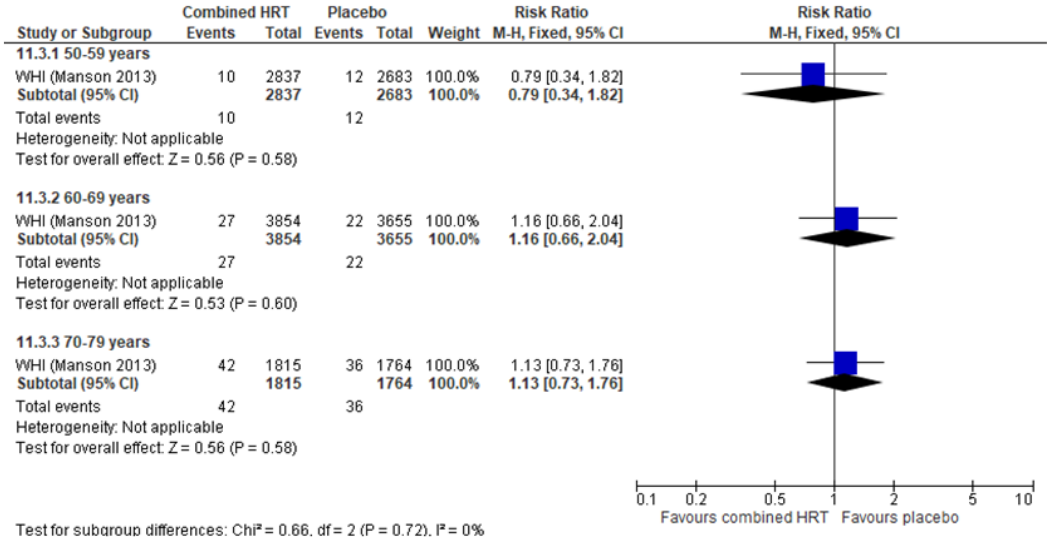
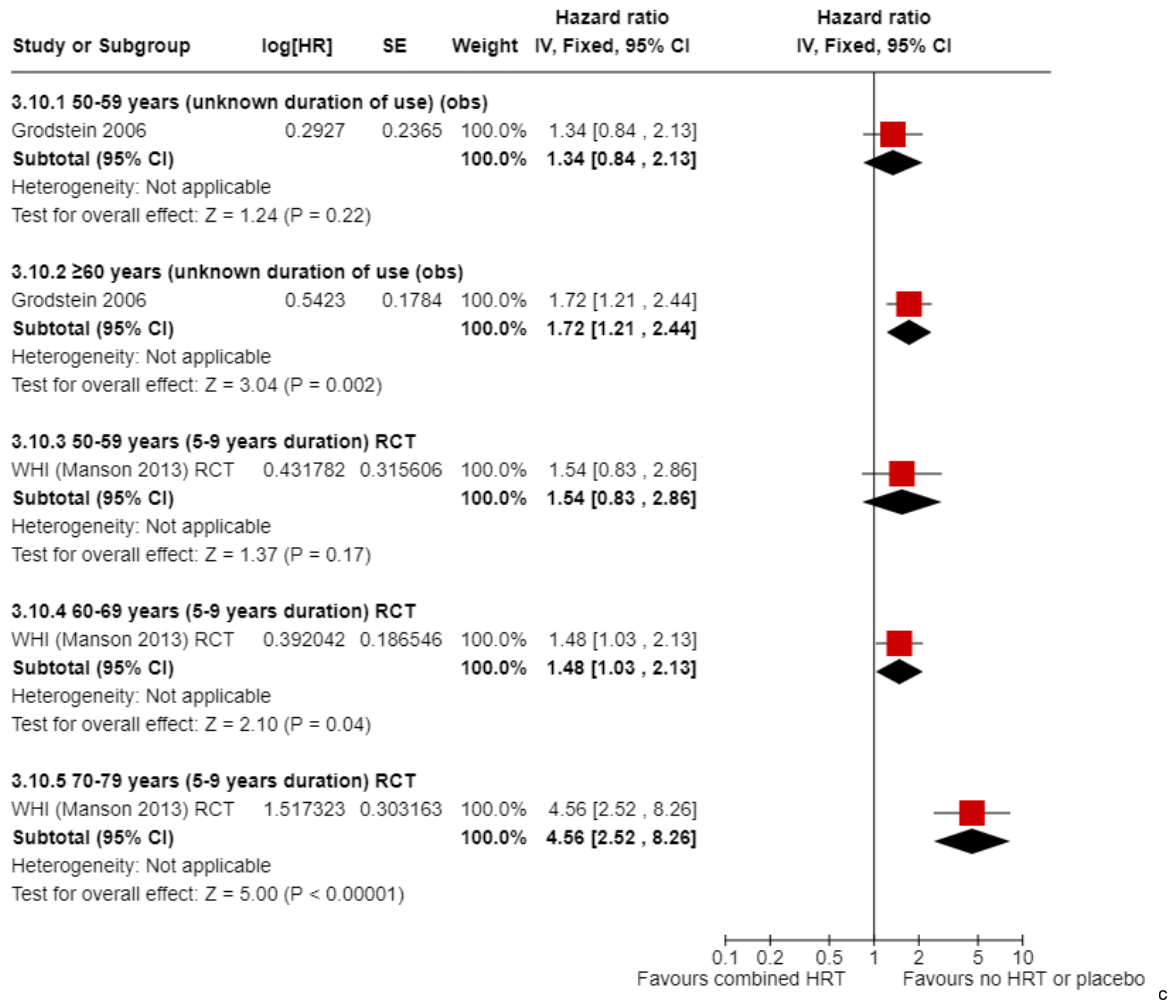
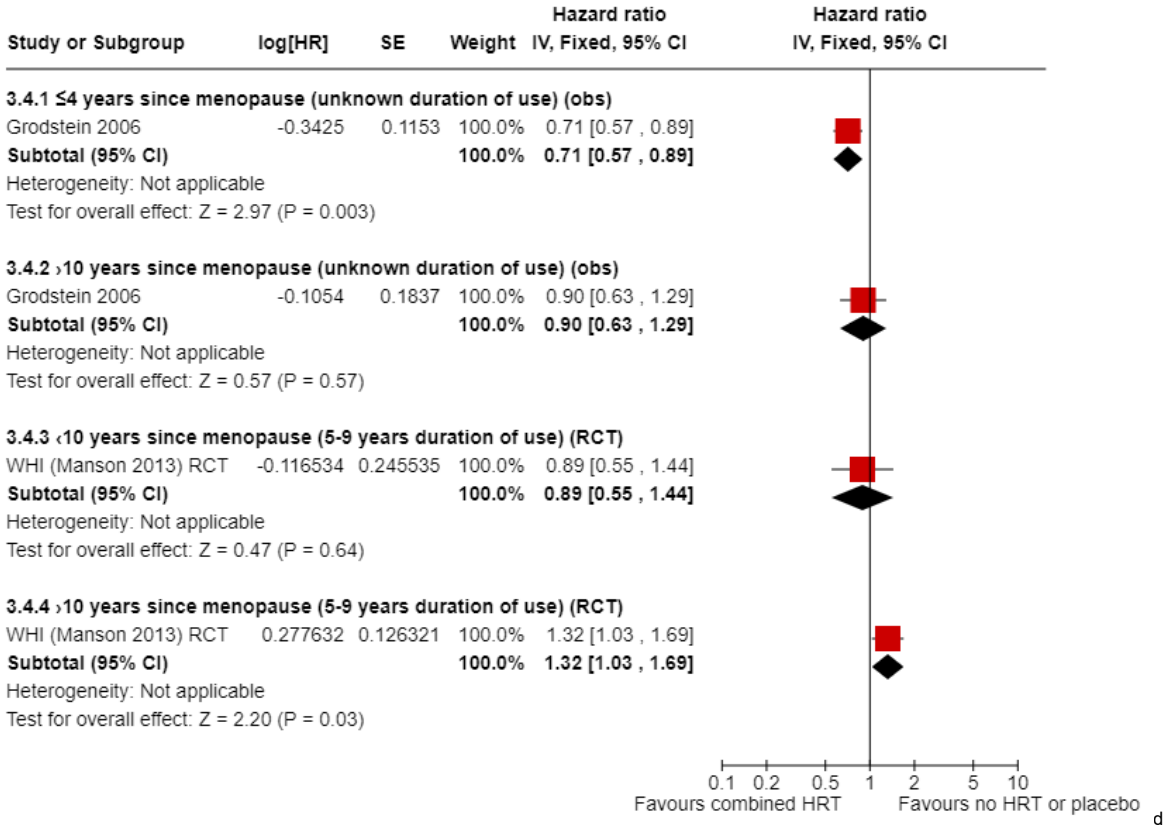


Figure 20: Combined oestrogen and progestogen (continuous) versus placebo or no HRT in current users by duration of HRT use, by age at first use: stroke – RCT and observational studies



[c] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for RCT data are risk ratios but presented under Hazard ratio labels for presentational purposes. See table 10 for full GRADE profile for RCT evidence, and table 21 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 10.57$, df=2 (P=0.005), $I^2 = 81.1\%$. Test for subgroup differences for observational evidence: $Chi^2 = 0.71$, df=1 (P=0.4), $I^2 = 0\%$.

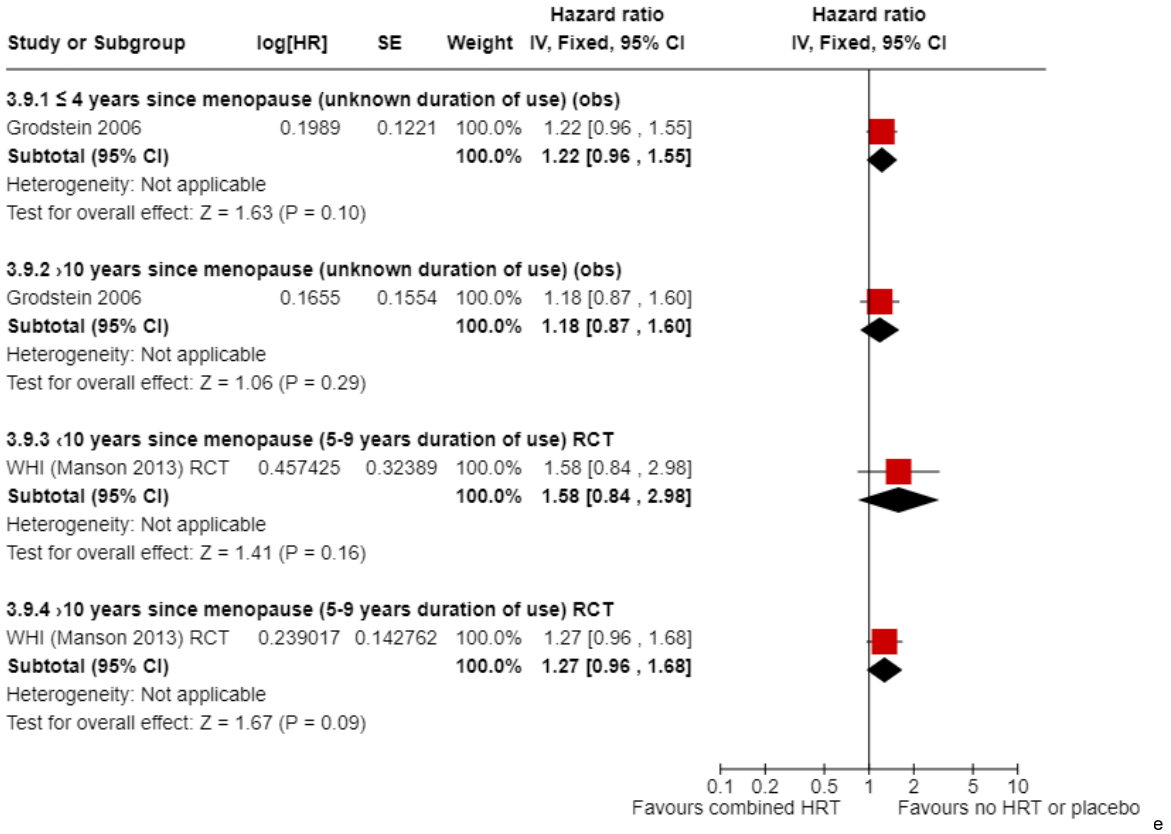
Figure 21: Combined oestrogen and progestogen (continuous) versus placebo or no HRT in current users by duration of HRT use, by time since menopause at first use: coronary heart disease (including MI) – RCT and observational studies



[d]

[d] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for RCT data are risk ratios but presented under Hazard ratio labels for presentational purposes. See table 11 for full GRADE profile for RCT evidence, and table 21 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 2.06$, df=1 (P=0.15), $I^2 = 51.4\%$. Test for subgroup differences for observational evidence: $Chi^2 = 1.20$, df=1 (P=0.27), $I^2 = 16.3\%$.

Figure 22: Combined oestrogen and progestogen (continuous) versus placebo or no HRT in current users by duration of HRT use, by time since menopause at first use: stroke – RCT and observational studies



[e]

[e] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for RCT data are risk ratios but presented under Hazard ratio labels for presentational purposes. See table 11 for full GRADE profile for RCT evidence, and table 21 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 0.38$, df=1 (P=0.54), $I^2 = 0\%$. Test for subgroup differences for observational evidence: $Chi^2 = 0.03$, df=1 (P=0.87), $I^2 = 0\%$.

Figure 23: Combined oestrogen and progestogen (continuous) versus placebo in current users with 5-9 years duration of HRT use, by ethnicity: stroke - RCT

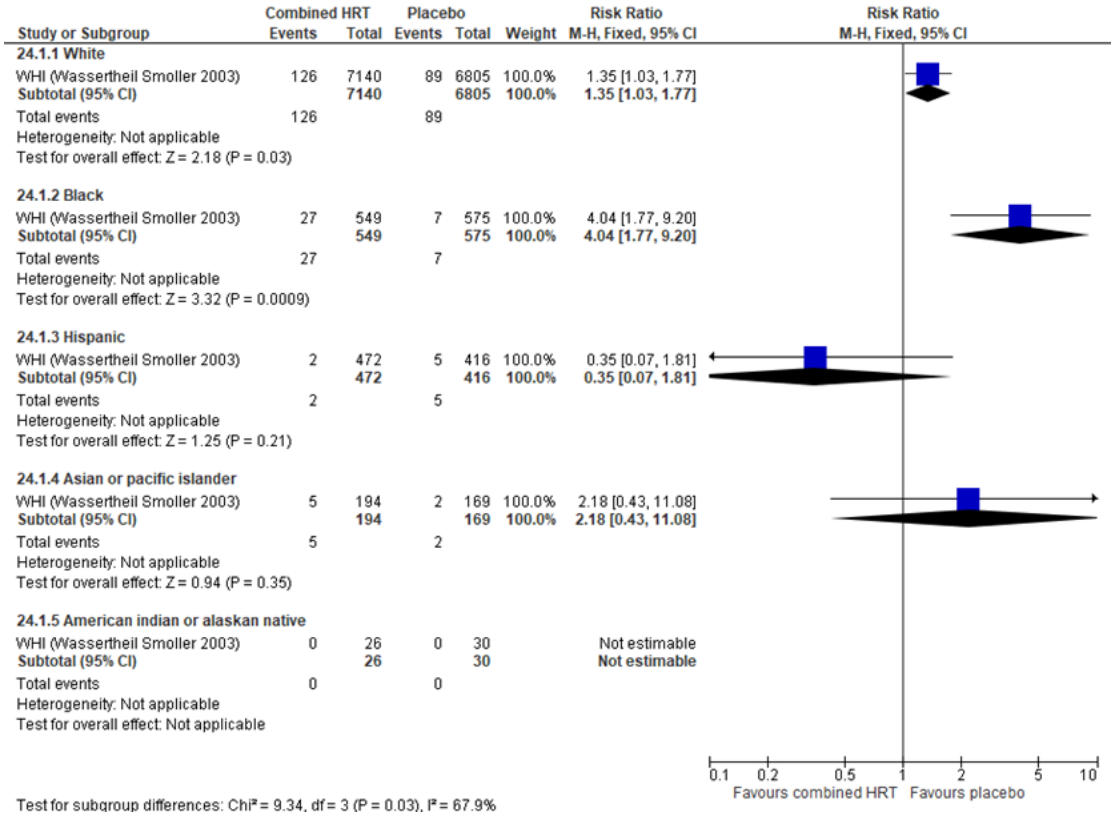


Figure 24: Combined oestrogen and progestogen (continuous) versus placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use: coronary heart disease (including MI) - RCT

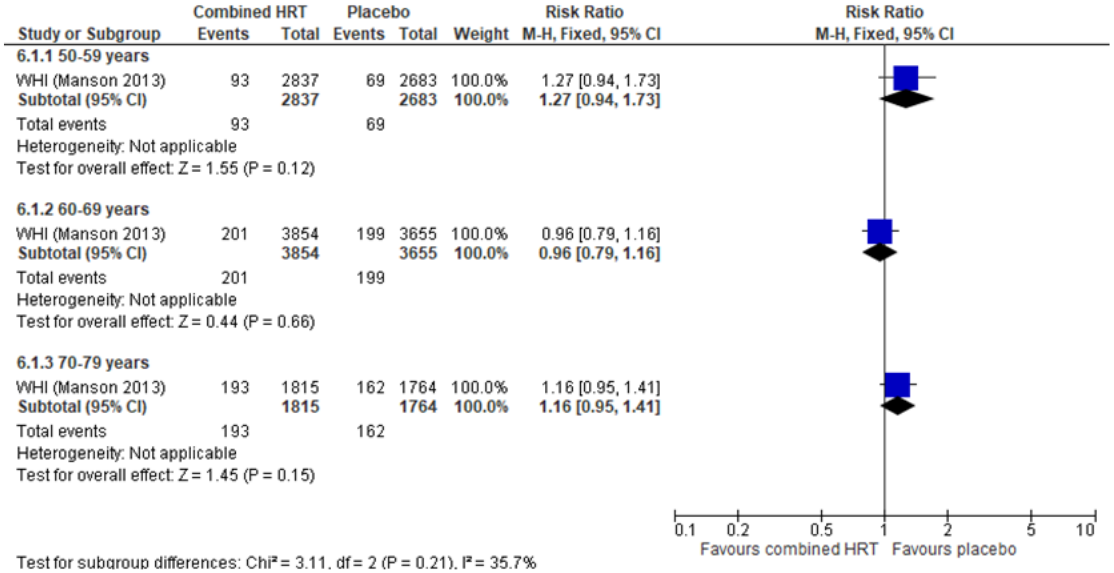


Figure 25: Combined oestrogen and progestogen (continuous) versus placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use: cardiovascular event composite score - RCT

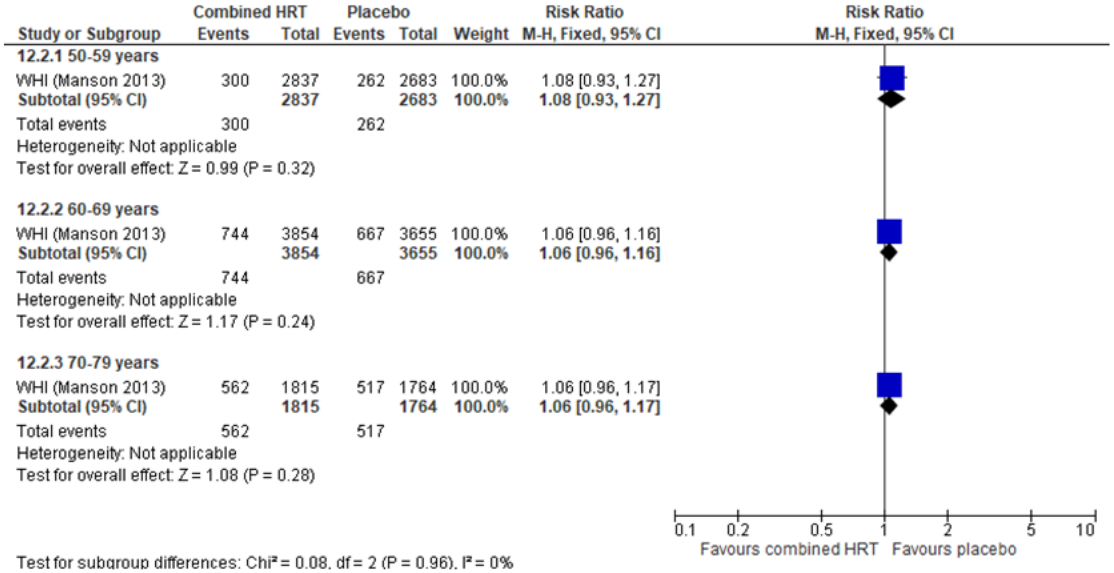


Figure 26: Combined oestrogen and progestogen (continuous) versus placebo in current and past users (unknown recency) with 5-9 years duration of HRT use, by age at first use at 13 years cumulative follow-up: mortality (cardiovascular disease related) - RCT

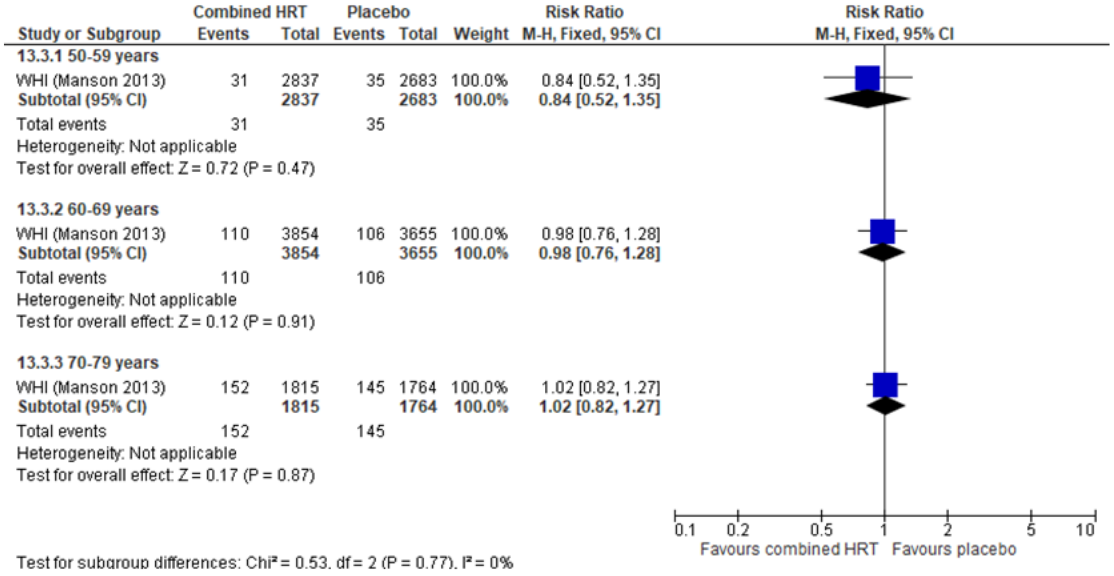


Figure 27: Combined oestrogen and progestogen (continuous) versus placebo in current and past users (unknown recency) with 5-9 years duration of HRT use, by age at first use at 13 years cumulative follow-up: stroke - RCT

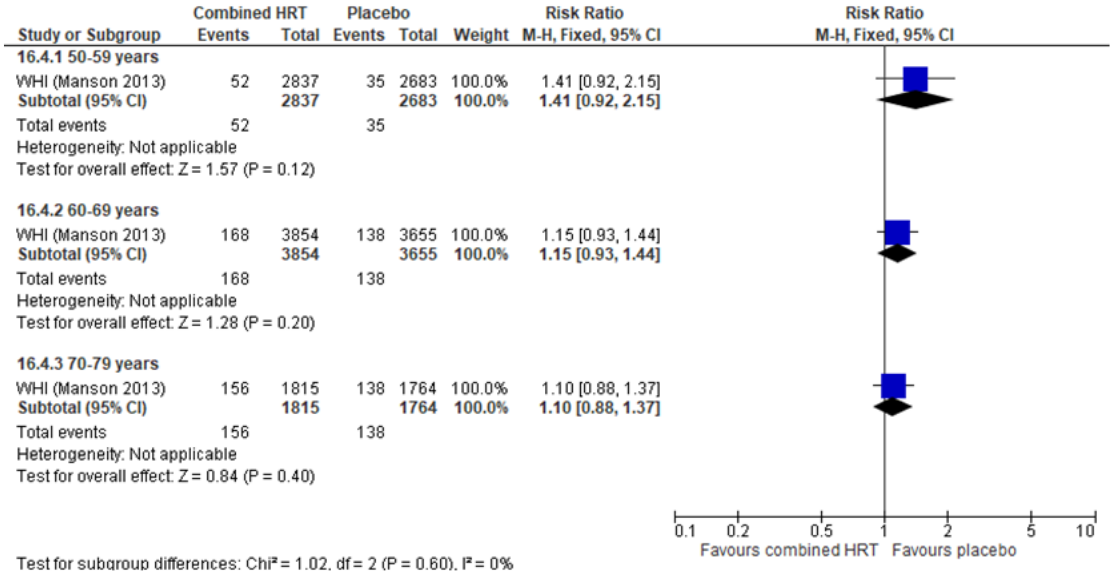
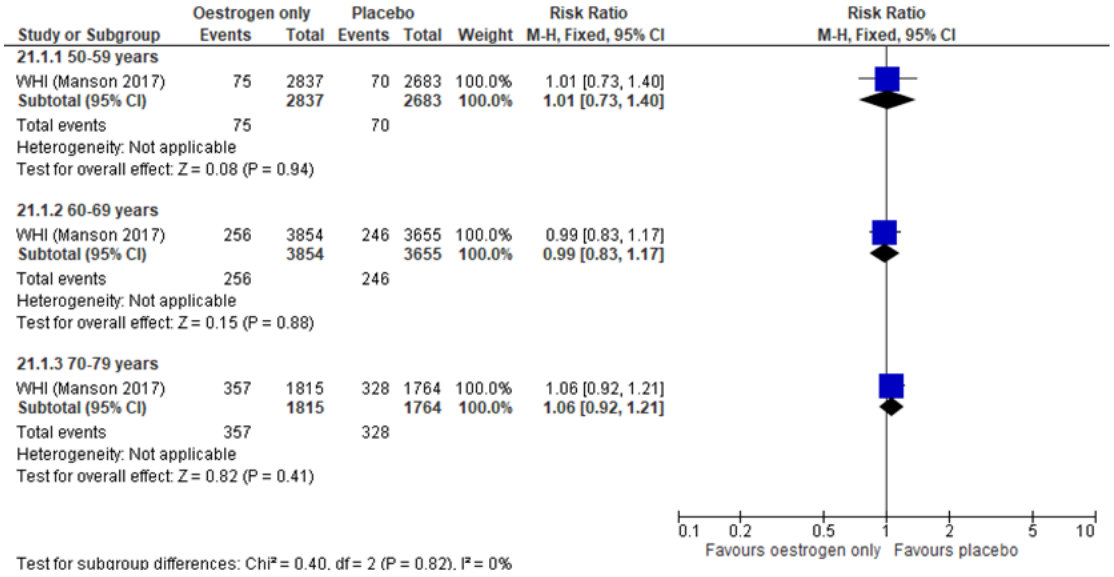


Figure 28: Combined oestrogen and progestogen (continuous) versus placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 18 years cumulative follow-up, by age at first use: mortality (cardiovascular disease related) - RCT



Combined HRT (sequential) versus placebo: RCT evidence

Figure 29: Combined oestrogen and progestogen (sequential) versus placebo, by recency and duration of HRT use: nonfatal MI

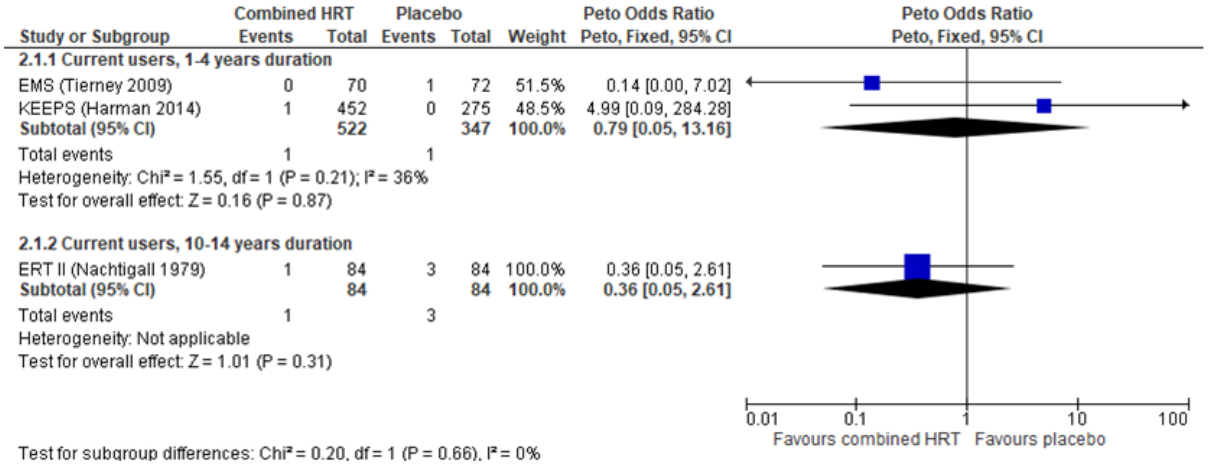


Figure 30: Combined oestrogen and progestogen (sequential) versus placebo, by recency and duration of HRT use: cardiac event composite score

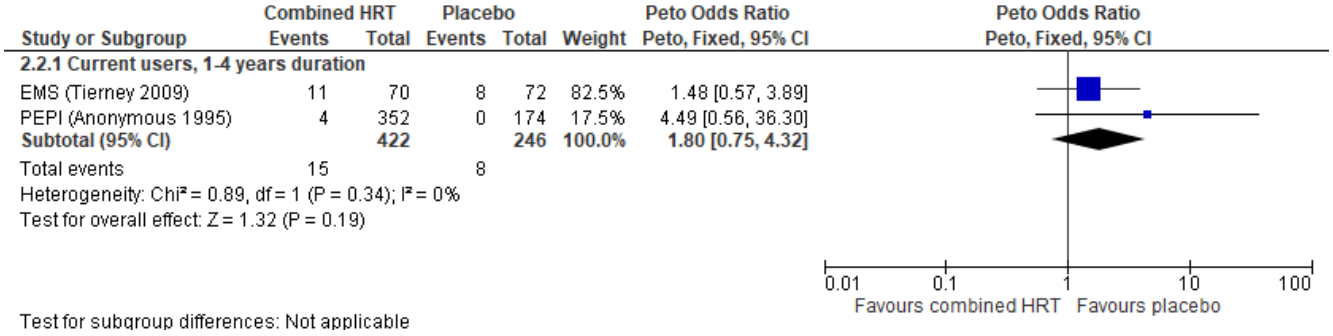


Figure 31: Combined oestrogen and progestogen (sequential) versus placebo, by recency and duration of HRT use: mortality (cardiovascular disease related)

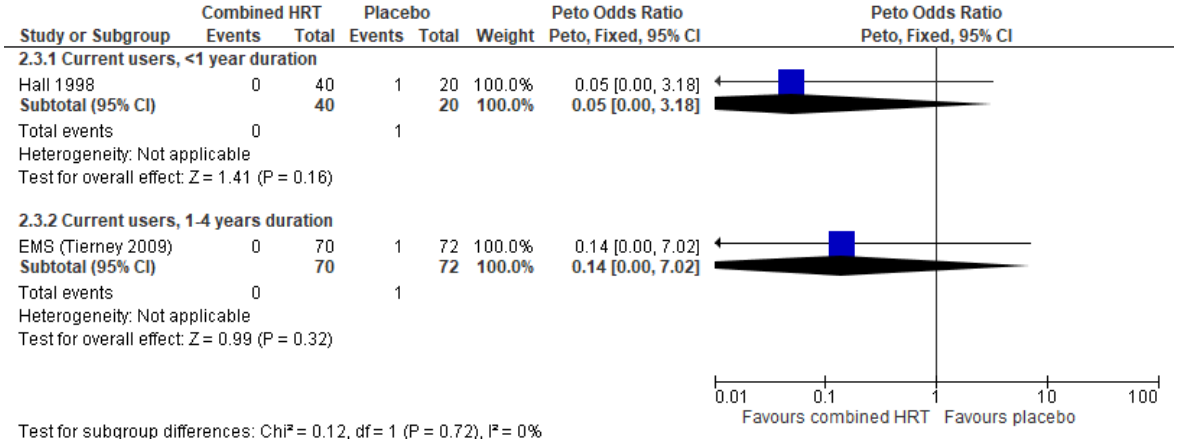


Figure 32: Combined oestrogen and progestogen (sequential) versus placebo, by recency and duration of HRT use: stroke

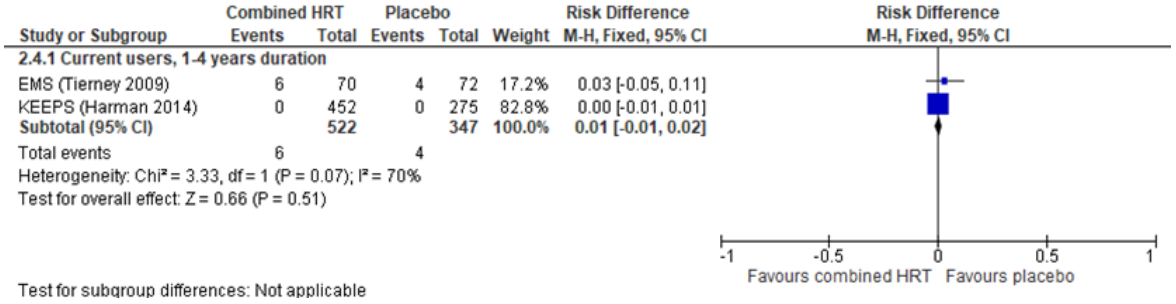


Figure 33: Combined oestrogen and progestogen (sequential) versus placebo, by recency and duration of HRT use: TIA

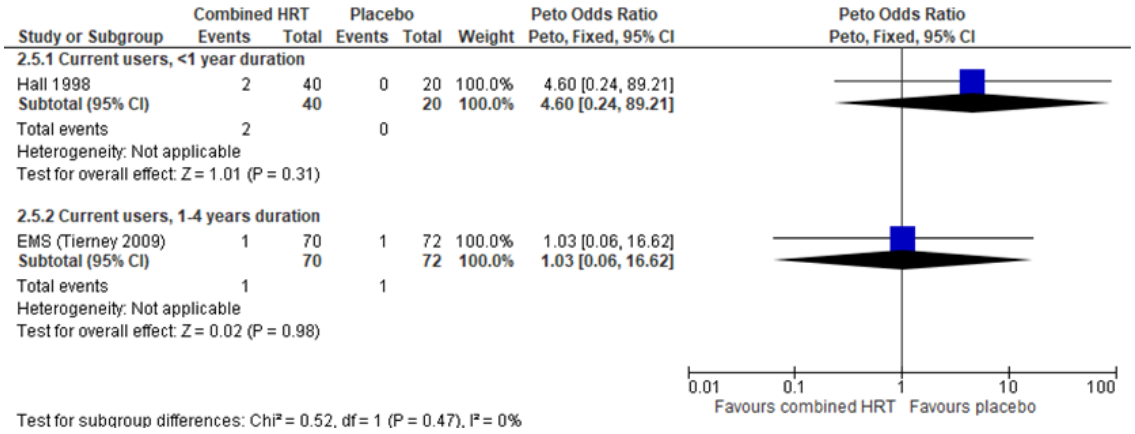


Figure 34: Combined oestrogen and progestogen (sequential) versus placebo in current users with <1 years duration of HRT use, by oestrogenic constituent: mortality (cardiovascular disease related)

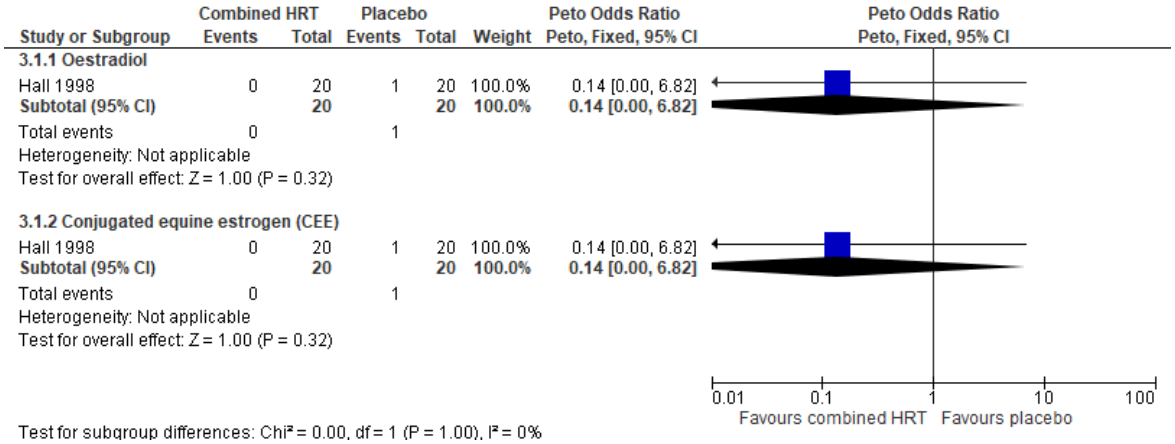


Figure 35: Combined oestrogen and progestogen (sequential) versus placebo in current users with <1 years duration of HRT use, by oestrogenic constituent: TIA

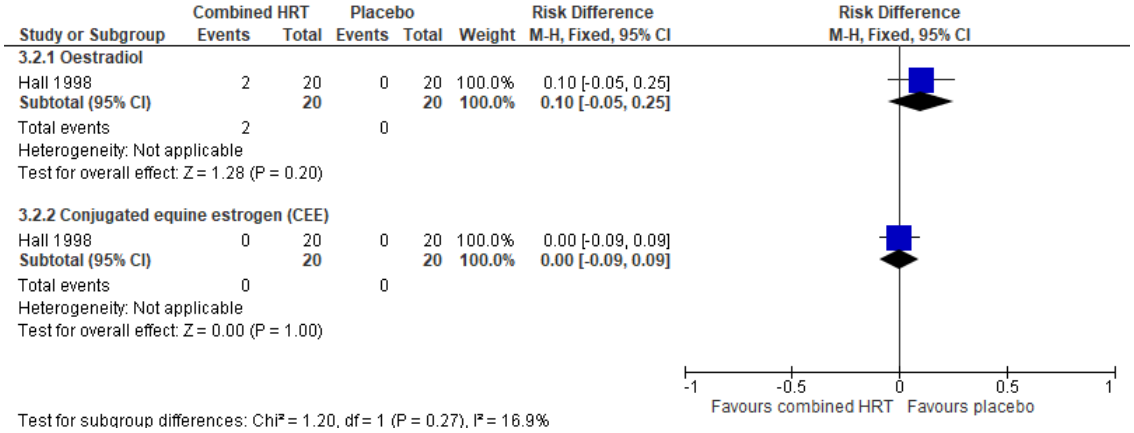


Figure 36: Combined oestrogen and progestogen (sequential) versus placebo in current users with <1 years duration of HRT use, by mode of administration: mortality (cardiovascular disease related)

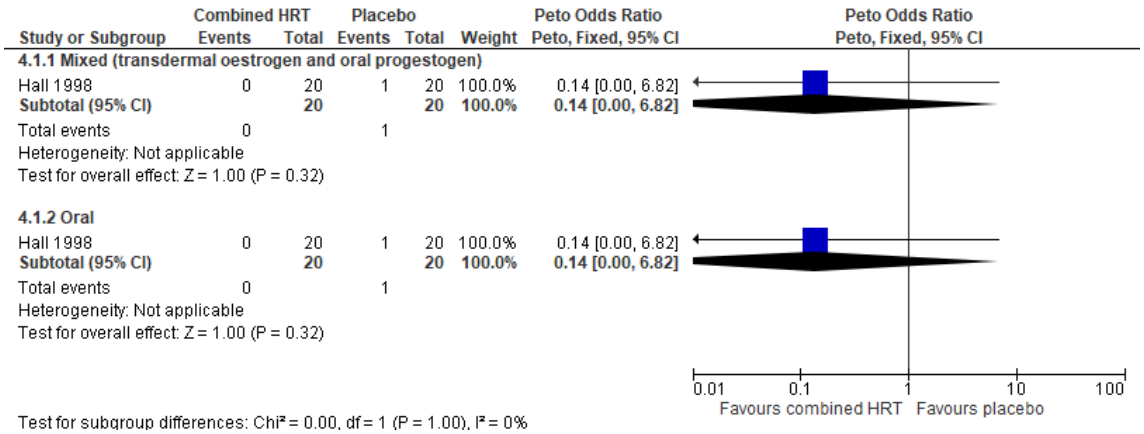


Figure 37: Combined oestrogen and progestogen (sequential) versus placebo in current users with <1 years duration of HRT use, by mode of administration: TIA

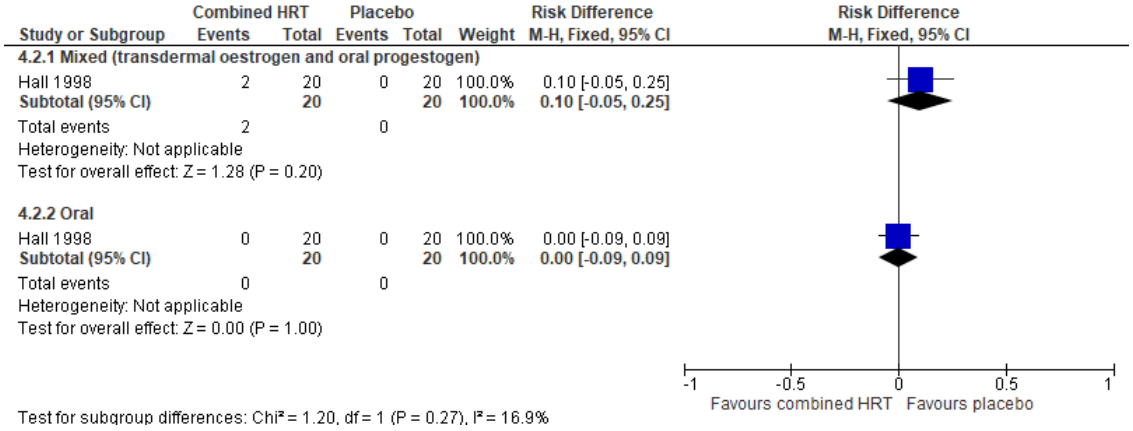


Figure 38: Combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: nonfatal MI

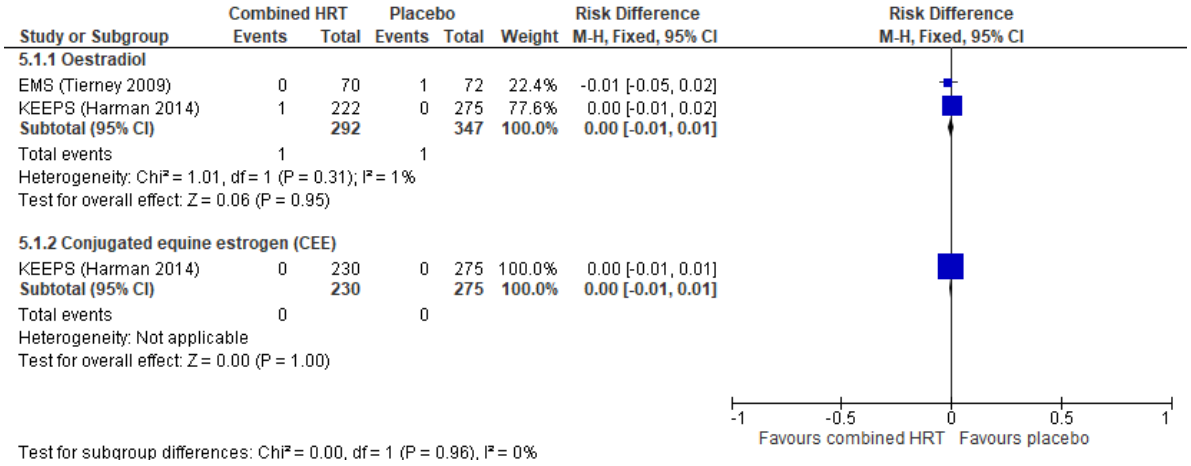


Figure 39: Combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: cardiac event composite score

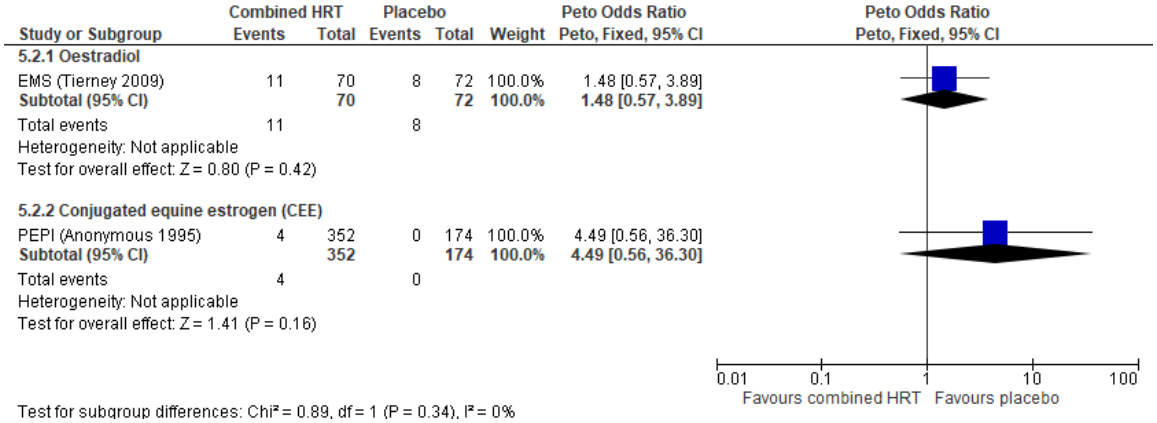


Figure 40: Combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: stroke

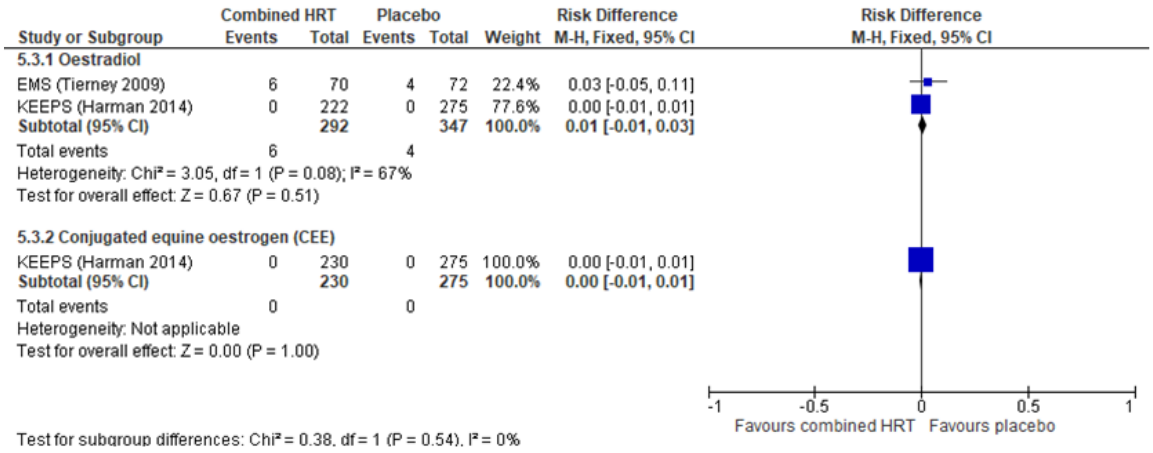


Figure 41: Combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by progestogenic constituent: nonfatal MI

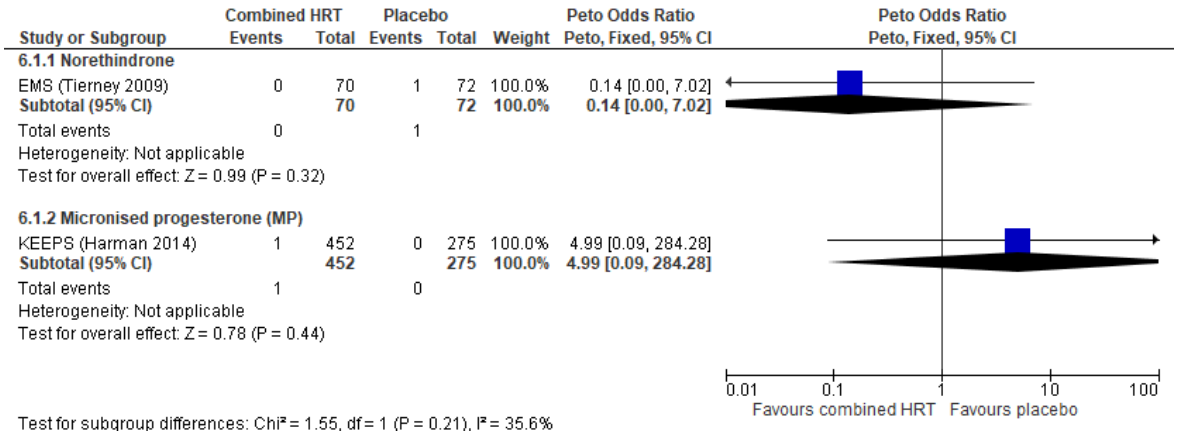


Figure 42: Combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by progestogenic constituent: cardiovascular event composite scores

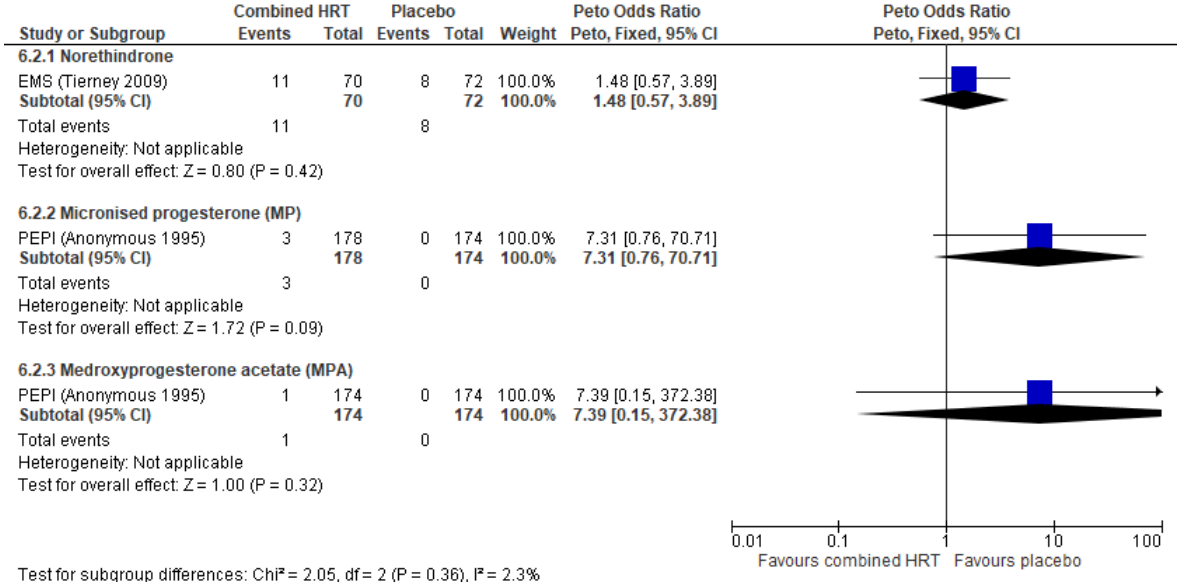


Figure 43: Combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by progestogenic constituent: stroke

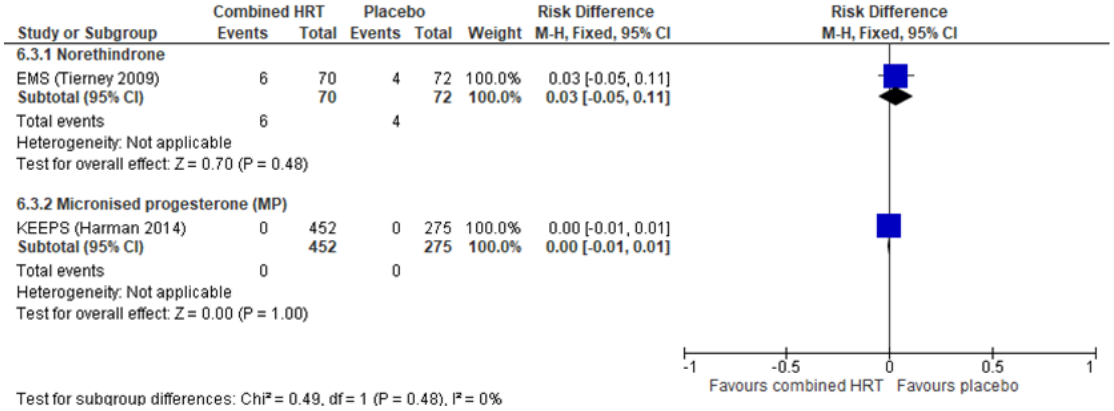


Figure 44: Combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by mode of administration: nonfatal MI

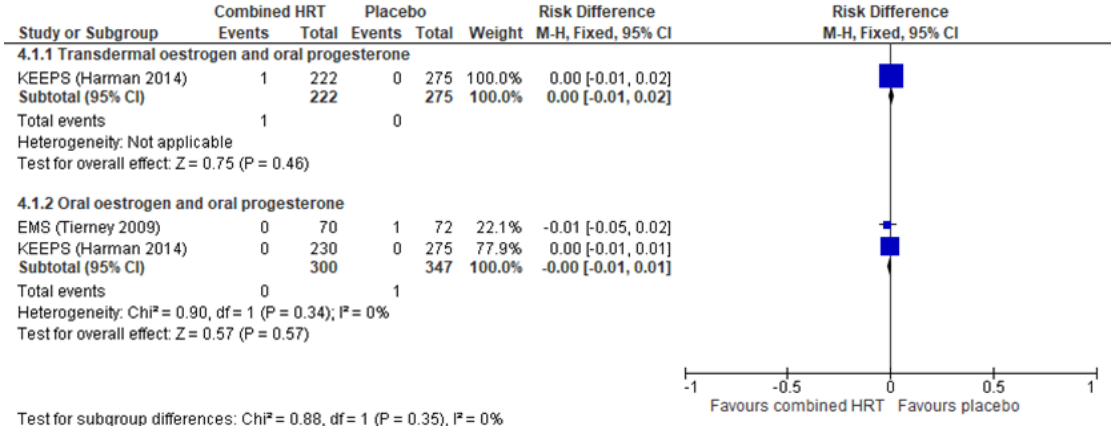
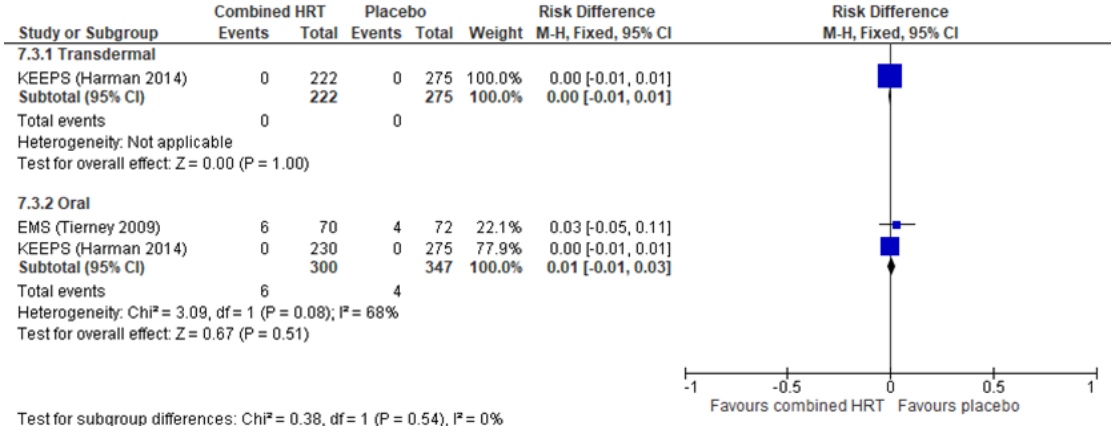


Figure 45: Combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by mode of administration: stroke



Combined HRT versus no HRT: Observational study evidence

Figure 46: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by continuous or cyclic HRT schedule: stroke HR

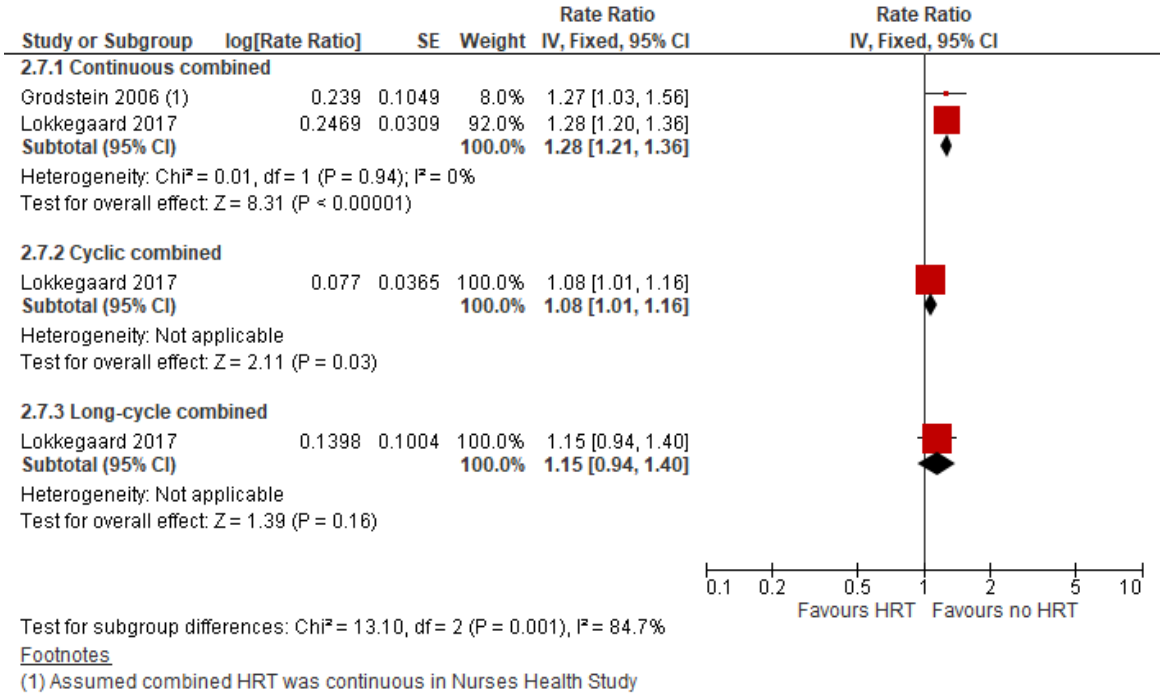


Figure 47: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by oestrogen dose (continuous combined): stroke

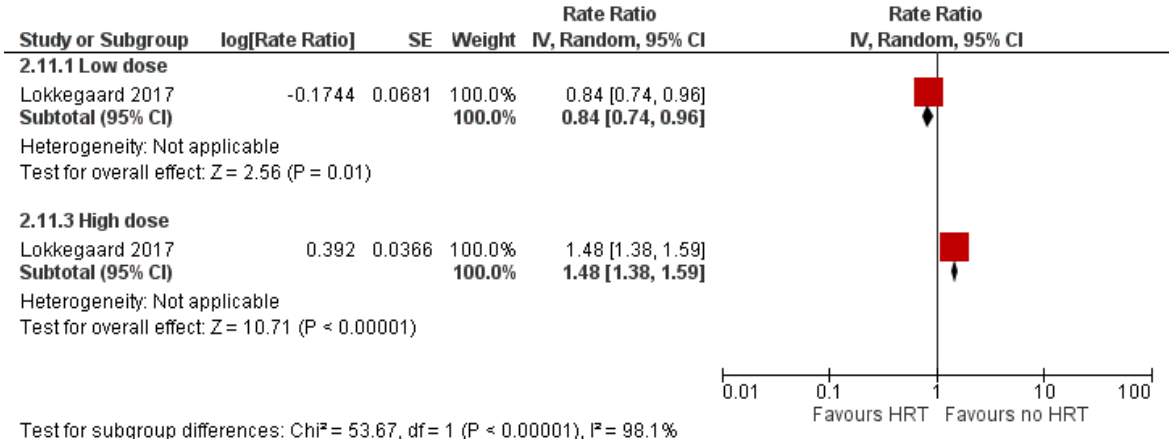


Figure 48: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by oestrogen dose (cyclic combined): stroke

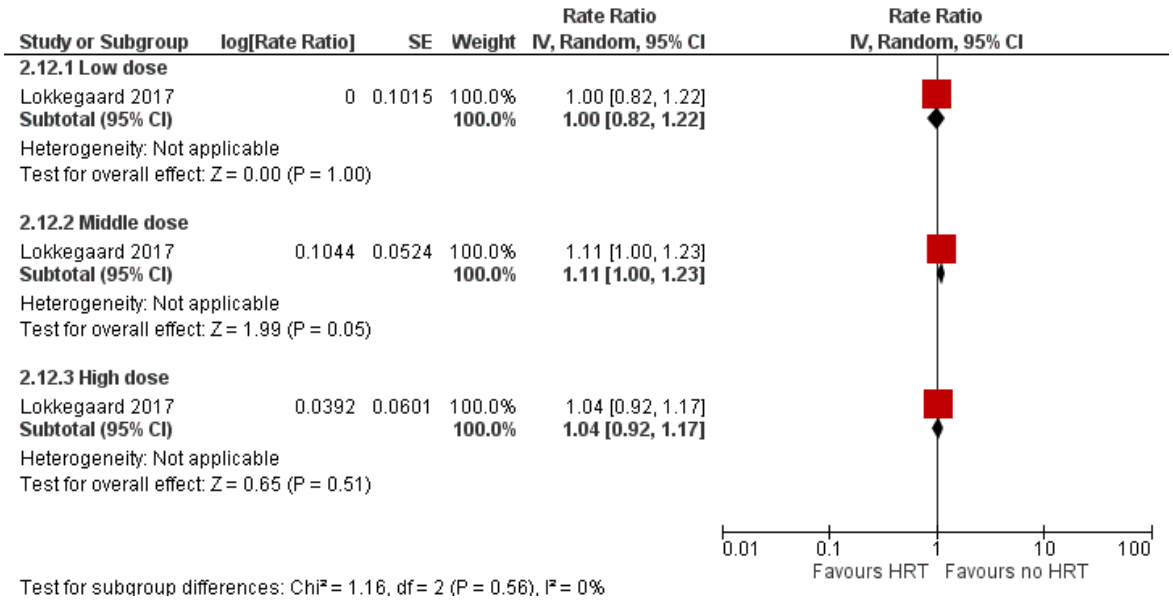

Study or Subgroup
log[Rate Ratio]
SE
Weight
Rate Ratio
IV, Random, 95% CI
Rate Ratio
IV, Random, 95% CI
2.12.1 Low dose
Lokkegaard 2017 0 0.1015 100.0% 1.00 [0.82, 1.22]
Subtotal (95% CI) 100.0% 1.00 [0.82, 1.22]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
2.12.2 Middle dose
Lokkegaard 2017 0.1044 0.0524 100.0% 1.11 [1.00, 1.23]
Subtotal (95% CI) 100.0% 1.11 [1.00, 1.23]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)
2.12.3 High dose
Lokkegaard 2017 0.0392 0.0601 100.0% 1.04 [0.92, 1.17]
Subtotal (95% CI) 100.0% 1.04 [0.92, 1.17]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
0.01
0.1
1
10
100
Favours HRT
Favours no HRT
Test for subgroup differences: Chi² = 1.16, df = 2 (P = 0.56), I² = 0%

Figure 49: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by progestogenic constituent: stroke OR

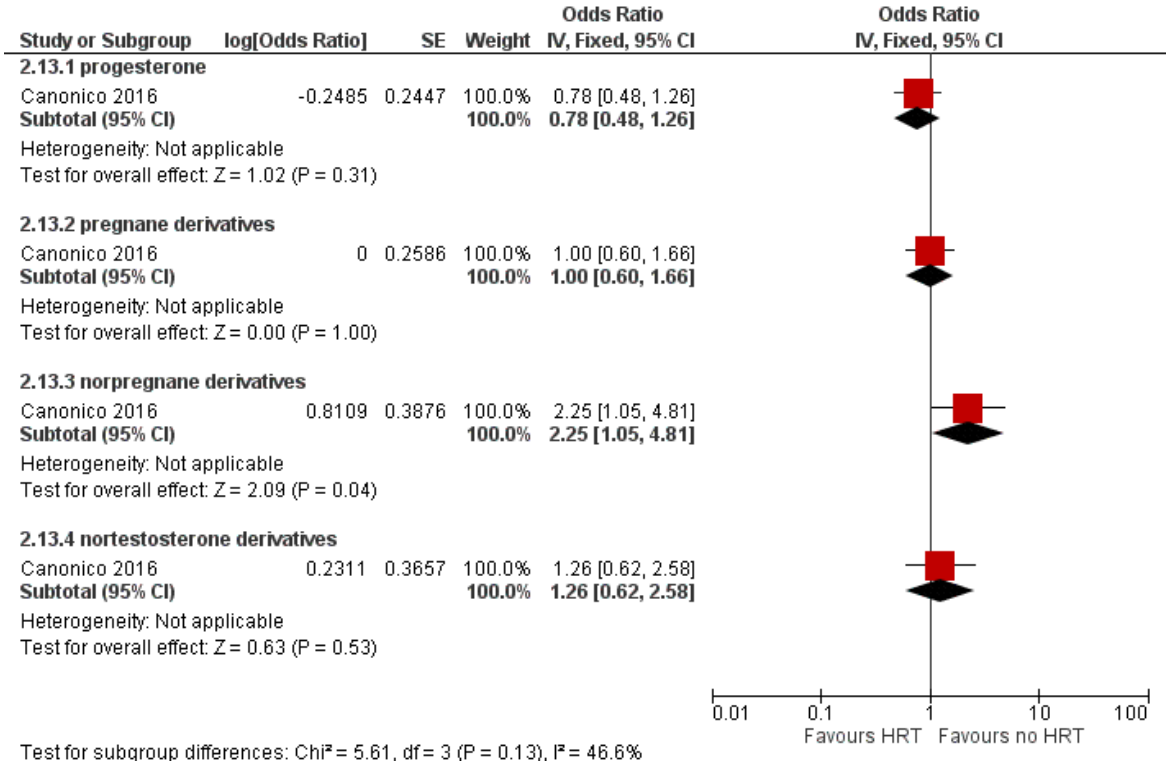


Figure 50: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by progestogenic constituent (continuous combined): stroke

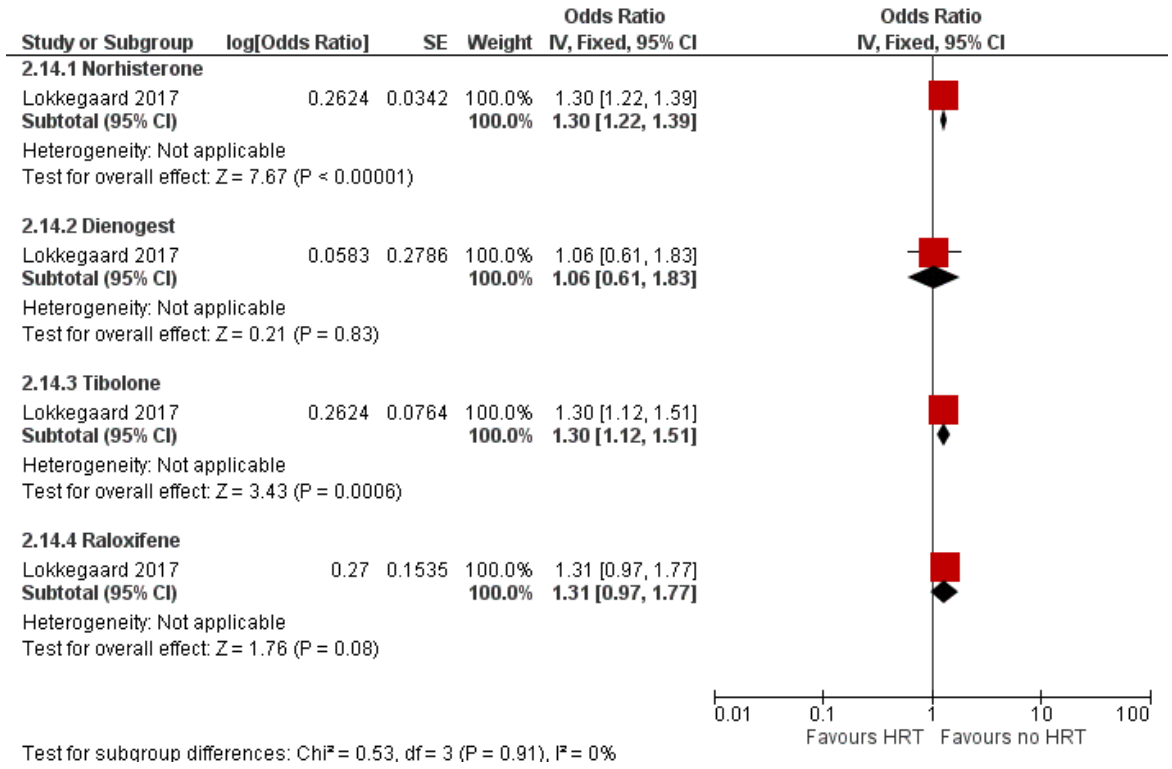


Figure 51: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by progestogenic constituent (cyclic combined): stroke

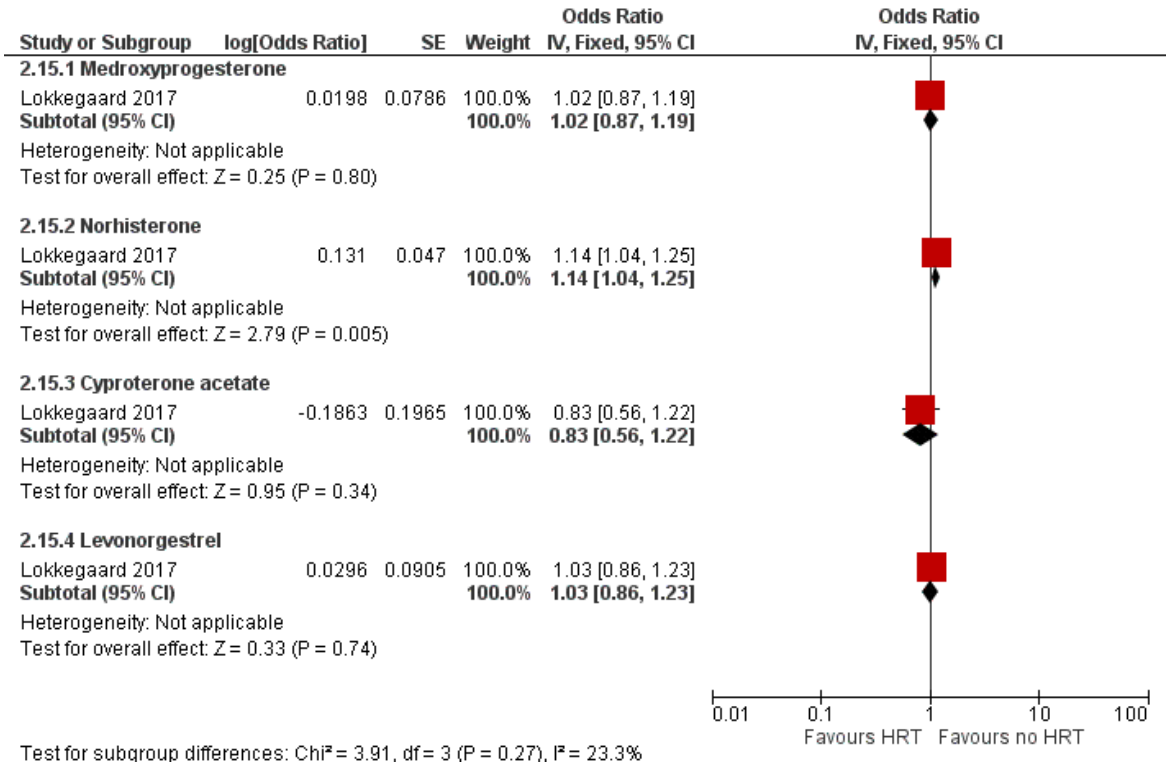

Study or Subgroup
log[Odds Ratio]
SE
Weight
Odds Ratio
IV, Fixed, 95% CI
Odds Ratio
IV, Fixed, 95% CI
2.15.1 Medroxyprogesterone
Lokkegaard 2017 0.0198 0.0786 100.0% 1.02 [0.87, 1.19]
Subtotal (95% CI) 100.0% 1.02 [0.87, 1.19]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
2.15.2 Norhisterone
Lokkegaard 2017 0.131 0.047 100.0% 1.14 [1.04, 1.25]
Subtotal (95% CI) 100.0% 1.14 [1.04, 1.25]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.79 (P = 0.005)
2.15.3 Cyproterone acetate
Lokkegaard 2017 -0.1863 0.1965 100.0% 0.83 [0.56, 1.22]
Subtotal (95% CI) 100.0% 0.83 [0.56, 1.22]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
2.15.4 Levonorgestrel
Lokkegaard 2017 0.0296 0.0905 100.0% 1.03 [0.86, 1.23]
Subtotal (95% CI) 100.0% 1.03 [0.86, 1.23]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
0.01
0.1
1
10
100
Favours HRT
Favours no HRT
Test for subgroup differences: Chi² = 3.91, df = 3 (P = 0.27), I² = 23.3%

Figure 52: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by route of administration: stroke

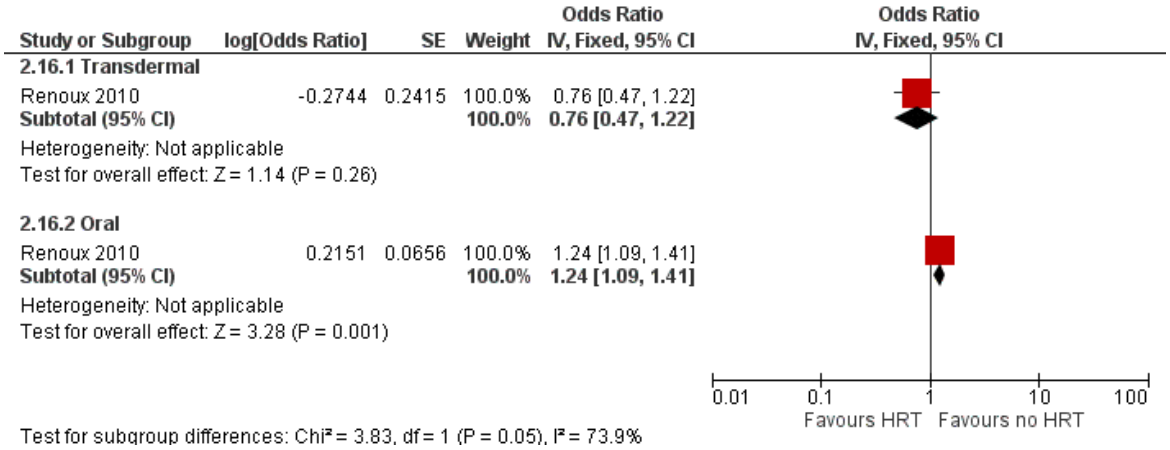


Figure 53: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by route of administration (continuous combined): stroke

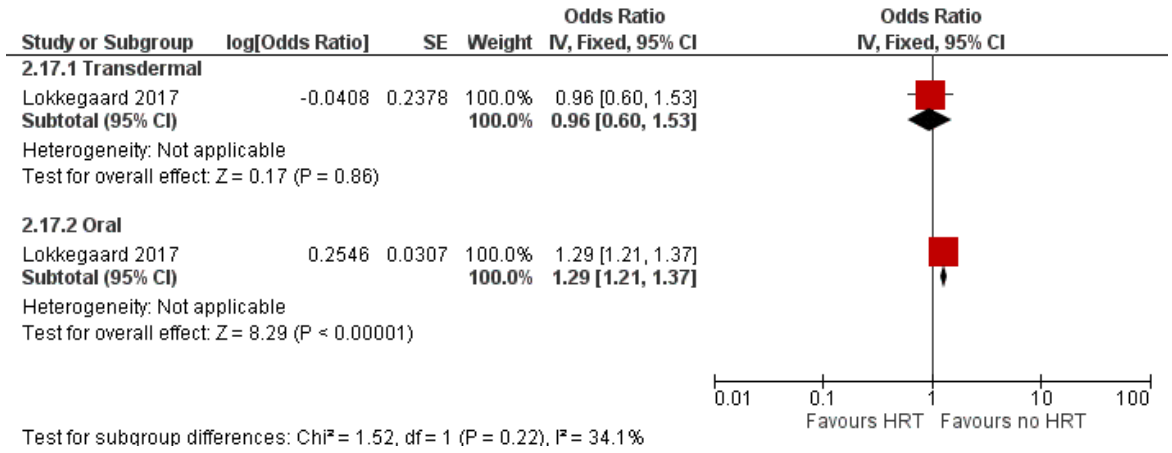


Figure 54: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by route of administration (cyclic combined)

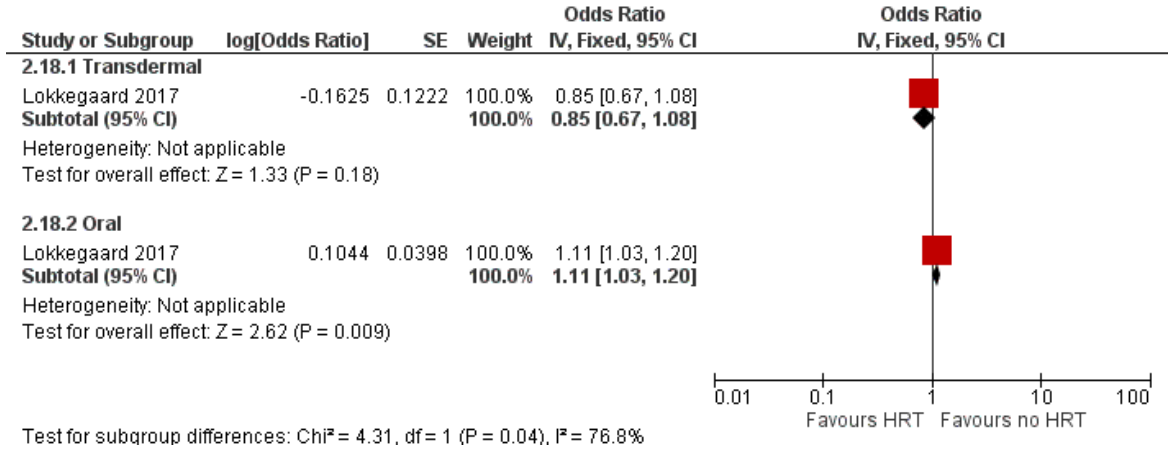
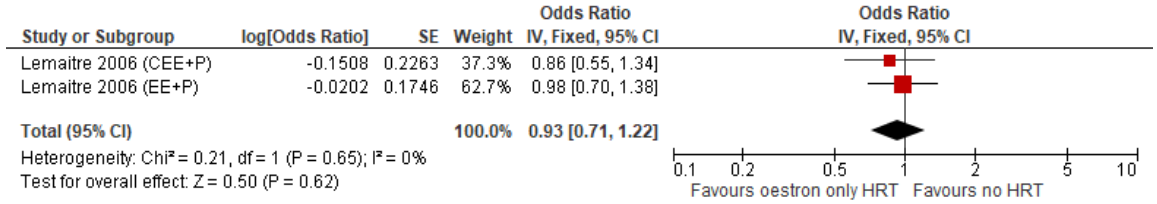
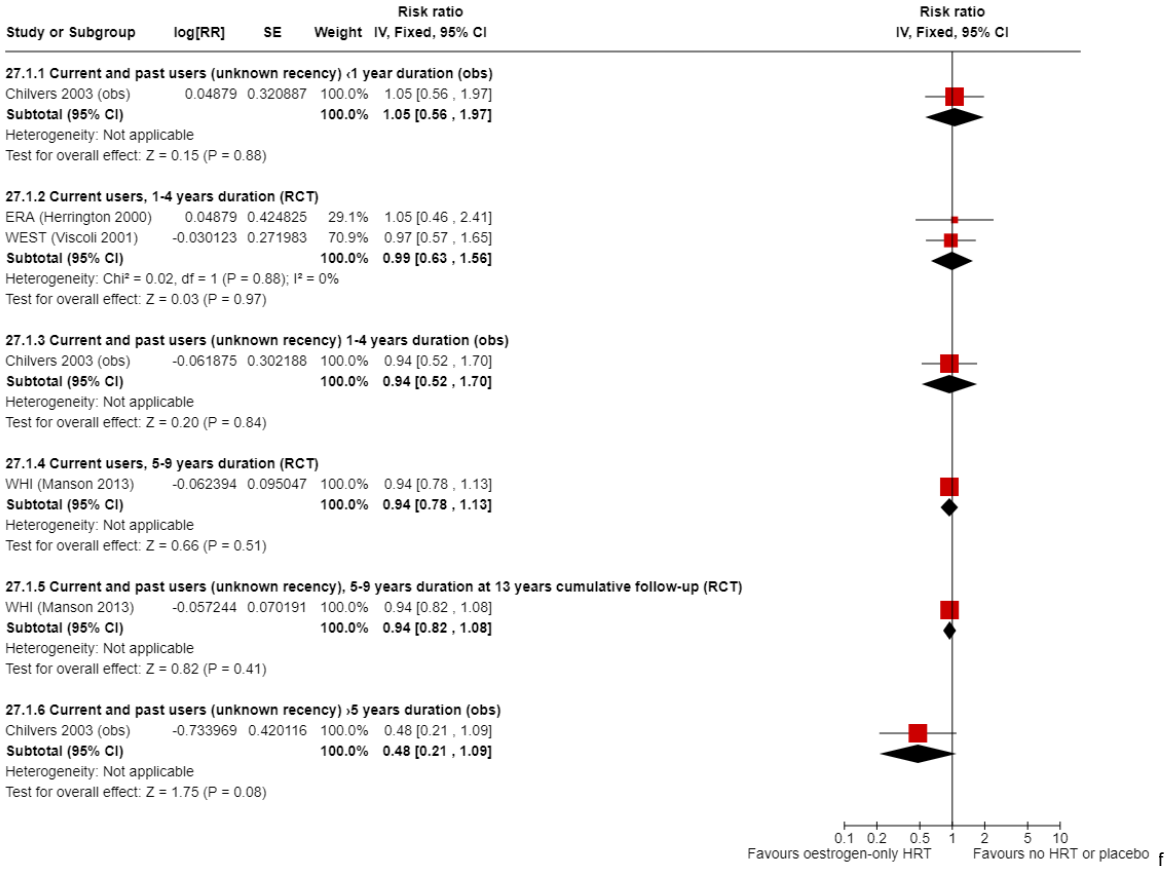


Figure 55: Combined oestrogen and progestogen versus no HRT in current users with unknown duration of HRT use (duration of use not reported: stroke – OR



Oestrogen-only versus placebo or no HRT

Figure 56: Oestrogen-only vs placebo or no HR, by recency and duration of HRT use: coronary heart disease (including MI) – RCT and observational studies



[f] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for observational data are odds ratios but presented under risk ratio labels for presentational purposes. See table 22 for full GRADE profile for RCT evidence, and table 29 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 0.05$, df=2 (P=0.98), $I^2 = 0\%$. Test for subgroup differences for observational evidence: $Chi^2 = 2.41$, df=2 (P=0.30), $I^2 = 17.0\%$.

Figure 57: Oestrogen-only versus no HRT in current users with unknown duration of HRT use (duration of use not reported): coronary heart disease (including MI) – HR – observational studies

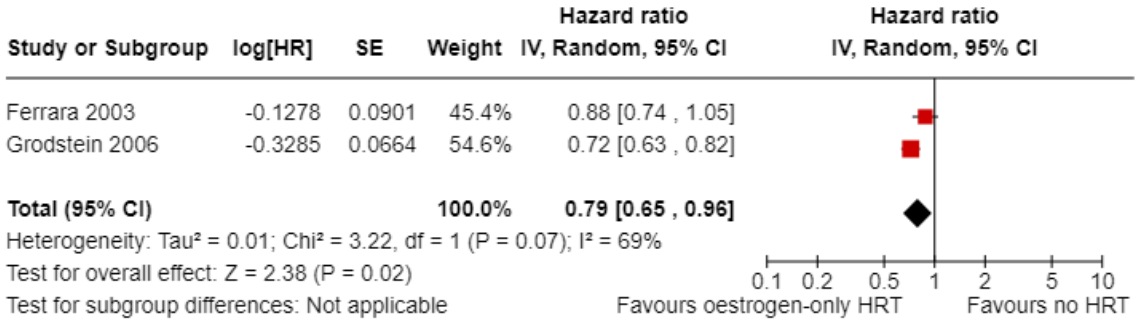


Figure 58: Oestrogen-only versus no HRT in current users with unknown duration of HRT use (duration of use not reported): coronary heart disease (including MI) – OR – observational studies

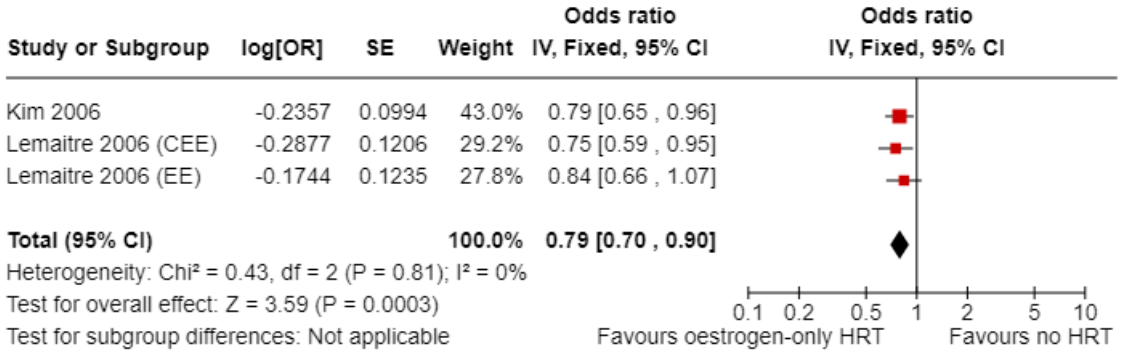


Figure 59: Oestrogen-only vs placebo, by recency and duration of HRT use: nonfatal MI - RCT

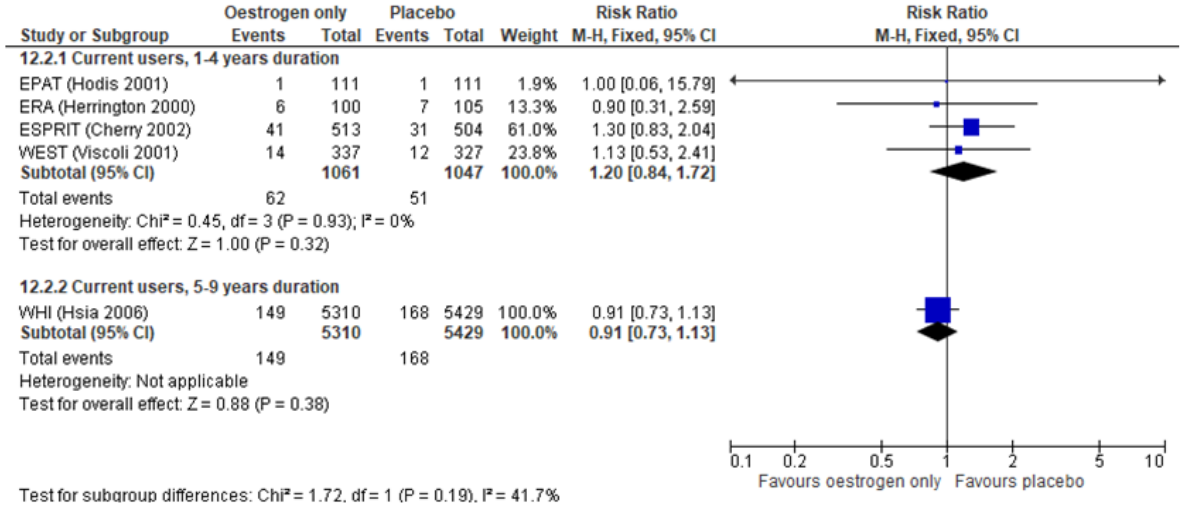


Figure 60: Oestrogen-only vs placebo, by recency and duration of HRT use: cardiovascular event composite scores - RCT

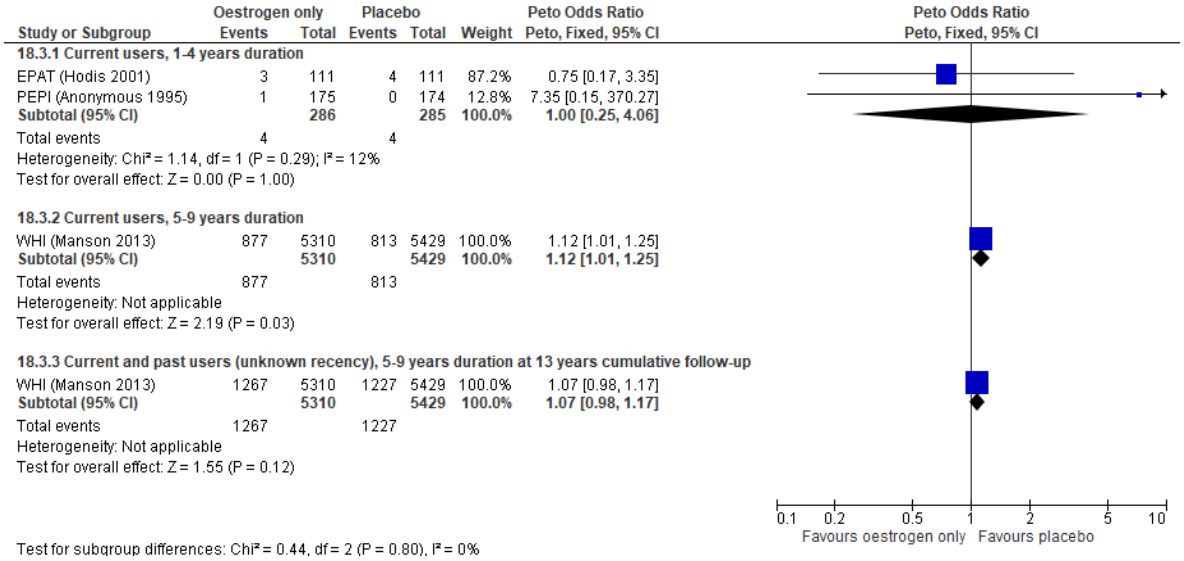
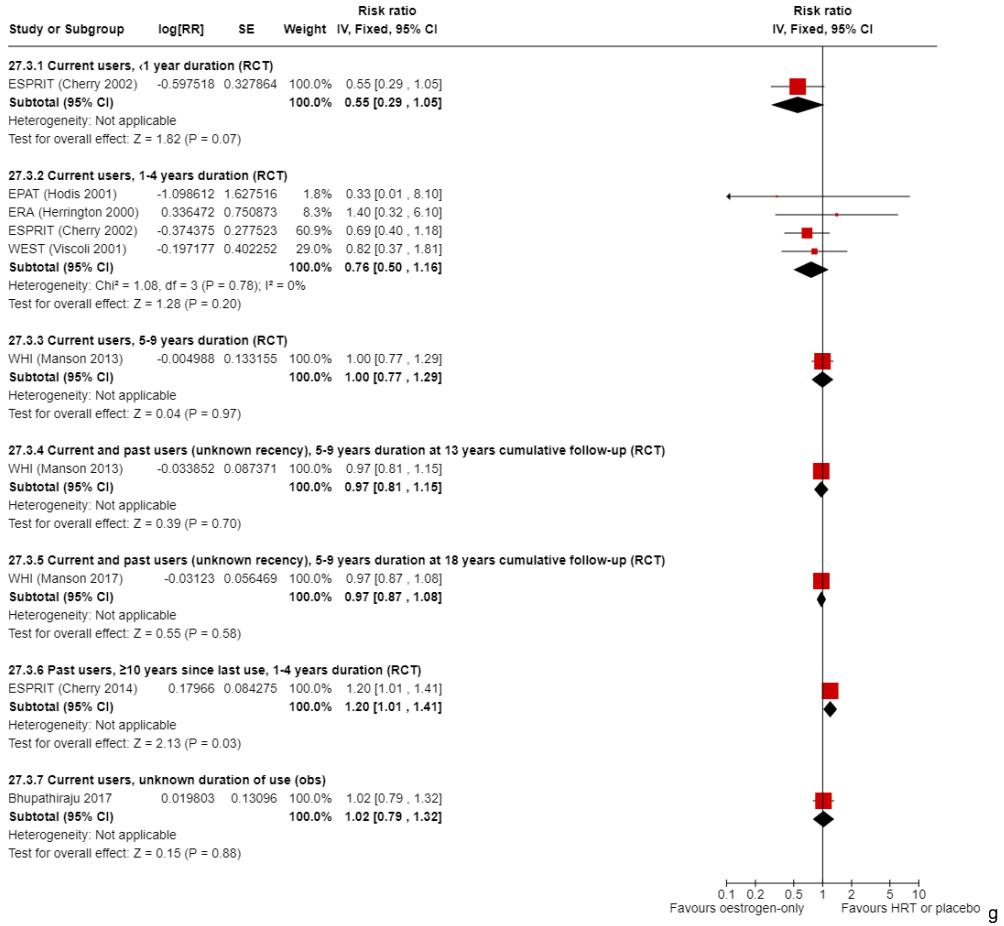


Figure 61: Oestrogen-only vs placebo or no HRT, by recency and duration of HRT use: mortality (cardiovascular disease related) – RCT and observational studies



[g] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for observational data is a Hazard ratio, but presented under risk ratio labels for presentational purposes. See table 22 for full GRADE profile for RCT evidence, and table 29 for full GRADE profile of observational evidence. Test for subgroup differences for observational evidence: $Chi^2 = 10.00$, df=5 (P=0.08), $I^2 = 50.0\%$.

Figure 62: Oestrogen-only vs placebo, by recency and duration of HRT use: stroke - RCT

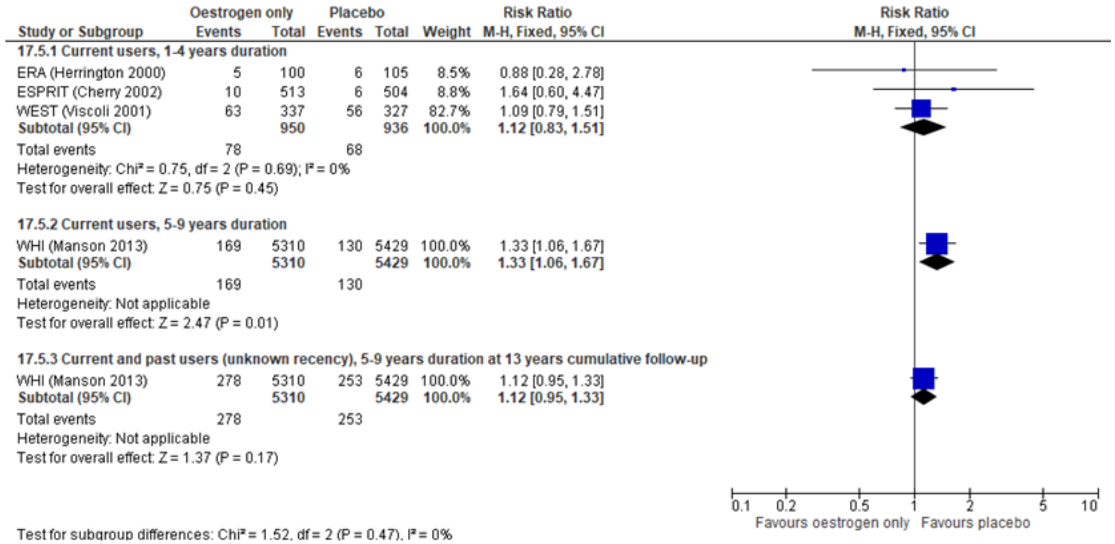


Figure 63: Oestrogen-only vs placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: coronary heart disease (including MI) - RCT

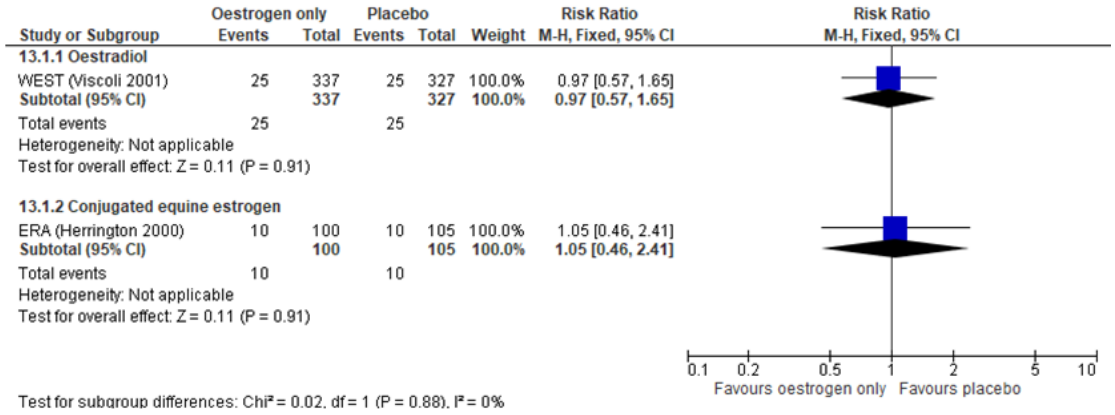

Oestrogen only
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
13.1.1 Oestradiol
WEST (Viscoli 2001) 25 337 25 327 100.0% 0.97 [0.57, 1.65]
Subtotal (95% CI) 337 327 100.0% 0.97 [0.57, 1.65]
Total events 25 25
Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)
13.1.2 Conjugated equine estrogen
ERA (Herrington 2000) 10 100 10 105 100.0% 1.05 [0.46, 2.41]
Subtotal (95% CI) 100 105 100.0% 1.05 [0.46, 2.41]
Total events 10 10
Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)
0.1 0.2 0.5 1 2 5 10
Favours oestrogen only Favours placebo
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%

Figure 64: Oestrogen-only vs placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: nonfatal MI - RCT

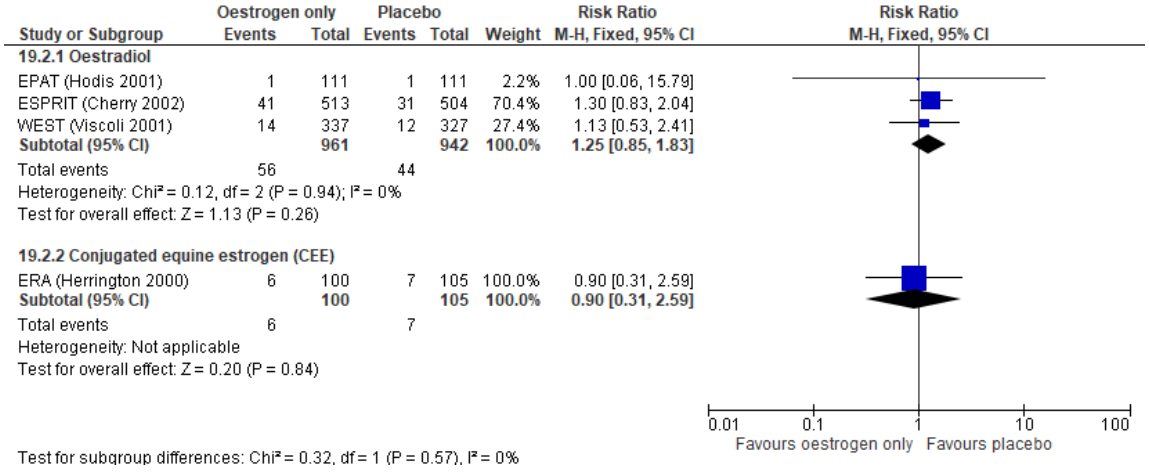


Figure 65: Oestrogen-only vs placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: cardiac event composite scores - RCT

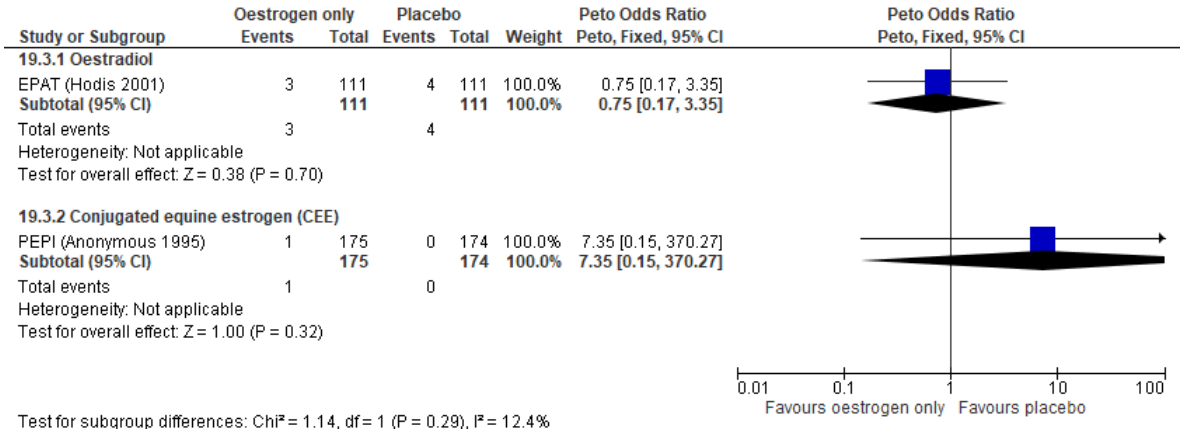


Figure 66: Oestrogen-only vs placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: mortality (cardiovascular disease related) - RCT

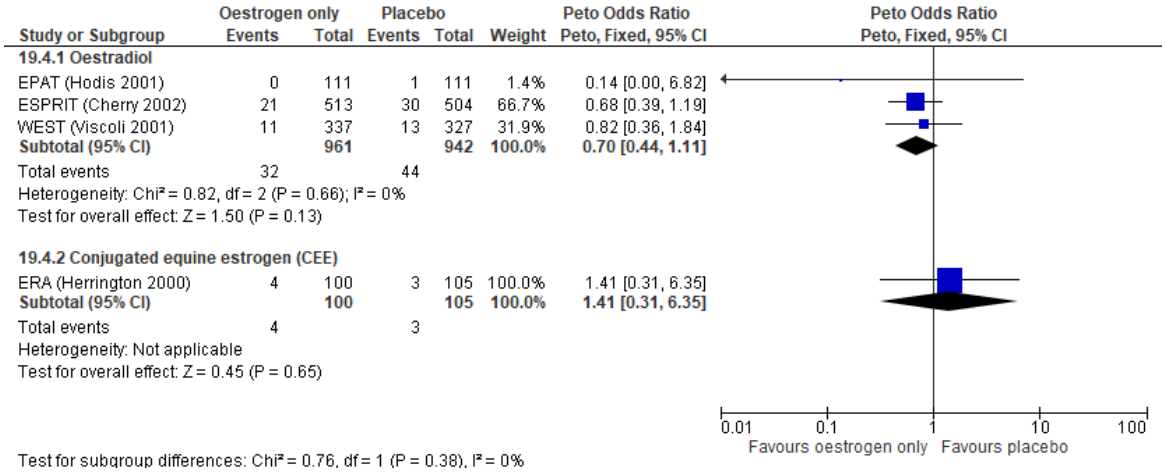


Figure 67: Oestrogen-only vs placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent: stroke - RCT

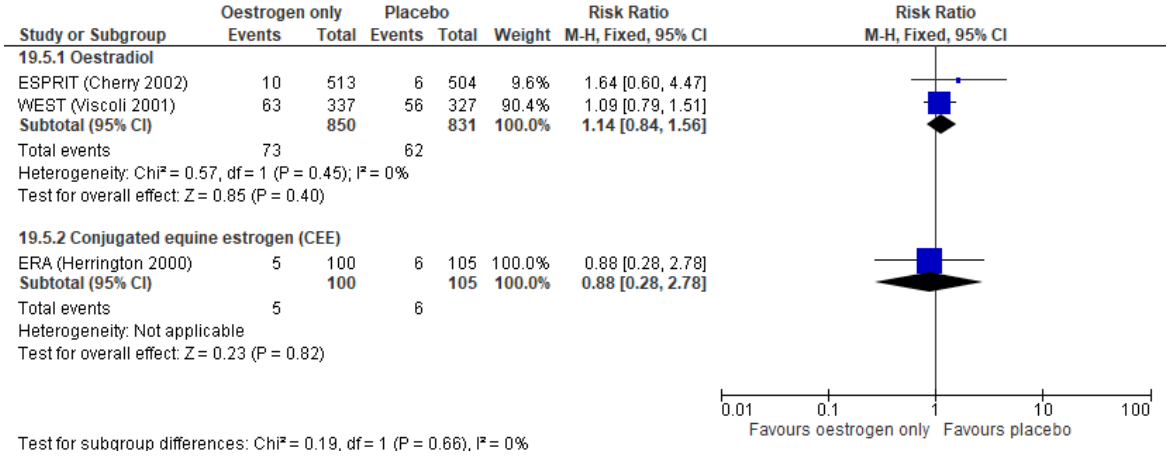
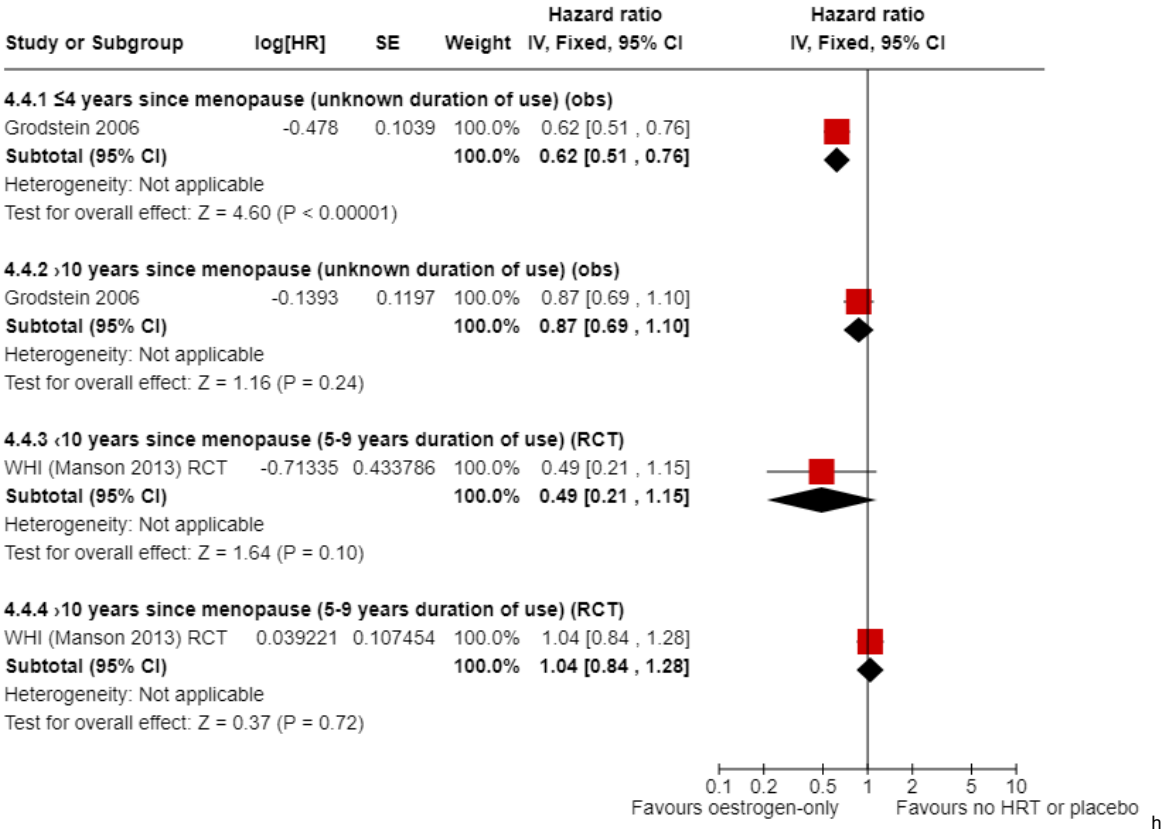


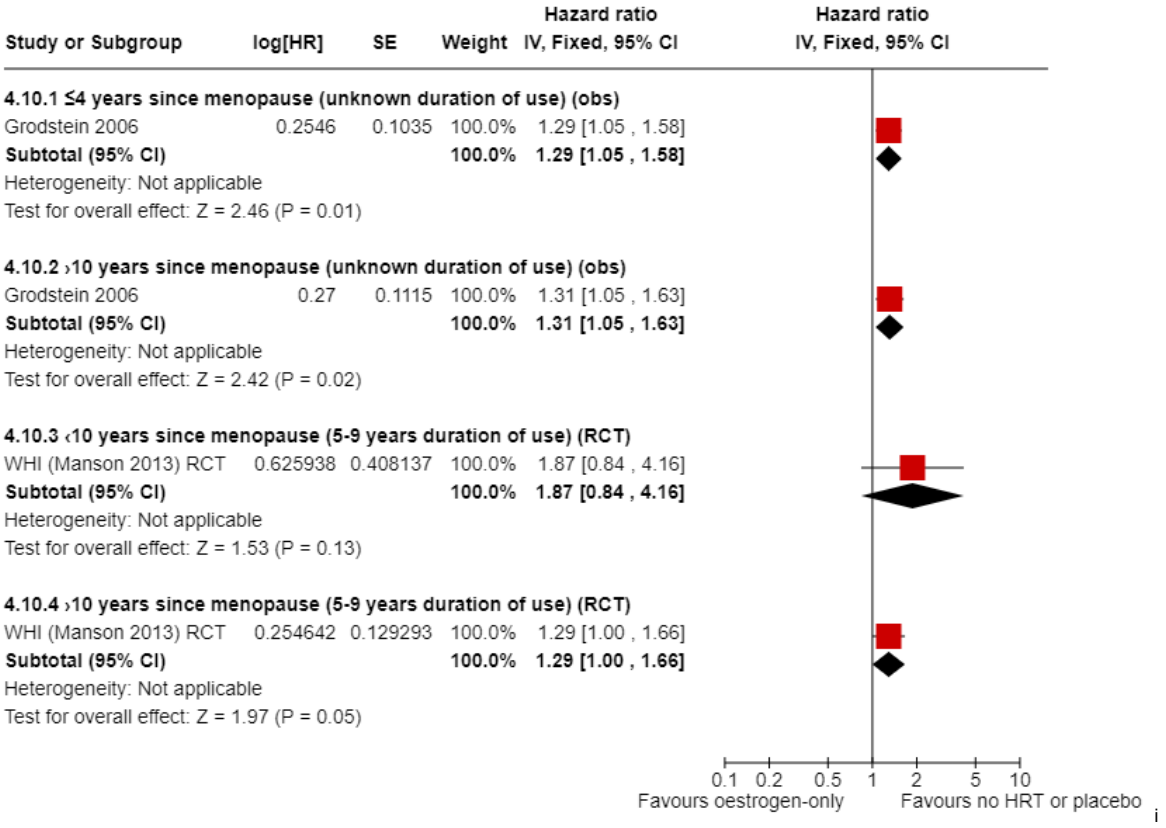
Figure 68: Oestrogen-only vs placebo or no HRT in current users by duration of HRT use, by time since menopause at first use: coronary heart disease (including MI) – RCT and observational studies



h

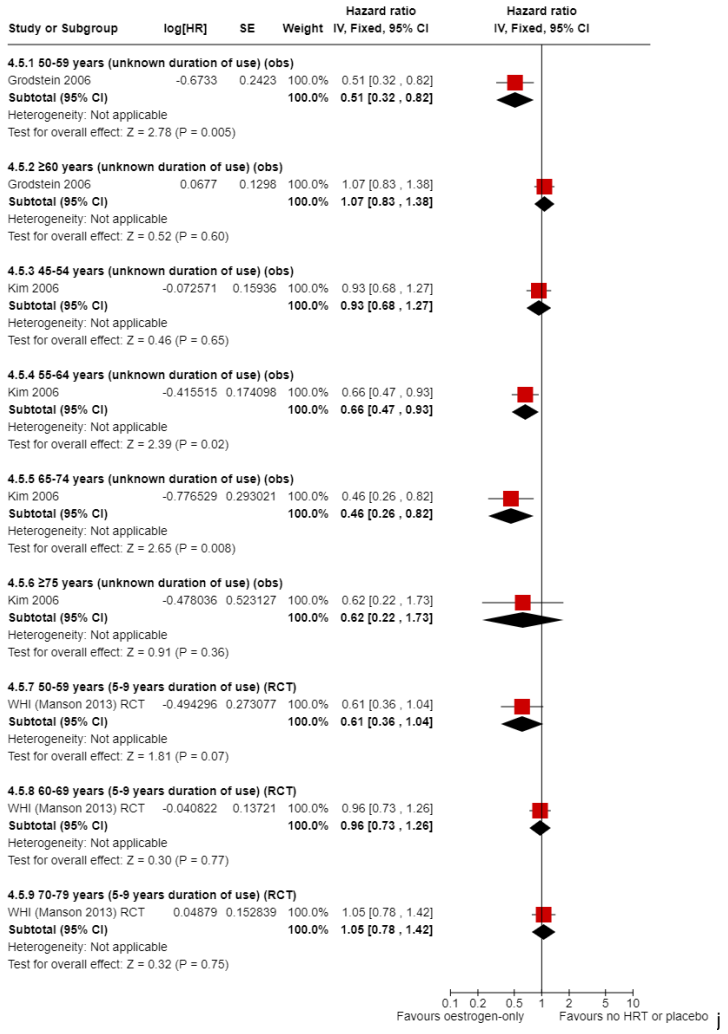
[h] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for RCT data are risk ratios but presented under Hazard ratio labels for presentational purposes. See table 24 for full GRADE profile for RCT evidence, and table 29 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 2.84$, df=1 (P=0.09), $I^2 = 64.7\%$. Test for subgroup differences for observational evidence: $Chi^2 = 4.57$, df=1 (P=0.03), $I^2 = 78.1\%$.

Figure 69: Oestrogen-only vs placebo or no HRT in current users by duration of HRT use, by time since menopause at first use: stroke – RCT and observational studies



[i] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for RCT data are risk ratios but presented under Hazard ratio labels for presentational purposes. See table 24 for full GRADE profile for RCT evidence, and table 29 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 0.75$, df=1 (P=0.39), $I^2 = 0\%$. Test for subgroup differences for observational evidence: $Chi^2 = 0.01$, df=1 (P=0.92), $I^2 = 0\%$.

Figure 70: Oestrogen-only vs placebo or no HRT in current users by duration of HRT use, by age at first use: coronary heart disease (including MI) – RCT and observational studies



[j] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for RCT data are risk ratios, and for Kim 2006 observational data are odds ratios, but presented under Hazard ratio labels for presentational purposes. See table 25 for full GRADE profile for RCT evidence, and table

Figure 71: Oestrogen-only vs placebo in current users with 5-9 years duration of HRT use, by age at first use: cardiovascular event composite scores - RCT

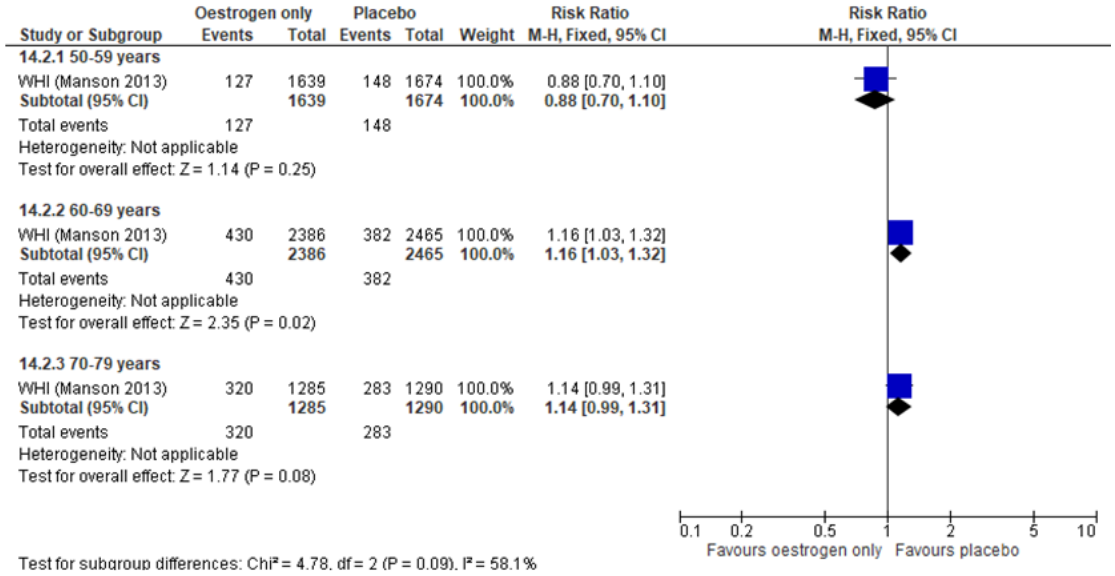


Figure 72: Oestrogen-only vs placebo in current users with 5-9 years duration of HRT use, by age at first use: mortality (cardiovascular disease related) - RCT

29 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 3.06$, df=2 (P=0.22), $I^2 = 34.5\%$. Test for subgroup differences for observational evidence: Grodstein 2006: $Chi^2 = 7.27$, df=1 (P=0.007), $I^2 = 86.2\%$; Kim 2006: $Chi^2 = 5.22$, df=3, (P=0.16), $I^2 = 42.6\%$

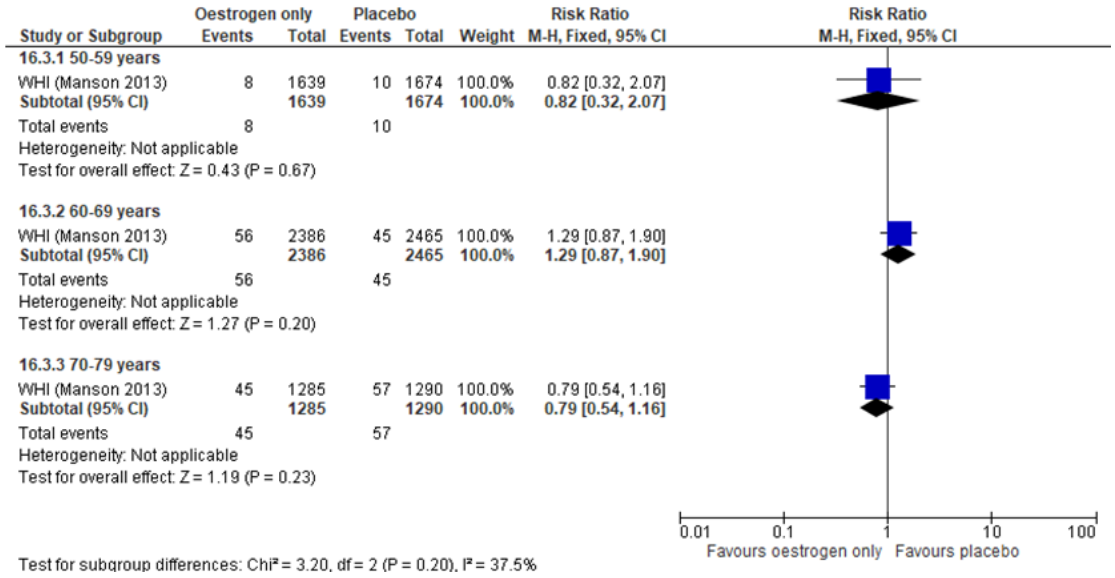
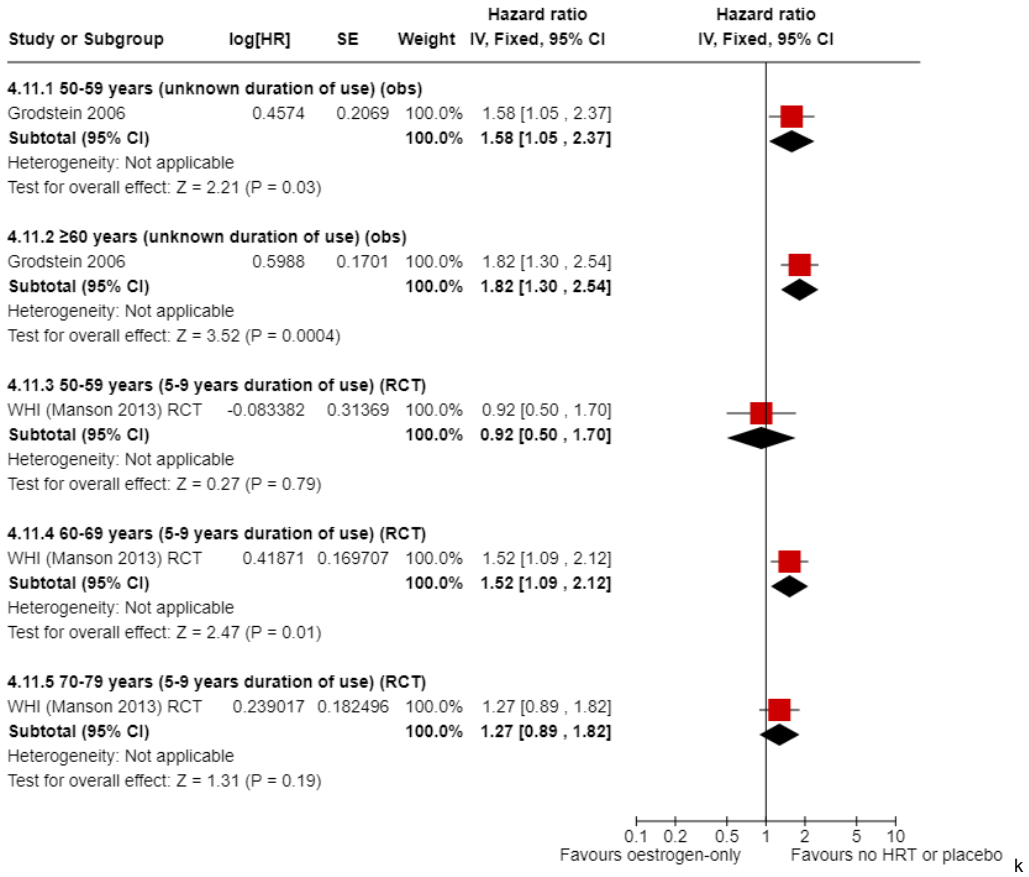


Figure 73: Oestrogen-only vs placebo or no HRT in current users by duration of HRT use, by age at first use: stroke – RCT and observational studies



[k] Separate analyses were performed for observational evidence and RCT evidence, however they are presented on the same forest plot for presentational purposes. Effect estimates for RCT data are risk ratios, but presented under Hazard ratio labels for presentational purposes. See table 25 for full GRADE profile for RCT evidence, and table 29 for full GRADE profile of observational evidence. Test for subgroup differences for RCT evidence: $Chi^2 = 2.06$, df=2 (P=0.36), $I^2 = 2.9\%$. Test for subgroup differences for observational evidence: $Chi^2 = 0.28$, df=1 (P=0.6), $I^2 = 0\%$

Figure 74: Oestrogen-only vs placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use: coronary heart disease (including MI) - RCT

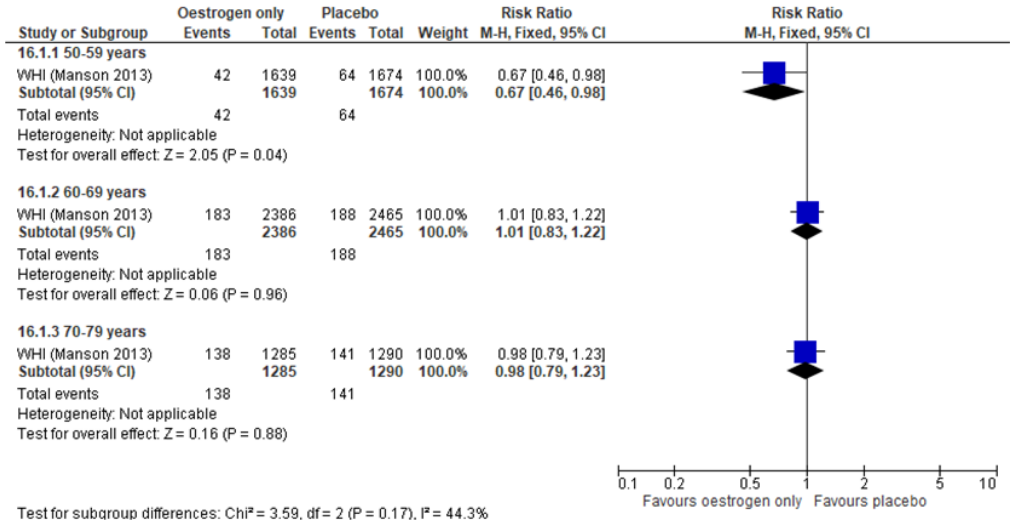


Figure 75: Oestrogen-only vs placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use: mortality cardiovascular disease related - RCT

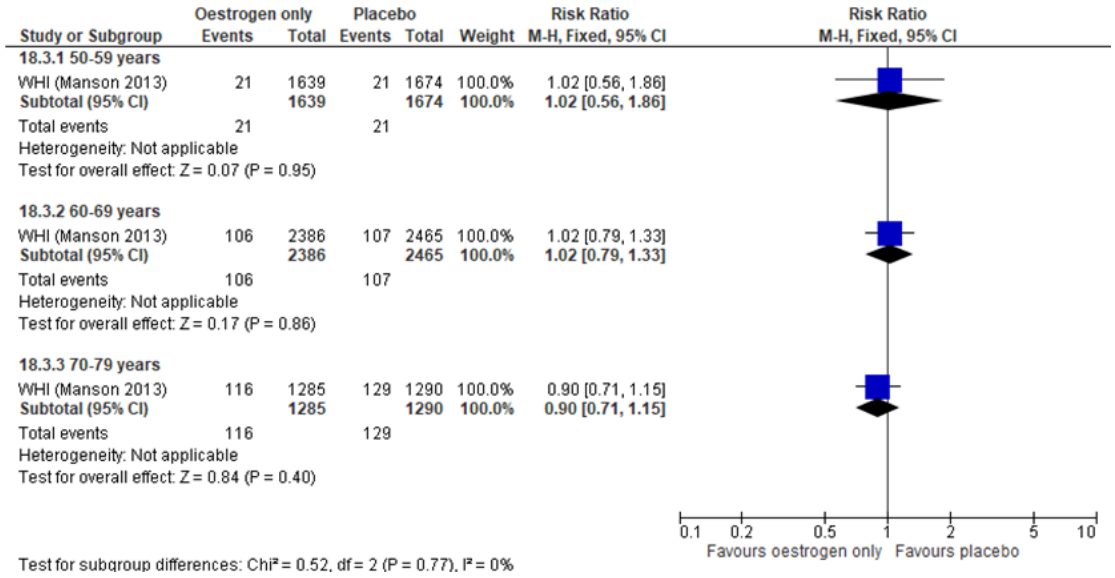


Figure 76: Oestrogen-only vs placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use: stroke - RCT

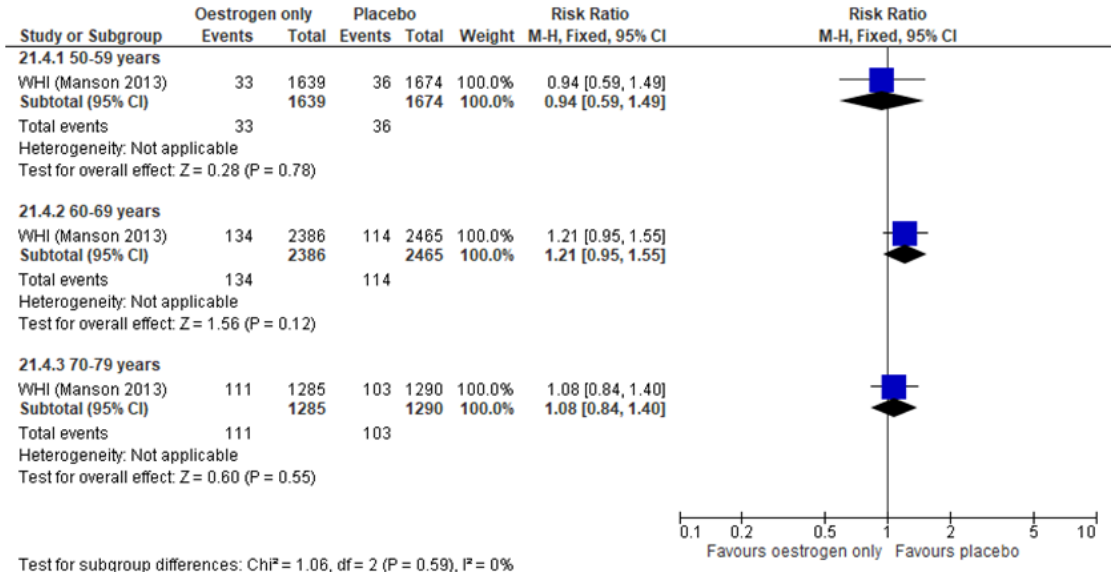


Figure 77: Oestrogen-only vs placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 18 years cumulative follow-up, by age at first use: mortality (cardiovascular disease related) - RCT

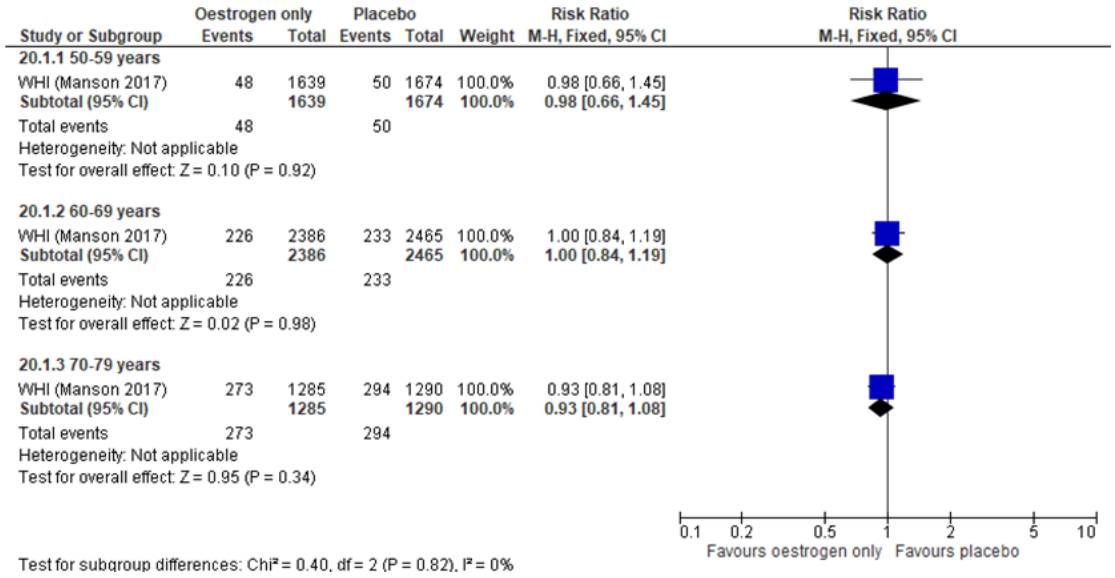
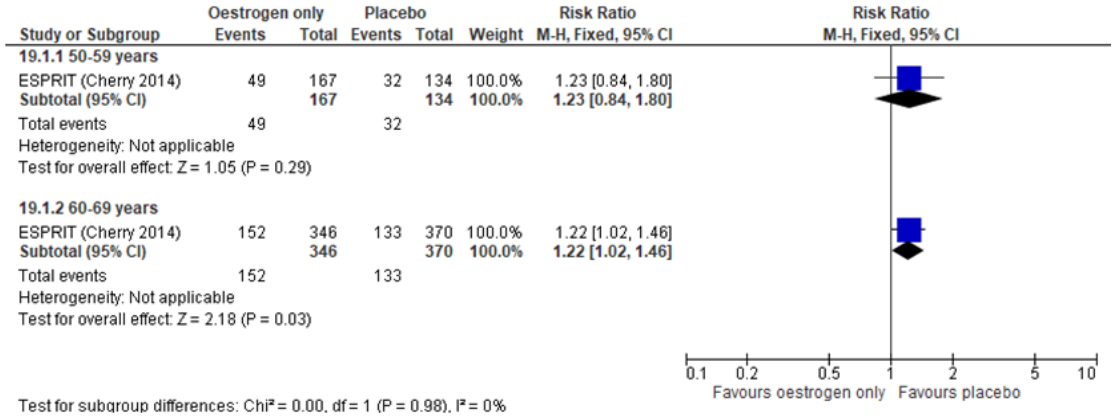


Figure 78: Oestrogen-only vs placebo in past users with ≥10 years since last use and 1-4 years duration of HRT use, by age at first use: mortality (cardiovascular disease related) - RCT



Oestrogen-only versus no HRT: Observational study evidence

Figure 79: Oestrogen-only versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by oestrogen dose: stroke

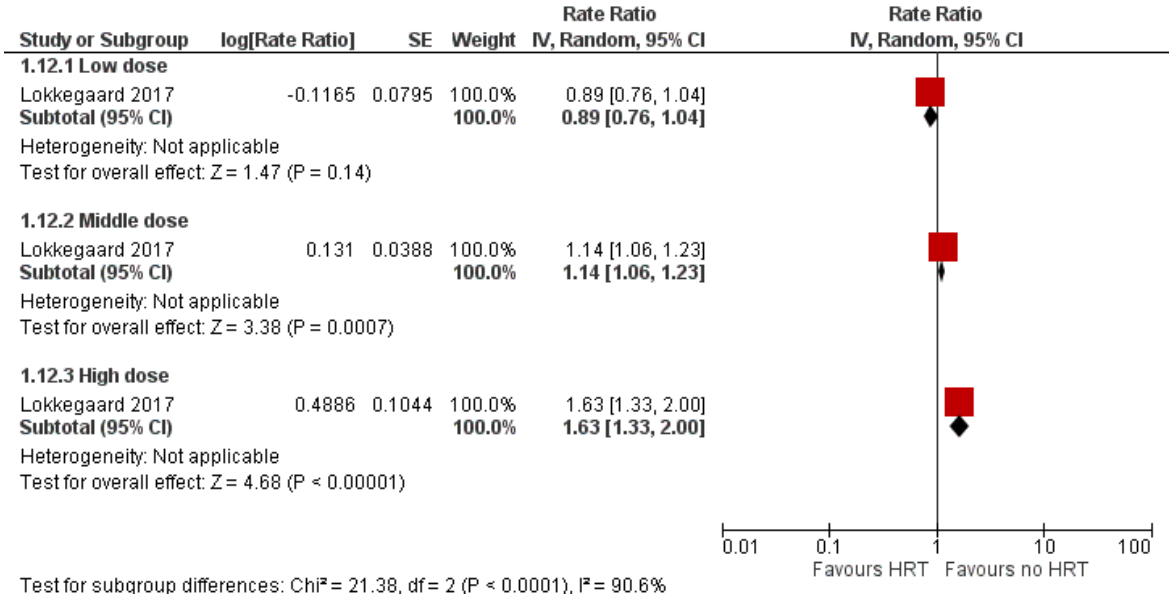
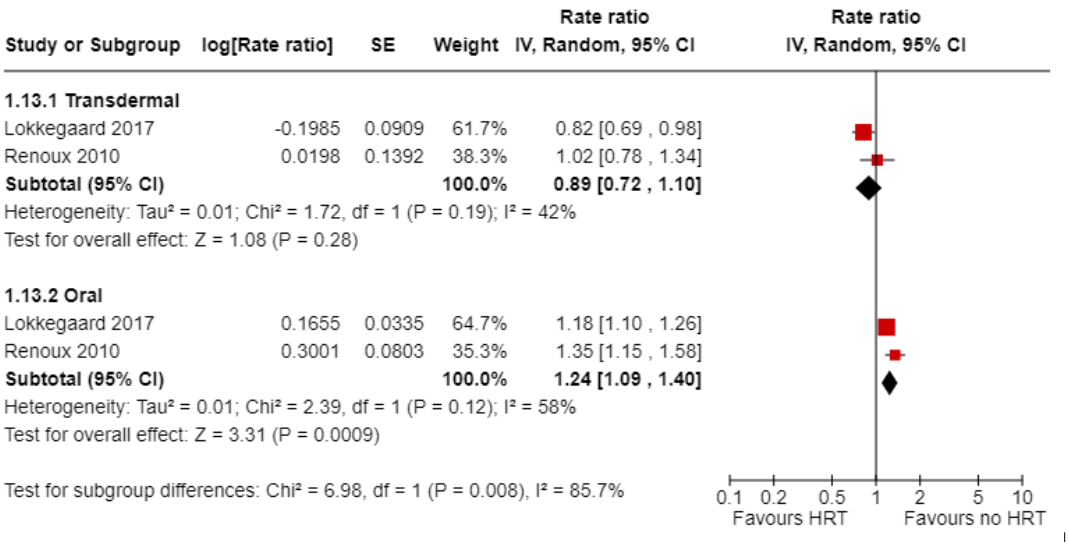


Figure 80: Oestrogen-only versus no HRT in current users with unknown duration of HRT use (duration of use not reported), by route of administration: stroke



[l] The effect estimate for the transdermal subgroup is OR 0.88 (0.75 to 1.02). The analysis model performed for the transdermal subgroup was fixed effects due to no serious inconsistency, but presented under random effects model in this forest plot for presentational purposes. See table 29 for full GRADE details.

Figure 81: Oestrogen-only versus no HRT in current users with unknown duration of HRT use (duration of use not reported): stroke - HR

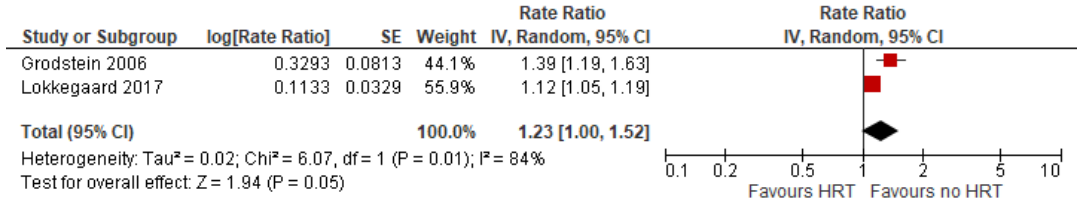
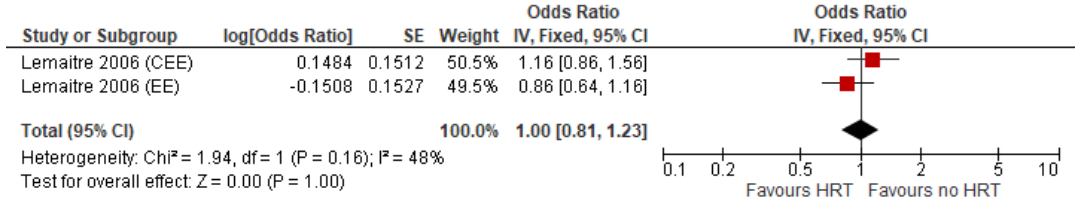


Figure 82: Oestrogen-only versus no HRT in current users with unknown duration of HRT use (duration of use not reported): stroke - OR



Appendix F GRADE tables

GRADE tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

See Absolute risk tables and calculationsAppendix L for the absolute risk tables.

Please note, stroke outcomes have been shaded in blue within the GRADE tables below.

Table 5: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo by recency and duration of HRT use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (continuous)	Placebo	Relative (95% CI)	Absolute		
Coronary heart disease (including MI)												
Current HRT user, by years of use												
<1 year duration (Better indicated by lower values)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	100/9886 (1%)	61/9485 (0.6%)	RR 1.61 (1.17 to 2.21)	4 more per 1000 (from 1 more to 8 more)	LOW	CRITICAL
1-4 years duration (Better indicated by lower values)												
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	238/1884 (12.6%)	243/1861 (13.1%)	RR 0.96 (0.81 to 1.14)	5 fewer per 1000 (from 25 fewer to 18 more)	MODERATE	CRITICAL
5-9 years duration (Better indicated by lower values)												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	486/9886 (4.9%)	452/9485 (4.8%)	RR 1.06 (0.94 to 1.19)	3 more per 1000 (from 3 fewer to 9 more)	MODERATE	CRITICAL
Current and past users (unknown recency), by years of use												
5-9 years duration at 13 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	487/8506 (5.7%)	430/8102 (5.3%)	RR 1.08 (0.95 to 1.22)	4 more per 1000 (from 3 fewer to 12 more)	HIGH	CRITICAL
Past users, <5 years since last use, by years of use												
5-9 years duration (Better indicated by lower values)												

1 (WHI: Heiss 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	101/8052 (1.3%)	104/7678 (1.4%)	RR 0.93 (0.71 to 1.22)	1 fewer per 1000 (from 4 fewer to 3 more)	MODERATE	CRITICAL
Nonfatal MI												
Current users, by years of use												
<1 year duration (Better indicated by lower values)												
2[6]	randomised trials	very serious[7]	serious[8]	serious[2]	serious[3]	none	45/1429 (3.1%)	35/1434 (2.4%)	POR 1.30 (0.83 to 2.03)	7 more per 1000 (from 4 fewer to 24 more)	VERY LOW	CRITICAL
1-4 years duration (Better indicated by lower values)												
4[9]	randomised trials	no serious risk of bias	serious[8]	serious[2]	serious[10]	none	122/4084 (3%)	133/4050 (3.3%)	POR 0.91 (0.71 to 1.18)	3 fewer per 1000 (from 9 fewer to 6 more)	VERY LOW	CRITICAL
5-9 years duration (Better indicated by lower values)												
2[5]	randomised trials	no serious risk of bias	serious[8]	serious[2]	serious[3]	none	334/9886 (3.4%)	310/9485 (3.3%)	POR 1.06 (0.9 to 1.25)	2 more per 1000 (from 3 fewer to 8 more)	VERY LOW	CRITICAL
Cardiac event composite score												
Current users, by years of use												
<1 year duration (Better indicated by lower values)												
1 (WHISP: Collins 2006)	randomised trials	very serious[7]	no serious inconsistency	serious[2]	very serious[11]	none	12/49 (24.5%)	18/51 (35.3%)	POR 0.60 (0.26 to 1.41)	106 fewer per 1000 (from 229 fewer to 82 more)	VERY LOW	CRITICAL
1-4 years duration (Better indicated by lower values)												
2[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/2370 (0.3%)	0/2363 (0%)	POR 7.39 (1.68 to 32.53)	-	HIGH	CRITICAL
5-9 years duration (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	786/8506 (9.2%)	663/8102 (8.2%)	POR 1.14 (1.03 to 1.27)	10 more per 1000 (from 2 more to 20 more)	MODERATE	CRITICAL
Current and past users (unknown recency), by years of use												
5-9 years duration at 13 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1606/8506 (18.9%)	1446/8102 (17.8%)	POR 1.07 (0.99 to 1.16)	10 more per 1000 (from 1 fewer to 23 more)	HIGH	CRITICAL
Past users, <5 years since last use, by years of use												
5-9 years duration (Better indicated by lower values)												

1 (WHI: Heiss 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	343/8052 (4.3%)	323/7678 (4.2%)	POR 1.01 (0.87 to 1.18)	0 more per 1000 (from 5 fewer to 7 more)	HIGH	CRITICAL
Mortality (cardiovascular disease related)												
Current users, by years of use												
<1 year duration (Better indicated by lower values)												
2[13]	randomised trials	very serious[7]	serious[8]	serious[2]	very serious[11]	none	17/1429 (1.2%)	13/1434 (0.9%)	POR 1.32 (0.64 to 2.7)	3 more per 1000 (from 3 fewer to 15 more)	VERY LOW	CRITICAL
1-4 years duration (Better indicated by lower values)												
3[14]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	69/3680 (1.9%)	58/3677 (1.6%)	POR 1.2 (0.84 to 1.71)	3 more per 1000 (from 2 fewer to 11 more)	LOW	CRITICAL
5-9 years duration of HRT use (Better indicated by lower values)												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	211/9886 (2.1%)	192/9485 (2%)	POR 1.09 (0.89 to 1.33)	2 more per 1000 (from 2 fewer to 7 more)	LOW	CRITICAL
Current and past users (unknown recency), by years of use												
5-9 years duration at 13 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	293/8506 (3.4%)	286/8102 (3.5%)	POR 0.97 (0.83 to 1.15)	1 fewer per 1000 (from 6 fewer to 5 more)	HIGH	CRITICAL
5-9 years duration at 18 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	688/8506 (8.1%)	644/8102 (7.9%)	POR 1.02 (0.91 to 1.14)	1 more per 1000 (from 7 fewer to 10 more)	HIGH	CRITICAL
Past users, <5 years since last use, by years of use												
5-9 years duration (Better indicated by lower values)												
1 (WHI: Heis 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	32/8052 (0.4%)	33/7678 (0.4%)	POR 0.92 (0.57 to 1.50)	0 fewer per 1000 (from 2 fewer to 2 more)	LOW	CRITICAL
Stroke												
Current users, by years of use												
<1 year duration (Better indicated by lower values)												
2[15]	randomised trials	very serious[7]	no serious inconsistency	serious[2]	very serious[11]	none	17/8555 (0.2%)	18/8153 (0.2%)	POR 0.9 (0.46 to 1.75)	0 fewer per 1000 (from 1 fewer to 2 more)	VERY LOW	CRITICAL
1-4 years duration (Better indicated by lower values)												

4[16]	randomised trials	serious[17]	no serious inconsistency	serious[2]	serious[3]	none	89/1959 (4.5%)	75/1930 (3.9%)	POR 1.2 (0.88 to 1.64)	7 more per 1000 (from 5 fewer to 23 more)	VERY LOW	CRITICAL
5-9 years duration (Better indicated by lower values)												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	330/9886 (3.3%)	267/9485 (2.8%)	POR 1.23 (1.04 to 1.45)	6 more per 1000 (from 1 more to 12 more)	LOW	CRITICAL
Current and past users (unknown recency), by years of use												
5-9 years duration at 13 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	376/8506 (4.4%)	311/8102 (3.8%)	POR 1.16 (0.99 to 1.35)	6 more per 1000 (from 0 fewer to 13 more)	MODERATE	CRITICAL
Past users, <5 years since last use, by years of use												
5-9 years duration (Better indicated by lower values)												
1 (WHI: Heiss 2008)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	76/8052 (0.94%)	64/7678 (0.83%)	POR 1.13 (0.81 to 1.58)	1 more per 1000 (from 2 fewer to 5 more)	MODERATE	CRITICAL
TIA												
Current users, by years of use												
1-4 years duration (Better indicated by lower values)												
1 (HERS: Simon 2001)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[10]	none	35/1380 (2.5%)	44/1383 (3.2%)	RR 0.80 (0.51 to 1.23)	6 fewer per 1000 (from 16 fewer to 7 more)	LOW	IMPORTANT

CI: confidence interval; HRT: hormonal replacement therapy, MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; RR: risk ratio; TIA: transient ischaemic attack.

[1] HERS: Hulley 1998, WHI: Rossouw 2002

[2] Population is indirect due to hormone replacement therapy used for prevention

[3] 95% CI crossed 1 MID (1.25)

[4] EPHT: Veerus 2006, ERA: Herrington 2000, HERS: Grady 2002

[5] HERS: Grady 2002, WHI: Manson 2013

[6] HERS: Hulley 1998, WHISP: Collins 2008

[7] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[8] Serious heterogeneity unexplained by subgroup analysis

[9] EPHT: Veerus 2006, ERA: Herrington 2000, HERS: Grady 2002, WISDOM: Vickers 2007

[10] 95% CI crossed 1 MIDs (0.80)

[11] 95% CI crossed 2 MIDs (0.80 and 1.25)

[12] PEPI: Anonymous 1995, WIDSOM: Vickers 2007

[13] HERS: Grady 2002, WHISP: Collins 2006

[14] ERA: Herrington 2000, HERS: Grady 2002, WISDOM: Vickers 2007

[15] WHI: Rossouw 2002, WHISP: Collins 2006

[16] EPHT: Veerus 2006, ERA: Herrington 2000, EVTET: Hoibraaten 2000, HERS: Simon 2001

[17] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*

Table 6: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current users with <1 year duration of HRT use, by oestrogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (continuous)	Placebo	Relative (95% CI)	Absolute		
Current users, with <1 year duration of use, by oestrogenic constituent												
Nonfatal MI												
Oestradiol (Better indicated by lower values)												
1 (WHISP: Collins 2006)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/49 (6.1%)	6/51 (11.8%)	RR 0.52 (0.14 to 1.97)	56 fewer per 1000 (from 101 fewer to 114 more)	VERY LOW	CRITICAL
Conjugated equine estrogen (Better indicated by lower values)												
1 (HERS: Hulley 1998)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	42/1380 (3%)	29/1383 (2.1%)	RR 1.45 (0.91 to 2.32)	9 more per 1000 (from 2 fewer to 28 more)	LOW	CRITICAL
Mortality (cardiovascular disease related)												
Oestradiol (Better indicated by lower values)												
1 (WHISP: Collins 2006)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/49 (0%)	2/51 (3.9%)	POR 0.14 (0.01 to 2.24)	34 fewer per 1000 (from 39 fewer to 45 more)	VERY LOW	CRITICAL
Conjugated equine estrogen (CEE) (Better indicated by lower values)												
1 (HERS: Grady 2002)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	17/1380 (1.2%)	11/1383 (0.8%)	POR 1.54 (0.73 to 3.25)	4 more per 1000 (from 2 fewer to 17 more)	VERY LOW	CRITICAL
Stroke												
Oestradiol (Better indicated by lower values)												
1 (WHISP: Collins 2006)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/49 (0%)	1/51 (2%)	POR 0.14 (0 to 7.1)	17 fewer per 1000 (from 20 fewer to 105 more)	VERY LOW	CRITICAL
Conjugated equine estrogen (CEE) (Better indicated by lower values)												
1 (WHI: Rossouw 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	17/8506 (0.2%)	17/8102 (0.2%)	POR 0.95 (0.49 to 1.87)	0 fewer per 1000 (from 1 fewer to 2 more)	LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy, MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; RR: risk ratio

[1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*

[2] *Population is indirect due to hormone replacement therapy used for prevention*

[3] *95% CI crossed 2 MIDs (0.80 and 1.25)*

[4] *95% CI crossed 1 MID (1.25)*

Table 7: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current users with <1 year duration of HRT use, by progestogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (continuous)	Placebo	Relative (95% CI)	Absolute		
Current users with <1 years duration, by progestogenic constituent												
Nonfatal MI												
Norethisterone acetate (NETA; better indicated by lower values)												
1 (WHISP: Collins 2006)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/49 (6.1%)	6/51 (11.8%)	RR 0.52 (0.14 to 1.97)	56 fewer per 1000 (from 101 fewer to 114 more)	VERY LOW	CRITICAL
Medroxyprogesterone acetate (MPA; better indicated by lower values)												
1 (HERS: Hulley 1998)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	42/1380 (3%)	29/1383 (2.1%)	RR 1.45 (0.91 to 2.32)	9 more per 1000 (from 2 fewer to 28 more)	LOW	CRITICAL
Mortality (cardiovascular disease related)												
Noresthisterone acetate (NETA; better indicated by lower values)												
1 (WHISP: Collins 2006)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/49 (0%)	2/51 (3.9%)	POR 0.14 (0.01 to 2.24)	34 fewer per 1000 (from 39 fewer to 45 more)	VERY LOW	CRITICAL
Medroxyprogesterone acetate (MPA; better indicated by lower values)												
1 (HERS: Hulley 1998)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	17/1380 (1.2%)	11/1383 (0.8%)	POR 1.54 (0.73 to 3.25)	4 more per 1000 (from 2 fewer to 17 more)	VERY LOW	CRITICAL
Stroke												
Noresthisterone acetate (NETA; better indicated by lower values)												
1 (WHISP: Collins 2006)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/49 (0%)	1/51 (2%)	POR 0.14 (0 to 7.1)	17 fewer per 1000 (from 20 fewer to 105 more)	VERY LOW	CRITICAL
Medroxyprogesterone acetate (MPA; better indicated by lower values)												
1 (WHI: Rossouw 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	17/8506 (0.2%)	17/8102 (0.2%)	POR 0.95 (0.49 to 1.87)	0 fewer per 1000 (from 1 fewer to 2 more)	LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy, MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias; RR: risk ratio

[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Population is indirect due to hormone replacement therapy used for prevention

[3] 95% CI crossed 2 MIDs (0.80 and 1.25)

[4] 95% CI crossed 1 MID (1.25)

Table 8: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (continuous)	Placebo	Relative (95% CI)	Absolute		
Stroke												
Current users with 1-4 years duration of use, by oestrogenic constituent												
Oestradiol (Better indicated by lower values)												
1 (EVTET: Hoibraaten 2000)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/71 (0%)	1/69 (1.4%)	POR 0.13 (0 to 6.63)	13 fewer per 1000 (from 14 fewer to 74 more)	VERY LOW	CRITICAL
Conjugated equine estrogen (CEE; better indicated by lower values)												
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	89/1888 (4.7%)	74/1861 (4%)	POR 1.22 (0.89 to 1.67)	8 more per 1000 (from 4 fewer to 25 more)	LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias.
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Population is indirect due to hormone replacement therapy used for prevention
[3] 95% CI crossed 2 MIDs (0.80 and 1.25)
[4] EPHT: Veerus 2006, ERA: Herrington 2000, HERS: Simon 2001
[5] 95% CI crossed 1 MID (1.25)

Table 9: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current users with 1-4 years duration of HRT use, by progestogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (continuous)	Placebo	Relative (95% CI)	Absolute		
Stroke												
Current users with 1-4 years duration of use, by progestogenic constituent												
Noresthisterone acetate (NETA; better indicated by lower values)												
1 (EVTET: Hoibraaten 2000)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/71 (0%)	1/69 (1.4%)	POR 0.13 (0 to 6.63)	13 fewer per 1000 (from 14 fewer to 74 more)	VERY LOW	CRITICAL
Medroxyprogesterone acetate (MPA; better indicated by lower values)												
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	89/1888 (4.7%)	74/1861 (4%)	POR 1.22 (0.89 to 1.67)	8 more per 1000 (from 4 fewer to 25 more)	LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MID: minimally important difference; POR: peto odds ratio; RoB: risk of bias.
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Population is indirect due to hormone replacement therapy used for prevention
[3] 95% CI crossed 2 MIDs (0.80 and 1.25)
[4] EPHT: Veerus 2006, ERA: Herrington 2000, HERS: Simon 2001
[5] 95% CI crossed 1 MID (1.25)

Table 10: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current users with 5-9 years duration of HRT use, by age at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (continuous)	Control	Relative (95% CI)	Absolute		
Current users with 5-9 years duration of use, by age at first use												
Coronary heart disease (including MI)												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	38/2837 (1.3%)	27/2683 (1%)	RR 1.33 (0.82 to 2.17)	3 more per 1000 (from 2 fewer to 12 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	79/3854 (2%)	73/3655 (2%)	RR 1.03 (0.75 to 1.41)	1 more per 1000 (from 5 fewer to 8 more)	LOW	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	79/1815 (4.4%)	59/1764 (3.3%)	RR 1.30 (0.93 to 1.81)	10 more per 1000 (from 2 fewer to 27 more)	MODERATE	CRITICAL
Cardiovascular event composite scores												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	135/2837 (4.8%)	104/2683 (3.9%)	RR 1.23 (0.96 to 1.58)	9 more per 1000 (from 2 fewer to 22 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	361/3854 (9.4%)	311/3655 (8.5%)	RR 1.10 (0.95 to 1.27)	9 more per 1000 (from 4 fewer to 23 more)	MODERATE	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	290/1815 (16%)	248/1764 (14.1%)	RR 1.14 (0.97 to 1.33)	20 more per 1000 (from 4 fewer to 46 more)	MODERATE	CRITICAL
Mortality (cardiovascular disease related)												
50-59 years (Better indicated by lower values)												

1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/2837 (0.4%)	12/2683 (0.4%)	RR 0.79 (0.34 to 1.82)	1 fewer per 1000 (from 3 fewer to 4 more)	LOW	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	27/3854 (0.7%)	22/3655 (0.6%)	RR 1.16 (0.66 to 2.04)	1 more per 1000 (from 2 fewer to 6 more)	LOW	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	42/1815 (2.3%)	36/1764 (2%)	RR 1.13 (0.73 to 1.76)	3 more per 1000 (from 6 fewer to 16 more)	LOW	CRITICAL
Stroke												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	26/2837 (0.9%)	16/2683 (0.6%)	RR 1.54 (0.83 to 2.86)	3 more per 1000 (from 1 fewer to 11 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	72/3854 (1.9%)	46/3655 (1.3%)	RR 1.48 (1.03 to 2.14)	6 more per 1000 (from 0 more to 14 more)	MODERATE	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/1815 (3.4%)	13/1764 (0.7%)	RR 4.56 (2.52 to 8.27)	26 more per 1000 (from 11 more to 54 more)	HIGH	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MID: minimally important difference; RoB: risk of bias; RR: risk ratio.
[1] 95% CI crossed 1 MID (1.25)
[2] 95% CI crossed 2 MIDs (0.80 and 1.25)

Table 11: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current users with 5-9 years duration of HRT use, by time since menopause at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined HRT (continuous)**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Current users with 5-9 years duration of HRT use, by time since menopause												
Coronary heart disease (including MI)												
< 10 years since menopause (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	32/2780 (1.2%)	35/2711 (1.3%)	RR 0.89 (0.55 to 1.44)	1 fewer per 1000 (from 6 fewer to 6 more)	LOW	CRITICAL

> 10 years since menopause (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	143/4899 (2.9%)	106/4797 (2.2%)	RR 1.32 (1.03 to 1.69)	7 more per 1000 (from 1 more to 15 more)	MODERATE	CRITICAL
Stroke												
<10 years since menopause (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	24/827 (2.9%)	15/817 (1.8%)	RR 1.58 (0.84 to 2.99)	11 more per 1000 (from 3 fewer to 37 more)	MODERATE	CRITICAL
>10 years since menopause (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	113/4899 (2.3%)	87/4797 (1.8%)	RR 1.27 (0.96 to 1.68)	5 more per 1000 (from 1 fewer to 12 more)	MODERATE	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; RoB: risk of bias; RR: risk ratio.
[1] 95% CI crossed 2 MIDs (0.80 and 1.25)
[2] 95% CI crossed 1 MID (1.25)

Table 12: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current users with 5-9 years duration of HRT use, by ethnicity

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined HRT (continuous)**	**Control**	**Relative (95% CI)**	**Absolute**		
Stroke												
Current users with 5-9 years duration of use, by ethnicity												
White (Better indicated by lower values)												
1 (WHI: Wassertheil Smoller 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	126/7140 (1.8%)	89/6805 (1.3%)	RR 1.35 (1.03 to 1.77)	5 more per 1000 (from 0 more to 10 more)	MODERATE	CRITICAL
Black (Better indicated by lower values)												
1 (WHI: Wassertheil Smoller 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/549 (4.9%)	7/575 (1.2%)	RR 4.04 (1.77 to 9.2)	37 more per 1000 (from 9 more to 100 more)	HIGH	CRITICAL
Hispanic (Better indicated by lower values)												
1 (WHI: Wassertheil Smoller 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/472 (0.4%)	5/416 (1.2%)	RR 0.35 (0.07 to 1.81)	8 fewer per 1000 (from 11 fewer to 10 more)	LOW	CRITICAL
Asian or pacific islander (Better indicated by lower values)												

1 (WHI: Wassertheil Smoller 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/194 (2.6%)	2/169 (1.2%)	RR 2.18 (0.43 to 11.08)	14 more per 1000 (from 7 fewer to 119 more)	LOW	CRITICAL
American indian or alaskan native (Better indicated by lower values)												
1 (WHI: Wassertheil Smoller 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/26 (0%)	0/30 (0%)	not pooled	not pooled	LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MID: minimally important difference; RR: risk ratio.
[1] 95% CI crossed 1 MID (1.25)
[2] 95% CI crossed 2 MIDs (0.80 and 1.25)
[3] Number of events <150

Table 13: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined HRT (continuous)**	**Control**	**Relative (95% CI)**	**Absolute**		
Current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use												
Coronary heart disease (including MI)												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	93/2837 (3.3%)	69/2683 (2.6%)	RR 1.27 (0.94 to 1.73)	7 more per 1000 (from 2 fewer to 19 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	201/3854 (5.2%)	199/3655 (5.4%)	RR 0.96 (0.79 to 1.16)	2 fewer per 1000 (from 11 fewer to 9 more)	MODERATE	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	193/1815 (10.6%)	162/1764 (9.2%)	RR 1.16 (0.95 to 1.41)	15 more per 1000 (from 5 fewer to 38 more)	MODERATE	CRITICAL
Cardiovascular event composite score												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	300/2837 (10.6%)	262/2683 (9.8%)	RR 1.08 (0.93 to 1.27)	8 more per 1000 (from 7 fewer to 26 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												

1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	744/3854 (19.3%)	667/3655 (18.2%)	RR 1.06 (0.96 to 1.16)	11 more per 1000 (from 7 fewer to 29 more)	HIGH	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	562/1815 (31%)	517/1764 (29.3%)	RR 1.06 (0.96 to 1.17)	18 more per 1000 (from 12 fewer to 50 more)	HIGH	CRITICAL
Mortality (cardiovascular disease related)												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31/2837 (1.1%)	35/2683 (1.3%)	RR 0.84 (0.52 to 1.35)	2 fewer per 1000 (from 6 fewer to 5 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	110/3854 (2.9%)	106/3655 (2.9%)	RR 0.98 (0.76 to 1.28)	1 fewer per 1000 (from 7 fewer to 8 more)	LOW	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	152/1815 (8.4%)	145/1764 (8.2%)	RR 1.02 (0.82 to 1.27)	2 more per 1000 (from 15 fewer to 22 more)	MODERATE	CRITICAL
Stroke												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	52/2837 (1.8%)	35/2683 (1.3%)	RR 1.41 (0.92 to 2.15)	5 more per 1000 (from 1 fewer to 15 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	168/3854 (4.4%)	138/3655 (3.8%)	RR 1.15 (0.93 to 1.44)	6 more per 1000 (from 3 fewer to 17 more)	MODERATE	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	156/1815 (8.6%)	138/1764 (7.8%)	RR 1.1 (0.88 to 1.37)	8 more per 1000 (from 9 fewer to 29 more)	MODERATE	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; RR: risk ratio.

[1] 95% CI crossed 1 MID (1.25)

[2] 95% CI crossed 1 MID (0.80)

[3] 95% CI crossed 2 MIDs (0.80 and 1.25)

Table 14: Evidence profile for comparison between combined oestrogen and progestogen (continuous) versus placebo in current and past users (unknown recency) with 5-9 years duration at 18 years cumulative follow-up, by age at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (continuous)	Control	Relative (95% CI)	Absolute		
Mortality (cardiovascular disease related)												
Current and past users (unknown recency) with 5-9 years duration at 18 years cumulative follow-up, by age at first use												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	75/2837 (2.6%)	70/2683 (2.6%)	RR 1.01 (0.73 to 1.4)	0 more per 1000 (from 7 fewer to 10 more)	LOW	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	256/3854 (6.6%)	246/3655 (6.7%)	RR 0.99 (0.83 to 1.17)	1 fewer per 1000 (from 11 fewer to 11 more)	HIGH	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	357/1815 (19.7%)	328/1764 (18.6%)	RR 1.06 (0.92 to 1.21)	11 more per 1000 (from 15 fewer to 39 more)	HIGH	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MID: minimally important difference; RR: risk ratio.
[1] 95% CI crossed 1 MID (0.80 and 1.25)

Combined HRT (sequential) versus placebo: RCT evidence

Table 15: Evidence profile for comparison between combined oestrogen and progestogen (sequential) versus placebo, by recency and duration of HRT use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (sequential)	Placebo	Relative (95% CI)	Absolute		
Nonfatal MI												
Current users, by years of use												
1-4 years duration (Better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	1/522 (0.2%)	1/347 (0.3%)	POR 0.79 (0.05 to 13.16)	1 fewer per 1000 (from 3 fewer to 34 more)	VERY LOW	CRITICAL
10-14 years duration (Better indicated by lower values)												

1 (ERT II: Nachtigall 1979)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/84 (1.2%)	3/84 (3.6%)	POR 0.36 (0.05 to 2.61)	23 fewer per 1000 (from 34 fewer to 52 more)	VERY LOW	CRITICAL
Cardiovascular event composite score												
Current users, by years of use												
1-4 years duration (Better indicated by lower values)												
2[6]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	15/422 (3.6%)	8/246 (3.3%)	POR 1.8 (0.75 to 4.32)	25 more per 1000 (from 8 fewer to 94 more)	VERY LOW	CRITICAL
Mortality (cardiovascular disease related)												
Current users, by years of use												
<1 year duration (Better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[5]	no serious inconsistency	serious[3]	very serious[4]	none	0/40 (0%)	1/20 (5%)	POR 0.05 (0 to 3.18)	47 fewer per 1000 (from 50 fewer to 93 more)	VERY LOW	CRITICAL
1-4 years duration (Better indicated by lower values)												
1 (EMS: Tierney 2009)	randomised trials	very serious[5]	no serious inconsistency	serious[3]	very serious[4]	none	0/70 (0%)	1/72 (1.4%)	POR 0.14 (0 to 7.02)	12 fewer per 1000 (from 14 fewer to 76 more)	VERY LOW	CRITICAL
Stroke												
Current users, by years of use												
1-4 years duration (Better indicated by lower values)												
2[1]	randomised trials	serious[2]	serious[7]	serious[3]	very serious[4,]	none	6/522 (1.1%)	4/347 (1.2%)	Not applicable	RD 0.01 (-0.01, 0.02)	VERY LOW	CRITICAL
TIA												
Current users, by years of use												
<1 year duration (Better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[5]	no serious inconsistency	serious[3]	very serious[4]	none	2/40 (5%)	0/20 (0%)	POR 4.6 (0.24 to 89.21)	-	VERY LOW	IMPORTANT
1-4 years duration (Better indicated by lower values)												
1 (EMS: Tierney 2009)	randomised trials	serious[2]	no serious inconsistency	serious[83]	very serious[4]	none	1/70 (1.4%)	1/72 (1.4%)	POR 1.03 (0.06 to 16.62)	0 more per 1000 (from 13 fewer to 176 more)	VERY LOW	IMPORTANT

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio; TIA: transient ischemic attack

[1] EMS: Tierney 2009, KEEPS: Harman 2014

[2] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[3] Population is indirect due to hormone replacement therapy used for prevention

[4] 95% CI crosses 2 MIDs (0.80 and 1.25)

[5] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[6] EMS: Tierney 2009, PEPI: Anonymous 1995

[7] Serious heterogeneity unexplained by subgroup analysis

Table 16: Evidence profile for comparison between combined oestrogen and progestogen (sequential) versus placebo in current users with <1 years duration of HRT use, by oestrogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (sequential)	Control	Relative (95% CI)	Absolute		
Current users with <1 years duration of HRT use, by oestrogenic constituent												
Mortality (cardiovascular disease related)												
Oestradiol (Better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/20 (0%)	1/20 (5%)	POR 0.14 (0 to 6.82)	43 fewer per 1000 (from 50 fewer to 214 more)	VERY LOW	CRITICAL
Conjugated equine estrogen (CEE) (Better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/20 (0%)	1/20 (5%)	POR 0.14 (0 to 6.82)	43 fewer per 1000 (from 50 fewer to 214 more)	VERY LOW	CRITICAL
TIA												
Oestradiol (Better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	2/20 (10%)	0/20 (0%)	Not applicable	RD 0.10 (-0.05, 0.25)	VERY LOW	IMPORTANT
Conjugated equine estrogen (CEE) (Better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	0/20 (0%)	0/20 (0%)	Not applicable	RD 0.00 (-0.09, 0.09)	VERY LOW	IMPORTANT

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio; TIA: transient ischemic attack
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Population is indirect due to hormone replacement therapy used for prevention
[3] 95% CI crossed 2 MIDs (0.80 and 1.25)
[4] Number of events <150

Table 17: Evidence profile for comparison between combined oestrogen and progestogen (sequential) versus placebo in current users with <1 years duration of HRT use, by mode of administration

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined HRT (sequential)	Control	Relative (95% CI)	Absolute		
Current users with <1 years duration of HRT use, by mode of administration												
Mortality (cardiovascular disease related)												
Mixed (transdermal oestrogen and oral progestogen; better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/20 (0%)	1/20 (5%)	POR 0.14 (0 to 6.82)	43 fewer per 1000 (from 50 fewer to 214 more)	VERY LOW	CRITICAL

Oral (Better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/20 (0%)	1/20 (5%)	POR 0.14 (0 to 6.82)	43 fewer per 1000 (from 50 fewer to 214 more)	VERY LOW	CRITICAL
TIA												
Mixed (transdermal oestrogen and oral progestogen; better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	2/20 (10%)	0/20 (0%)	Not applicable	RD 0.10 (-0.05, 0.25)	VERY LOW	IMPORTANT
Oral (Better indicated by lower values)												
1 (Hall 1998)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	0/20 (0%)	0/20 (0%)	Not applicable	RD 0.00 (-0.09, 0.09)	VERY LOW	IMPORTANT

CI: confidence interval; HRT: hormonal replacement therapy; MID: minimally important difference; POR: peto odds ratio; TIA: transient ischemic attack

[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Population is indirect due to hormone replacement therapy used for prevention

[3] 95% CI crossed 2 MIDs (0.80 and 1.25)

[4] Number of events <150

Table 18: Evidence profile for comparison between combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined HRT (sequential)**	**Control**	**Relative (95% CI)**	**Absolute**		
Current users with 1-4 years duration of HRT use, by oestrogenic constituent												
Nonfatal MI												
Oestradiol (Better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	1/292 (0.3%)	1/347 (0.3%)	Not applicable	RD 0.00 (-0.01, 0.01)	VERY LOW	CRITICAL
Conjugated equine estrogen (CEE; better indicated by lower values)												
1 (KEEPS: Harman 2014)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/230 (0%)	0/275 (0%)	Not applicable	RD 0.00 (-0.01, 0.01)	VERY LOW	CRITICAL
Cardiac event composite score												
Oestradiol (Better indicated by lower values)												
1 (EMS: Tierney 2009)	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[5]	none	11/70 (15.7%)	8/72 (11.1%)	POR 1.48 (0.57 to 3.89)	45 more per 1000 (from 45 fewer to 216 more)	VERY LOW	CRITICAL
Conjugated equine estrogen (CEE; better indicated by lower values)												
1 PEPI (Anonymous1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	4/352 (1.1%)	0/174 (0%)	POR 4.49 (0.56 to 36.3)	-	LOW	CRITICAL
Stroke												

Oestradiol (Better indicated by lower values)												
2[1]	randomised trials	serious[2]	serious[6]	serious[3]	very serious[4]	none	6/292 (2.1%)	4/347 (1.2%)	Not applicable	RD 0.01 (-0.01, 0.03)	VERY LOW	CRITICAL
Conjugated equine oestrogen (CEE; better indicated by lower values)												
1 (KEEPS: Harman 2014)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/230 (0%)	0/275 (0%)	Not applicable	RD 0.00 (-0.01, 0.01)	VERY LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio
[1] EMS: Tierney 2009, KEEPS: Harman 2014
[2] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[3] Population is indirect due to hormone replacement therapy used for prevention
[4] Number of events <150
[5] 95% CI crossed 2 MIDs (0.80 and 1.25)
[6] Serious heterogeneity unexplained by subgroup analysis

Table 19: Evidence profile for comparison between combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by progestogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined HRT (sequential)**	**Control**	**Relative (95% CI)**	**Absolute**		
Current users with 1-4 years duration of HRT use, by progestogenic constituent												
Nonfatal MI												
Norethindrone (Better indicated by lower values)												
1 (EMS: Tierney 2009)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/70 (0%)	1/72 (1.4%)	POR 0.14 (0 to 7.02)	12 fewer per 1000 (from 14 fewer to 76 more)	VERY LOW	CRITICAL
Micronised progesterone (MP; better indicated by lower values)												
1 (KEEPS: Harman 2014)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/452 (0.2%)	0/275 (0%)	POR 4.99 (0.09 to 284.28)	-	VERY LOW	CRITICAL
Cardiovascular event composite score												
Norethindrone (Better indicated by lower values)												
1 (EMS: Tierney 2009)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	11/70 (15.7%)	8/72 (11.1%)	POR 1.48 (0.57 to 3.89)	45 more per 1000 (from 45 fewer to 216 more)	VERY LOW	CRITICAL
Micronised progesterone (MP; better indicated by lower values))												
1 (PEPI: Anonymous 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/178 (1.7%)	0/174 (0%)	POR 7.31 (0.76 to 70.71)	-	LOW	CRITICAL
Medroxyprogesterone acetate (MPA; better indicated by lower values)												

1 (PEPI: Anonymous 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/174 (0.6%)	0/174 (0%)	POR 7.39 (0.15 to 372.38)	-	LOW	CRITICAL
Stroke												
Norethindrone (Better indicated by lower values)												
1 (EMS: Tierney 2009)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	6/70 (8.6%)	4/72 (5.6%)	Not applicable	RD 0.03 (-0.05, 0.11)	VERY LOW	CRITICAL
Micronised progesterone (MP; better indicated by lower values)												
1 (KEEPS: Harman 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/452 (0%)	0/275 (0%)	Not applicable	RD 0.00 (-0.01, 0.01)	VERY LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Population is indirect due to hormone replacement therapy used for prevention
[3] 95% CI crossed 2 MIDs (0.80 and 1.25)
[4] Number of events <150

Table 20: Evidence profile for comparison between combined oestrogen and progestogen (sequential) versus placebo in current users with 1-4 years duration of HRT use, by mode of administration

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined HRT (sequential)**	**Control**	**Relative (95% CI)**	**Absolute**		
Current users with 1-4 years duration of HRT use, by mode of administration												
Nonfatal MI												
Transdermal oestrogen and oral progesterone (Better indicated by lower values)												
1 (KEEPS: Harman 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/222 (0.5%)	0/275 (0%)	Not applicable	RD 0.00 (-0.01, 0.02)	VERY LOW	CRITICAL
Oral oestrogen and oral progesterone (Better indicated by lower values)												
2[3]	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	0/300 (0%)	1/347 (0.3%)	Not applicable	RD -0.00 (-0.01, 0.01)	VERY LOW	CRITICAL
Stroke												
Transdermal (Better indicated by lower values)												
1 (KEEPS: Harman 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/222 (0%)	0/275 (0%)	Not applicable	RD 0.00 (-0.01, 0.01)	VERY LOW	CRITICAL
Oral (Better indicated by lower values)												
2[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/300 (2%)	4/347 (1.2%)	Not applicable	RD 0.01	VERY LOW	CRITICAL

										(-0.01, 0.03)		

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction.
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Number of events <150
[3] EMS: Tierney 2009, KEEPS: Harman 2014
[4] Population is indirect due to hormone replacement therapy used for prevention
[5] Number of events <150

Combined HRT versus no HRT: Observational study evidence

Table 21: Evidence profile for comparison between combined oestrogen and progestogen versus no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combined HRT**	**No HRT**	**Relative (95% CI)**	**Absolute**		
Coronary heart disease (including MI)												
Current and past users (unknown recency), by years of use												
< 1 year duration (Better indicated by lower values)												
1 (Chilvers 2003)	Case control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	49 cases 100 controls		OR 1.09 (0.67 to 1.77)	Not reported	VERY LOW	CRITICAL
1 to 4 years duration (Better indicated by lower values)												
1 (Chilvers 2003)	Case control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	41 cases 109 controls		OR 0.71 (0.42 to 1.19)	Not reported	VERY LOW	CRITICAL
> 5 years duration (Better indicated by lower values)												
1 (Chilvers 2003)	Case control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	15 cases 65 controls		OR 0.39 (0.19 to 0.81)	Not reported	VERY LOW	CRITICAL

Current users, with unknown duration of use (duration not reported), by time since menopause at first use												
≤4 years since menopause (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	Not reported	Not reported	HR 0.71 (0.57 to 0.89)	Not reported	LOW	CRITICAL
>10 years since menopause (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	Not reported	Not reported	HR 0.9 (0.63 to 1.29)	Not reported	VERY LOW	CRITICAL
Current users, with unknown duration of use (duration not reported), by age at first use (OR)												
45-54 years (Better indicated by lower values)												
1 (Kim 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	113 cases 972 controls		OR 0.74 (0.59 to 0.93)	Not reported	VERY LOW	CRITICAL
55-64 years (Better indicated by lower values)												
1 (Kim 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	70 cases 590 controls		OR 0.7 (0.53 to 0.93)	Not reported	VERY LOW	CRITICAL
65-74 years (Better indicated by lower values)												
1 (Kim 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	13 cases 132 controls		OR 0.59 (0.31 to 1.12)	Not reported	VERY LOW	CRITICAL
≥ 75 years (Better indicated by lower values)												
1 (Kim 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2 cases 16 controls		OR 0.43 (0.08 to 2.23)	Not reported	VERY LOW	CRITICAL
Stroke, Current users with unknown duration of HRT use (duration not reported)												

By continuous or cyclic HRT schedule												
Continuous combined (Better indicated by lower values)												
2[3]	Cohort studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	Not reported		OR 1.28 (1.21 to 1.36)	Not reported	LOW	CRITICAL
Cyclic combined (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	779/341061 (0.23%)	12788/999 999 (1.3%)	HR 1.08 (1.01 to 1.16)	1 more per 1000 (from 0 more to 2 more)	Moderate	CRITICAL
Long-cycle combined (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	94/37935 (0.25%)	12788/999 999 (1.3%)	HR 1.15 (0.94 to 1.4)	2 more per 1000 (from 1 fewer to 5 more)	LOW	CRITICAL
By time since menopause at first use												
HRT started within 4 years of menopause (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	Not reported	Not reported	HR 1.22 (0.96 to 1.55)	Not reported	LOW	CRITICAL
HRT started more than 10 years after menopause (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	Not reported	Not reported	HR 1.18 (0.87 to 1.6)	Not reported	LOW	CRITICAL
By age at first use (HR)												
HRT started age 50-59 years (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	Not reported	Not reported	HR 1.34 (0.84 to 2.13)	Not reported	LOW	CRITICAL

HRT started age ≥ 60 years (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	Not reported	Not reported	HR 1.72 (1.21 to 2.44)	Not reported	LOW	CRITICAL
By oestrogen dose (continuous combined)												
Low dose (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	201/98748 (0.2%)	Not reported	RR 0.84 (0.74 to 0.96)	Not reported	LOW	CRITICAL
High dose (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	810/213790 (0.38%)	Not reported	RR 1.48 (1.38 to 1.59)	Not reported	VERY LOW	CRITICAL
By oestrogen dose (cyclic combined)												
Low dose (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/47007 (0.21%)	Not reported	RR 1 (0.82 to 1.22)	Not reported	MODERATE	CRITICAL
Middle dose (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	390/166153 (0.23%)	Not reported	RR 1.11 (1 to 1.23)	Not reported	MODERATE	CRITICAL
High dose (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	300/165837 (0.18%)	Not reported	RR 1.04 (0.92 to 1.17)	Not reported	MODERATE	CRITICAL
By progestogenic constituent (OR)												

Progesterone (Better indicated by lower values)											
1 (Canonico 2016)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	60 cases 380 controls	OR 0.78 (0.48 to 1.26)	Not reported	VERY LOW	CRITICAL
Pregnane derivatives (Better indicated by lower values)											
1 (Canonico 2016)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	58 cases 197 controls	OR 1 (0.6 to 1.66)	Not reported	VERY LOW	CRITICAL
Norpregnane derivatives (Better indicated by lower values)											
1 (Canonico 2016)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	17 cases 27 controls	OR 2.25 (1.05 to 4.81)	Not reported	VERY LOW	CRITICAL
Nortestosterone derivatives (Better indicated by lower values)											
1 (Canonico 2016)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	17 cases 46 controls	OR 1.26 (0.62 to 2.58)	Not reported	VERY LOW	CRITICAL
By progestogenic constituent (continuous combined)											
Norhisterone (Better indicated by lower values)											
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	977 cases 290940 controls	OR 1.3 (1.22 to 1.39)	Not reported	LOW	CRITICAL
Dienogest (Better indicated by lower values)											
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13 cases 5685 controls	OR 1.06 (0.61 to 1.83)	Not reported	VERY LOW	CRITICAL
Tibolone (Better indicated by lower values)											
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	174 cases 49693 controls	OR 1.3 (1.12 to 1.51)	Not reported	LOW	CRITICAL

Raloxifene (Better indicated by lower values)											
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	42 cases 11238 controls	OR 1.31 (0.97 to 1.77)	Not reported	LOW	CRITICAL
Progestogenic constituent (cyclic combined)											
Medroxyprogesterone (Better indicated by lower values)											
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	161 cases 75691 controls	OR 1.02 (0.87 to 1.19)	Not reported	MODERATE	CRITICAL
Norhisterone (Better indicated by lower values)											
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	494 cases 202511 controls	OR 1.14 (1.04 to 1.25)	Not reported	MODERATE	CRITICAL
Cyproterone acetate (Better indicated by lower values)											
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25 cases 15588 controls	OR 0.83 (0.56 to 1.22)	Not reported	LOW	CRITICAL
Levonorgestrel (Better indicated by lower values)											
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	124 cases 56571 controls	OR 1.03 (0.86 to 1.23)	Not reported	MODERATE	CRITICAL
By route of administration											
Transdermal (Better indicated by lower values)											
1 (Renoux 2010)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	22 cases 124 controls	OR 0.76 (0.47 to 1.22)	Not reported	VERY LOW	CRITICAL
Oral (Better indicated by lower values)											

1 (Renoux 2010)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	356 cases 1223 controls		OR 1.24 (1.09 to 1.41)	Not reported	VERY LOW	CRITICAL
By route of administration (continuous combined)												
Transdermal (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	66 cases 8326 controls		OR 0.96 (0.6 to 1.53)	Not reported	VERY LOW	CRITICAL
Oral (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	996 cases 300963 controls		OR 1.29 (1.21 to 1.37)	Not reported	LOW	CRITICAL
By route of administration (cyclic combined)												
Transdermal (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18 cases 40730 controls		OR 0.85 (0.67 to 1.08)	Not reported	LOW	CRITICAL
Oral (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	807 cases 338267 controls		OR 1.11 (1.03 to 1.2)	Not reported	MODERATE	CRITICAL
Coronary heart disease (including MI)												
Current users, by years of use												
Unknown duration of HRT use (duration of use not reported) – HR (Better indicated by lower values)												
2[5]	Cohort studies	no serious risk of bias	no serious inconsistency	serious[6]	serious[2]	none	Not reported	Not reported	HR 0.72 (0.62 to 0.82)	Not reported	VERY LOW	CRITICAL

Unknown duration of HRT use (duration of use not reported) – OR (Better indicated by lower values)												
3[7]	Nested case-control study; Case control studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	Not reported	Not reported	OR 0.78 (0.69 to 0.89)	Not reported	VERY LOW	CRITICAL
Cardiovascular mortality												
Current user with unknown duration of HRT use (duration of use not reported (better indicated by lower values)												
1 (Bhupathiraju 2017)	Cohort study	serious[8]	no serious inconsistency	no serious indirectness	very serious[1]	none	17/37834 (0.04%)	-	RR 1.00 (0.59 to 1.7)	Not reported	VERY LOW	CRITICAL
Stroke												
Current users with unknown duration of HRT use (duration of use not reported) – OR (Better indicated by lower values)												
2[9]	Case control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	Not reported		OR 0.93 (0.71 to 1.22)	Not reported	VERY LOW	CRITICAL
TIA												
Current users with unknown duration of HRT use (duration of use not reported; better indicated by lower values)												
1 (Arana 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	47 cases 701 controls		OR 1.34 (0.94 to 1.91)	Not reported	VERY LOW	CRITICAL

CEE: conjugated equine estrogen; CI: confidence interval; EE: esterified estrogen; HRT: hormonal replacement therapy; MID: minimally important difference; RR: risk ratio; TIA: transient ischemic attack.
[1] 95% CI crosses 2 MIDs (0.80 and 1.25)
[2] 95% CI crosses 1 MID (0.80)
[3] Grodstein 2006; Lokkegaard 2017
[4] 95% CI crosses 1 MID (1.25)
[5] Ferrara 2003; Grodstein 2006
[6] Population is indirect as they are diabetic women and not fully representative of the average population
[7] Kim 2006; Lemaitre 2006 – CEE+P; Lemaitre 2006 – EE+P
[8] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
[9] Lemaitre 2006-CEE+P; Lemaitre-2006 EE+P

Oestrogen-only HRT versus placebo: RCT evidence

Table 22: Evidence profile for comparison between oestrogen-only versus placebo, by recency and duration of HRT use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only	Placebo by recency and duration	Relative (95% CI)	Absolute		
Coronary heart disease (including MI)												
Current HRT user, by years of use												
1-4 years duration (Better indicated by lower values)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	35/437 (8%)	35/432 (8.1%)	RR 0.99 (0.63 to 1.55)	1 fewer per 1000 (from 30 fewer to 45 more)	VERY LOW	CRITICAL
5-9 years duration (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	204/5310 (3.8%)	222/5429 (4.1%)	RR 0.94 (0.78 to 1.13)	2 fewer per 1000 (from 9 fewer to 5 more)	MODERATE	CRITICAL
Current and past users (unknown recency), by years of use												
5-9 years duration of HRT use at 13 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	363/5310 (6.8%)	393/5429 (7.2%)	RR 0.94 (0.82 to 1.08)	4 fewer per 1000 (from 13 fewer to 6 more)	HIGH	CRITICAL
Nonfatal MI												
Current users, by years of use												
1-4 years duration (Better indicated by lower values)												
4[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[6]	none	62/1061 (5.8%)	51/1047 (4.9%)	RR 1.20 (0.84 to 1.72)	10 more per 1000 (from 8 fewer to 35 more)	LOW	CRITICAL
5-9 years duration (Better indicated by lower values)												
1 (WHI: Hsia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	149/5310 (2.8%)	168/5429 (3.1%)	RR 0.91 (0.73 to 1.13)	3 fewer per 1000 (from 8 fewer to 4 more)	MODERATE	CRITICAL
Cardiovascular event composite scores												
Current users												
1-4 years duration (Better indicated by lower values)												
2[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/286 (1.4%)	4/285 (1.4%)	POR 1 (0.25 to 4.06)	0 fewer per 1000 (from 10 fewer to 41 more)	LOW	CRITICAL

5-9 years duration (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	877/5310 (16.5%)	813/5429 (15%)	POR 1.12 (1.01 to 1.25)	15 more per 1000 (from 1 more to 31 more)	MODERATE	CRITICAL
Current and past user (unknown recency), by years of use												
5-9 years duration at 13 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1267/5310 (23.9%)	1227/5429 (22.6%)	POR 1.07 (0.98 to 1.17)	12 more per 1000 (from 4 fewer to 29 more)	HIGH	CRITICAL
Mortality (cardiovascular disease related)												
Current users, by years of use												
<1 year duration (Better indicated by lower values)												
1 (ESPRIT: Cherry 2002)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	14/513 (2.7%)	25/504 (5%)	RR 0.55 (0.29 to 1.05)	22 fewer per 1000 (from 35 fewer to 2 more)	LOW	CRITICAL
1-4 years duration (Better indicated by lower values)												
4[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	36/1061 (3.4%)	47/1047 (4.5%)	RR 0.76 (0.5 to 1.15)	11 fewer per 1000 (from 22 fewer to 7 more)	LOW	CRITICAL
5-9 years duration of HRT use (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	109/5310 (2.1%)	112/5429 (2.1%)	RR 1 (0.77 to 1.29)	0 fewer per 1000 (from 5 fewer to 6 more)	LOW	CRITICAL
Current and past users (unknown recency), by years of use												
5-9 years duration at 13 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	243/5310 (4.6%)	257/5429 (4.7%)	RR 0.97 (0.81 to 1.15)	1 fewer per 1000 (from 9 fewer to 7 more)	HIGH	CRITICAL
5-9 years duration at 18 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	547/5310 (10.3%)	577/5429 (10.6%)	RR 0.97 (0.87 to 1.08)	3 fewer per 1000 (from 14 fewer to 9 more)	HIGH	CRITICAL
Past users with ≥10 years since last use, by years of use												
1-4 years duration of HRT use (Better indicated by lower values)												
1 (ESPRIT: Cherry 2014)	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[6]	none	201/513 (39.2%)	165/504 (32.7%)	RR 1.2 (1.01 to 1.41)	65 more per 1000 (from 3 more to 134 more)	LOW	CRITICAL
Stroke												
Current users, by years of use												
1-4 years duration (Better indicated by lower values)												

3[8]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[6]	none	78/950 (8.2%)	68/936 (7.3%)	RR 1.12 (0.83 to 1.51)	9 more per 1000 (from 12 fewer to 37 more)	LOW	CRITICAL
5-9 years duration (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	169/5310 (3.2%)	130/5429 (2.4%)	RR 1.33 (1.06 to 1.67)	8 more per 1000 (from 1 more to 16 more)	MODERATE	CRITICAL
Current and past users (unknown recency)												
5-9 years duration at 13 years cumulative follow-up (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	278/5310 (5.2%)	253/5429 (4.7%)	RR 1.12 (0.95 to 1.33)	6 more per 1000 (from 2 fewer to 15 more)	MODERATE	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio; RR: risk ratio

[1] ERA: Herrington 2000, WEST: Viscoli 2001

[2] Population is indirect due to hormone replacement therapy used for prevention

[3] 95% CI crossed 2 MIDs (0.80 and 1.25)

[4] 95% CI crossed 1 MID (0.80)

[5] EPAT: Hodis 2001, ERA: Herrington 2000, ESPRIT: Cherry 2002, WEST: Viscoli 2001)

[6] 95% CI crossed 1 MID (1.25)

[7] EPAT: Hodis 2001, PEPI: Anonymous 1995

[8] ERA: Herrington 2000, ESPRIT: Cherry 2002, WEST: Viscoli 2001

Table 23: Evidence profile for comparison between oestrogen-only versus placebo in current users with 1-4 years duration of HRT use, by oestrogenic constituent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oestrogen-only**	**Control**	**Relative (95% CI)**	**Absolute**		
Current users with 1-4 years duration of HRT use, by oestrogenic constituent												
Coronary heart disease (including MI)												
Oestradiol (Better indicated by lower values)												
1 (WEST: Viscoli 2001)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	25/337 (7.4%)	25/327 (7.6%)	RR 0.97 (0.57 to 1.65)	2 fewer per 1000 (from 33 fewer to 50 more)	VERY LOW	CRITICAL
Conjugated equine estrogen (Better indicated by lower values)												
1 (ERA: Herrington 2000)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	10/100 (10%)	10/105 (9.5%)	RR 1.05 (0.46 to 2.41)	5 more per 1000 (from 51 fewer to 134 more)	VERY LOW	CRITICAL
Nonfatal MI												
Oestradiol (Better indicated by lower values)												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	56/961 (5.8%)	44/942 (4.7%)	RR 1.25 (0.85 to 1.83)	12 more per 1000 (from 7 fewer to 39 more)	LOW	CRITICAL

Conjugated equine estrogen (CEE) (Better indicated by lower values)												
1 (ERA: Herrington 2000)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	6/100 (6%)	7/105 (6.7%)	RR 0.9 (0.31 to 2.59)	7 fewer per 1000 (from 46 fewer to 106 more)	VERY LOW	CRITICAL
Cardiac event composite scores												
Oestradiol												
1 (EPAT: Hodis 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/111 (2.7%)	4/111 (3.6%)	POR 0.75 (0.17 to 3.35)	9 fewer per 1000 (from 30 fewer to 75 more)	LOW	CRITICAL
Conjugated equine estrogen (CEE) (Better indicated by lower values)												
1 (PEPI: Anonymous 1995)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/175 (0.6%)	0/174 (0%)	POR 7.35 (0.15 to 370.27)	-	LOW	CRITICAL
Mortality (cardiovascular disease related)												
Oestradiol (Better indicated by lower values)												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	32/961 (3.3%)	44/942 (4.7%)	POR 0.7 (0.44 to 1.11)	14 fewer per 1000 (from 26 fewer to 5 more)	LOW	CRITICAL
Conjugated equine estrogen (CEE) (Better indicated by lower values)												
1 (ERA: Herrington 2000)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	4/100 (4%)	3/105 (2.9%)	POR 1.41 (0.31 to 6.35)	11 more per 1000 (from 20 fewer to 129 more)	VERY LOW	CRITICAL
Stroke												
Oestradiol (Better indicated by lower values)												
2[6]	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	73/850 (8.6%)	62/831 (7.5%)	RR 1.14 (0.84 to 1.56)	10 more per 1000 (from 12 fewer to 42 more)	LOW	CRITICAL
Conjugated equine estrogen (CEE) (Better indicated by lower values)												
1 (ERA: Herrington 2000)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	5/100 (5%)	6/105 (5.7%)	RR 0.88 (0.28 to 2.78)	7 fewer per 1000 (from 41 fewer to 102 more)	VERY LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; POR: peto odds ratio; RR: risk ratio.

[1] Population is indirect due to hormone replacement therapy used for prevention

[2] 95% CI crossed 2 MIDs (0.80 and 1.25)

[3] EPAT: Hodis 2001, ESPRIT: Cherry 2002, WEST: Viscoli 2001)

[4] 95% CI crossed 1 MID (1.25)

[5] 95% CI crossed 1 MID (0.80)

[6] ESPRIT: Cherry 2002, WEST: Viscoli 2001

Table 24: Evidence profile for comparison between oestrogen-only versus placebo in current users with 5-9 years duration of HRT use, by time since menopause at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oestrogen-only**	**Control**	**Relative (95% CI)**	**Absolute**		

Current users with 5-9 years duration of HRT use, by time since menopause at first use												
Coronary heart disease (including MI)												
<10 years since menopause (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	8/827 (1%)	16/817 (2%)	RR 0.49 (0.21 to 1.15)	10 fewer per 1000 (from 15 fewer to 3 more)	MODERATE	CRITICAL
>10 years since menopause (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	166/3668 (4.5%)	166/3819 (4.3%)	RR 1.04 (0.84 to 1.28)	2 more per 1000 (from 7 fewer to 12 more)	MODERATE	CRITICAL
Stroke												
<10 years since menopause (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	17/827 (2.1%)	9/817 (1.1%)	RR 1.87 (0.84 to 4.16)	10 more per 1000 (from 2 fewer to 35 more)	MODERATE	CRITICAL
>10 years since menopause (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	130/3668 (3.5%)	105/3819 (2.7%)	RR 1.29 (1 to 1.66)	8 more per 1000 (from 0 more to 18 more)	MODERATE	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; RR: risk ratio
[1] 95% CI crossed 1 MID (0.80)
[2] 95% CI crossed 1 MID (1.25)

Table 25: Evidence profile for comparison between oestrogen-only versus placebo in current users with 5-9 years duration of HRT use, by age at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oestrogen-only**	**Control**	**Relative (95% CI)**	**Absolute**		
Current users with 5-9 years duration of HRT use, by age at first use												
Coronary heart disease (including MI)												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21/1639 (1.3%)	35/1674 (2.1%)	RR 0.61 (0.36 to 1.05)	8 fewer per 1000 (from 13 fewer to 1 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												

1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	100/2386 (4.2%)	108/2465 (4.4%)	RR 0.96 (0.73 to 1.25)	2 fewer per 1000 (from 12 fewer to 11 more)	MODERATE	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	83/1285 (6.5%)	79/1290 (6.1%)	RR 1.05 (0.78 to 1.42)	3 more per 1000 (from 13 fewer to 26 more)	LOW	CRITICAL
Cardiovascular event composite scores												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	127/1639 (7.7%)	148/1674 (8.8%)	RR 0.88 (0.7 to 1.1)	11 fewer per 1000 (from 27 fewer to 9 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	430/2386 (18%)	382/2465 (15.5%)	RR 1.16 (1.03 to 1.32)	25 more per 1000 (from 5 more to 50 more)	MODERATE	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	320/1285 (24.9%)	283/1290 (21.9%)	RR 1.14 (0.99 to 1.31)	31 more per 1000 (from 2 fewer to 68 more)	MODERATE	CRITICAL
Mortality (cardiovascular disease related)												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/1639 (0.5%)	10/1674 (0.6%)	RR 0.82 (0.32 to 2.07)	1 fewer per 1000 (from 4 fewer to 6 more)	LOW	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	56/2386 (2.3%)	45/2465 (1.8%)	RR 1.29 (0.87 to 1.9)	5 more per 1000 (from 2 fewer to 16 more)	MODERATE	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	45/1285 (3.5%)	57/1290 (4.4%)	RR 0.79 (0.54 to 1.16)	9 fewer per 1000 (from 20 fewer to 7 more)	MODERATE	CRITICAL
Stroke												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	19/1639 (1.2%)	21/1674 (1.3%)	RR 0.92 (0.5 to 1.71)	1 fewer per 1000 (from 6 fewer to 9 more)	LOW	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	84/2386 (3.5%)	57/2465 (2.3%)	RR 1.52 (1.09 to 2.12)	12 more per 1000 (from 2 more to 26 more)	MODERATE	CRITICAL

70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	66/1285 (5.1%)	52/1290 (4%)	RR 1.27 (0.89 to 1.82)	11 more per 1000 (from 4 fewer to 33 more)	MODERATE	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; RR: risk ratio
[1] 95% CI crossed 1 MID (0.80)
[2] 95% CI crossed 2 MIDs (0.80 and 1.25)
[3] 95% CI crossed 1 MID (1.25)

Table 26: Evidence profile for comparison between oestrogen-only versus placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oestrogen-only**	**Control**	**Relative (95% CI)**	**Absolute**		
Current and past users (unknown recency) with 5-9 years duration of HRT use at 13 years cumulative follow-up, by age at first use												
Coronary heart disease (including MI)												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	42/1639 (2.6%)	64/1674 (3.8%)	RR 0.67 (0.46 to 0.98)	13 fewer per 1000 (from 1 fewer to 21 fewer)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	183/2386 (7.7%)	188/2465 (7.6%)	RR 1.01 (0.83 to 1.22)	1 more per 1000 (from 13 fewer to 17 more)	HIGH	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	138/1285 (10.7%)	141/1290 (10.9%)	RR 0.98 (0.79 to 1.23)	2 fewer per 1000 (from 23 fewer to 25 more)	MODERATE	CRITICAL
Cardiovascular event composite score												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	202/1639 (12.3%)	231/1674 (13.8%)	RR 0.89 (0.75 to 1.07)	15 fewer per 1000 (from 34 fewer to 10 more)	MODERATE	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	624/2386 (26.2%)	580/2465 (23.5%)	RR 1.11 (1.01 to 1.23)	26 more per 1000 (from 2 more to 54 more)	HIGH	CRITICAL
70-79 years (Better indicated by lower values)												

1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	441/1285 (34.3%)	416/1290 (32.2%)	RR 1.06 (0.95 to 1.19)	19 more per 1000 (from 16 fewer to 61 more)	HIGH	CRITICAL
Mortality (cardiovascular disease related)												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	21/1639 (1.3%)	21/1674 (1.3%)	RR 1.02 (0.56 to 1.86)	0 more per 1000 (from 6 fewer to 11 more)	LOW	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	106/2386 (4.4%)	107/2465 (4.3%)	RR 1.02 (0.79 to 1.33)	1 more per 1000 (from 9 fewer to 14 more)	LOW	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	116/1285 (9%)	129/1290 (10%)	RR 0.9 (0.71 to 1.15)	10 fewer per 1000 (from 29 fewer to 15 more)	MODERATE	CRITICAL
Stroke												
50-59 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	33/1639 (2%)	36/1674 (2.2%)	RR 0.94 (0.59 to 1.49)	1 fewer per 1000 (from 9 fewer to 11 more)	LOW	CRITICAL
60-69 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	134/2386 (5.6%)	114/2465 (4.6%)	RR 1.21 (0.95 to 1.55)	10 more per 1000 (from 2 fewer to 25 more)	MODERATE	CRITICAL
70-79 years (Better indicated by lower values)												
1 (WHI: Manson 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	111/1285 (8.6%)	103/1290 (8%)	RR 1.08 (0.84 to 1.4)	6 more per 1000 (from 13 fewer to 32 more)	MODERATE	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; RR: risk ratio

[1] 95% CI crossed 1 MID (0.80)

[2] 95% CI crossed 2 MIDs (0.80 and 1.25)

[3] 95% CI crossed 1 MID (1.25)

Table 27: Evidence profile for comparison between oestrogen-only versus placebo in current and past users (unknown recency) with 5-9 years duration of HRT use at 18 years cumulative follow-up, by age at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oestrogen-only**	**Control**	**Relative (95% CI)**	**Absolute**		

Current and past users (unknown recency) with 5-9 years duration of HRT use at 18 years cumulative follow-up, by age at first use											
Mortality (cardiovascular disease related)											
50-59 years (Better indicated by lower values)											
1 (WHI: Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	48/1639 (2.9%)	50/1674 (3%)	RR 0.98 (0.66 to 1.45)	1 fewer per 1000 (from 10 fewer to 13 more)	LOW	CRITICAL
60-69 years (Better indicated by lower values)											
1 (WHI: Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	226/2386 (9.5%)	233/2465 (9.5%)	RR 1 (0.84 to 1.19)	0 fewer per 1000 (from 15 fewer to 18 more)	HIGH	CRITICAL
70-79 years (Better indicated by lower values)											
1 (WHI: Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	273/1285 (21.2%)	294/1290 (22.8%)	RR 0.93 (0.81 to 1.08)	16 fewer per 1000 (from 43 fewer to 18 more)	HIGH	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MI: myocardial infarction; MID: minimally important difference; RR: risk ratio
[1] 95% CI crossed 2 MIDs (0.80 and 1.25)

Table 28: Evidence profile for comparison between oestrogen-only versus placebo in past users with ≥10 years since last use and 1-4 years duration of HRT use, by age at first use

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oestrogen-only:**	**Control**	**Relative (95% CI)**	**Absolute**		
Past users with ≥10 years since last use and 1-4 years duration of HRT use, by age at first use												
Mortality (cardiovascular disease related)												
50-59 years (Better indicated by lower values)												
1 (ESPRIT: Cherry 2014)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	49/167 (29.3%)	32/134 (23.9%)	RR 1.23 (0.84 to 1.8)	55 more per 1000 (from 38 fewer to 191 more)	LOW	CRITICAL
60-69 years (Better indicated by lower values)												
1 (ESPRIT: Cherry 2014)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	152/346 (43.9%)	133/370 (35.9%)	RR 1.22 (1.02 to 1.46)	79 more per 1000 (from 7 more to 165 more)	LOW	CRITICAL

CI: confidence interval; HRT: hormonal replacement therapy; MID: minimally important difference; RR: risk ratio.
[1] Population is indirect due to hormone replacement therapy used for prevention
[2] 95% CI crossed 1 MID (1.25)

Oestrogen-only versus no HRT: Observational study evidence

Table 29: Evidence profile for comparison between Oestrogen-only versus no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen-only HRT verses no HRT	Control	Relative (95% CI)	Absolute		
Coronary heart disease (including MI)												
Current and past users (unknown recency), by years of use												
< 1 year duration (Better indicated by lower values												
1 (Chilvers 2003)	Case control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	28 cases 60 controls		OR 1.05 (0.56 to 1.97)	Not reported	VERY LOW	CRITICAL
1 to 4 years duration (Better indicated by lower values)												
1 (Chilvers 2003)	Case control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	29 cases 66 controls		OR 0.94 (0.52 to 1.7)	Not reported	VERY LOW	CRITICAL
> 5 years duration of HRT use (Better indicated by lower values)												
1 (Chilvers 2003)	Case control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	10 cases 44 controls		OR 0.48 (0.21 to 1.09)	Not reported	VERY LOW	CRITICAL
Current users with unknown duration of HRT use (duration of use not reported)												
By time since menopause												
≤4 years of menopause (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	130/140515 (0.09%)	Not reported	HR 0.62 (0.51 to 0.76)	Not reported	VERY LOW	CRITICAL

>10 years after menopause (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	84/37978 (0.22%)	Not reported	HR 0.87 (0.69 to 1.1)	Not reported	LOW	CRITICAL
By age at first use (HR)												
HRT started age 50-59 years (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	Not reported	Not reported	HR 0.51 (0.32 to 0.82)	Not reported	LOW	CRITICAL
HRT started age ≥ 60 years (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	Not reported	Not reported	HR 1.07 (0.83 to 1.38)	Not reported	LOW	CRITICAL
By age at first use (OR)												
HRT started age 45-54 years (Better indicated by lower values)												
1 (Kim 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	63 cases 417 controls		OR 0.93 (0.68 to 1.27)	Not reported	VERY LOW	CRITICAL
HRT started age 55-64 years (Better indicated by lower values)												
1 (Kim 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	49 cases 404 controls		OR 0.66 (0.47 to 0.93)	Not reported	VERY LOW	CRITICAL
HRT started age 65-74 years (Better indicated by lower values)												
1 (Kim 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	17 cases 162 controls		OR 0.46 (0.26 to 0.82)	Not reported	VERY LOW	CRITICAL
HRT started age ≥ 75 years (Better indicated by lower values)												

1 (Kim 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5 cases 4 controls		OR 0.62 (0.22 to 1.71)	Not reported	VERY LOW	CRITICAL
Stroke												
Current users with unknown duration of HRT use (duration of use not reported)												
By time since menopause at first use												
HRT started within 4 years of menopause (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	Not reported	Not reported	HR 1.29 (1.05 to 1.58)	Not reported	LOW	CRITICAL
HRT started more than 10 years after menopause (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	Not reported	Not reported	HR 1.31 (1.05 to 1.63)	Not reported	LOW	CRITICAL
By age at first use (HR)												
HRT started age 50-59 years (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	Not reported	Not reported	HR 1.58 (1.05 to 2.37)	Not reported	LOW	CRITICAL
HRT started age ≥ 60 years (Better indicated by lower values)												
1 (Grodstein 2006)	Cohort study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	Not reported	Not reported	HR 1.82 (1.3 to 2.54)	Not reported	VERY LOW	CRITICAL
By oestrogen dose												
Low dose (Better indicated by lower values)												

1 (Lokkegaard 2017)	Cohort study	serious[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	160/70656 (0.23%)	Not reported	RR 0.89 (0.76 to 1.04)	Not reported	VERY LOW	CRITICAL
Middle dose (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	695/217757 (0.32%)	Not reported	RR 1.14 (1.06 to 1.23)	Not reported	VERY LOW	CRITICAL
High dose (Better indicated by lower values)												
1 (Lokkegaard 2017)	Cohort study	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	91/20214 (0.45%)	Not reported	RR 1.63 (1.33 to 2)	Not reported	VERY LOW	CRITICAL
By route of administration												
Transdermal (Better indicated by lower values)												
2[5]	Cohort study; Nested case-control study	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	204 cases 0 controls		OR 0.88 (0.75 to 1.02)	Not reported	VERY LOW	CRITICAL
Oral (Better indicated by lower values)												
2[5]	Cohort study; Nested case-control study	serious[4]	serious[6]	no serious indirectness	serious[3]	none	Not reported		RR 1.24 (1.09 to 1.4)	Not reported	VERY LOW	CRITICAL
Coronary heart disease (including MI)												
Current users, by years of use												
Unknown duration of HRT use (duration of use not reported) - HR (Better indicated by lower values)												
2[7]	Cohort studies	no serious risk of bias	serious[6]	serious[8]	serious[2]	none	Not reported	Not reported	HR 0.79 (0.65 to 0.96)	Not reported	VERY LOW	CRITICAL
Unknown duration of HRT use (duration of use not reported) – OR (Better indicated by lower values)												

3[9]	Nested case-control study; Case control studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	Not reported	Not reported	OR 0.79 (0.70 to 0.90)	Not reported	VERY LOW	CRITICAL
Cardiovascular mortality												
Current users with unknown duration of HRT use (duration of use not reported (better indicated by lower values)												
1 (Bhupathiraju 2017)	Cohort study	serious[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	142/66545 (0.21%)	Not reported	HR 1.02 (0.79 to 1.32)	Not reported	VERY LOW	CRITICAL .
Stroke												
Current users, by years of use												
Unknown duration of HRT use (duration of use not reported) – HR (Better indicated by lower values)												
2[10]	Case control study	serious[4]	very serious[11]	no serious indirectness	serious[3]	none	Not reported	Not reported	RR 1.23 (1.00 to 1.52) [RR 1.39, RR 1.12[12]]	Not reported	VERY LOW	CRITICAL
Unknown duration of HRT use (duration of use not reported) OR (Better indicated by lower values)												
2[13]	Case control study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported		OR 1.00 (0.81 to 1.23)	Not reported	LOW	CRITICAL
TIA												
Current users with unknown duration of HRT use (duration of use not reported; better indicated by lower values)												
1 (Arana 2006)	Nested case-control study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	33 cases 521 controls		OR 1.36 (0.92 to 2.01)	Not reported	VERY LOW	CRITICAL

CEE: conjugated equine estrogen; CI: confidence interval; EE: esterified estrogen; HRT: hormonal replacement therapy; MID: minimally important difference; RR: risk ratio; TIA: transient ischemic attack.

[1] 95% CI crosses 2 MIDs (0.80 and 1.25)

[2] 95% CI crosses 1 MID (0.80)

[3] 95% CI crosses 1 MID (1.25)

[4] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I

[5] Lokkegaard 2017; Renoux 2010
[6] Serious heterogeneity unexplained by subgroup analysis
[7] Ferrara 2003; Grodstein 2006
[8] Population is indirect as they are diabetic women and not fully representative of the average population
[9] Kim 2006; Lemaitre 2006 – CEE+P; Lemaitre 2006 – EE+P

[10] Grostein 2006; Lokkegaard 2017
[11] Very serious heterogeneity unexplained by subgroup analysis
[12] Single-study point estimates were additionally reported due to very serious heterogeneity (I-squared value > 80%)
[13] Lemaitre 2006-CEE; Lemaitre-2006 EE

Appendix G Economic evidence study selection

Study selection for: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for further information.

Appendix H Economic evidence tables

Economic evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

Excluded effectiveness studies

Table 30: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Alexandersen, P, Tanko, L B, Bagger, Y Z et al. (2006) The long-term impact of 2-3 years of hormone replacement therapy on cardiovascular mortality and atherosclerosis in healthy women. Climacteric : the journal of the International Menopause Society 9(2): 108-18	- Cohort already included
Baik, S.H.; Baye, F.; McDonald, C.J. (2022) Effects of Hormone Therapy on survival, cancer, cardiovascular and dementia risks in 7 million menopausal women over age 65: a retrospective observational study. medRxiv	- Paper available as preprint only - not peer reviewed
Bath, Philip M W and Gray, Laura J (2005) Association between hormone replacement therapy and subsequent stroke: a meta-analysis. BMJ (Clinical research ed.) 330(7487): 342	- Systematic review. The study combined data from randomised and non-randomised studies and could not be included as whole. The included studies list was checked for any relevant studies and where appropriate, these were included
Bezwada, Prema; Shaikh, Atif; Misra, Deepika (2017) The Effect of Transdermal Estrogen Patch Use on Cardiovascular Outcomes: A Systematic Review. Journal of women's health (2002) 26(12): 1319-1325	- Systematic review. The study did not include any meta-analysis and could not be included as whole. The included studies list was checked for any relevant studies and where appropriate, these were included
Billeci, Antonia M R, Paciaroni, Maurizio, Caso, Valeria et al. (2008) Hormone replacement therapy and stroke. Current vascular pharmacology 6(2): 112-23	- Study design. The study was not a systematic review, randomised controlled trial, or observational study
Boardman, Henry M P, Hartley, Louise, Eisinga, Anne et al. (2015) Hormone therapy for preventing cardiovascular disease in post-menopausal women. The Cochrane database of systematic reviews: cd002229	- Systematic review. The study combined data for participants who received combined HRT and oestrogen-only HRT. The study could not be included as whole however the included studies list was checked for any relevant studies and where appropriate, these were included
Brownley, Kimberly A, Hinderliter, Alan L, West, Sheila G et al. (2004) Cardiovascular effects of 6 months of hormone replacement therapy versus placebo: differences associated with years since	- Outcomes. The study does not report any primary outcomes that match the protocol

Study	Reason for exclusion
menopause. American journal of obstetrics and gynecology 190(4): 1052-8	
Carrasquilla, German D, Berglund, Anita, Gigante, Bruna et al. (2015) Does menopausal hormone therapy reduce myocardial infarction risk if initiated early after menopause? A population-based case-control study. Menopause (New York, N.Y.) 22(6): 598-606	- Intervention. The study combined data for participants who received combined oestrogen and progestogen and oestrogen-only hormone replacement therapy
Carrasquilla, German D, Frumento, Paolo, Berglund, Anita et al. (2017) Postmenopausal hormone therapy and risk of stroke: A pooled analysis of data from population-based cohort studies. PLoS medicine 14(11): e1002445	- Intervention. Hormone replacement therapy use was not analysed according to duration or recency
Chang, Wei-Chuan; Wang, Jen-Hung; Ding, Dah-Ching (2022) Menopausal hormone therapy with conjugated equine estrogen is associated with a higher risk of hemorrhagic stroke than therapy with estradiol: a retrospective population-based cohort study. Maturitas 165: 72-77	- Comparison - not placebo or no HRT
Chen, Jian-Shu, Mou, Yu-Ping, Li, Cai-E et al. (2021) Effects of hormone replacement therapy on left ventricular diastolic function in postmenopausal women: a systematic review and meta-analysis. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 37(4): 300-306	- Conference abstract
Chen, L, Mishra, G D, Dobson, A J et al. (2017) Protective effect of hormone therapy among women with hysterectomy/oophorectomy. Human reproduction (Oxford, England) 32(4): 885-892	- Intervention. The use of oestrogen-only & combined HRT are not reported separately and HRT use not analysed according to duration or recency - Population does not match the review protocol: *41% were pre-menopausal at the start of the study*
Chester, Rebecca C; Kling, Juliana M; Manson, JoAnn E (2018) What the Women's Health Initiative has taught us about menopausal hormone therapy. Clinical cardiology 41(2): 247-252	- Study design. The study is not a systematic review, randomised controlled trial, or observational study
Chlebowski, Rowan T, Barrington, Wendy, Aragaki, Aaron K et al. (2017) Estrogen alone and health outcomes in black women by African ancestry: a secondary analyses of a randomized controlled trial. Menopause (New York, N.Y.) 24(2): 133-141	- Cohort already included: *WHI trial*
Cho, L. and Mukherjee, D. (2005) Hormone replacement therapy and secondary cardiovascular prevention: A meta-analysis of randomized trials. Cardiology 104(3): 143-147	- Systematic review. The systematic review includes study that are not relevant to this review and so cannot be included as whole. The included studies list was checked for any relevant studies and where appropriate, these were included

Study	Reason for exclusion
Clarke, S C, Kelleher, J, Lloyd-Jones, H et al. (2002) A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. BJOG : an international journal of obstetrics and gynaecology 109(9): 1056-62	- Intervention. Oestrogen-only & combined HRT were not reported separately
Coker, L H, Hogan, P E, Bryan, N R et al. (2009) Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. Neurology 72(2): 125-34	- Outcomes. Reported outcomes do not match the review protocols
Criqui, M H, Suarez, L, Barrett-Connor, E et al. (1988) Postmenopausal estrogen use and mortality. Results from a prospective study in a defined, homogeneous community. American journal of epidemiology 128(3): 606-14	- Intervention. HRT use was not analysed according to duration or recency: *Duration and recency of HRT use is unclear*
de Vries, C S; Bromley, S E; Farmer, R D T (2006) Myocardial infarction risk and hormone replacement: differences between products. Maturitas 53(3): 343-50	- Intervention. Oestrogen-only & combined HRT were not reported separately: *For analysis by duration and recency all HRT use is combined.*
Dinger, J; Bardenheuer, K; Heinemann, K (2016) Drospirenone plus estradiol and the risk of serious cardiovascular events in postmenopausal women. Climacteric : the journal of the International Menopause Society 19(4): 349-56	- Comparison. Not placebo or no HRT
Doren, M. (2009) Association between hormone replacement therapy and subsequent arterial and venous vascular events: A meta-analysis. European Heart Journal 30(7): 866-867	- Study design. Comment on another publication
El Khoudary, Samar R, Zhao, Qian, Venugopal, Vidya et al. (2019) Effects of Hormone Therapy on Heart Fat and Coronary Artery Calcification Progression: Secondary Analysis From the KEEPS Trial. Journal of the American Heart Association 8(15): e012763	- Outcomes. The reported outcomes do not match the review protocol
Ettinger, B, Friedman, G D, Bush, T et al. (1996) Reduced mortality associated with long-term postmenopausal estrogen therapy. Obstetrics and gynecology 87(1): 6-12	- Intervention. HRT use was not analysed according to duration or recency
Falkeborn, M, Persson, I, Terent, A et al. (1993) Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. Archives of internal medicine 153(10): 1201-9	- Comparison. Not placebo or no HRT: *Comparison was population risk of stroke*
Finucane, F F, Madans, J H, Bush, T L et al. (1993) Decreased risk of stroke among postmenopausal hormone users. Results from a national cohort. Archives of internal medicine 153(1): 73-9	- Intervention. Oestrogen-only & combined HRT were not reported separately
Fioretti, F, Tavani, A, Gallus, S et al. (2000) Menopause and risk of non-fatal acute myocardial infarction: an Italian case-control study and a review of the literature. Human reproduction (Oxford, England) 15(3): 599-603	- Study design. Observational study: data on HRT use not collected at time of prescription or before the outcome was known

Study	Reason for exclusion
Fung, M M; Barrett-Connor, E; Bettencourt, R R (1999) Hormone replacement therapy and stroke risk in older women. Journal of women's health 8(3): 359-64	- Intervention. Oestrogen-only & combined HRT were not reported separately
Furberg, Curt D, Vittinghoff, Eric, Davidson, Michael et al. (2002) Subgroup interactions in the Heart and Estrogen/Progestin Replacement Study: lessons learned. Circulation 105(8): 917-22	- Cohort already included: *HERS study*
Gabriel, Sanchez R, Carmona, L, Roque, M et al. (2005) Hormone replacement therapy for preventing cardiovascular disease in post-menopausal women. The Cochrane database of systematic reviews: cd002229	- Systematic review. The systematic review assessed the effects of HRT for the primary and secondary prevention of cardiovascular diseases, not HRT on menopausal symptoms and so the systematic review cannot be included as whole. The included studies list was checked for any relevant studies and where appropriate, these were included
Gartlehner, Gerald, Patel, Sheila V, Feltner, Cynthia et al. (2017) Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 318(22): 2234-2249	- Systematic review. The systematic review assessed the effects of HRT for the primary prevention of chronic conditions, not HRT on menopausal symptoms. The systematic review cannot be included as whole, however the included studies list was checked for any relevant studies and where appropriate, these were included
Gartlehner, Gerald, Patel, Sheila V, Viswanathan, Meera et al. (2017) Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: An Evidence Review for the U.S. Preventive Services Task Force.	- Systematic review. The systematic review assessed the effects of HRT for the primary prevention of chronic conditions, not HRT on menopausal symptoms. The systematic review cannot be included as whole, however the included studies list was checked for any relevant studies and where appropriate, these were included
Gast, Gerrie-Cor M, Pop, Victor J M, Samsioe, Goran N et al. (2011) Hormone therapy and coronary heart disease risk by vasomotor menopausal symptoms. Maturitas 70(4): 373-8	- Intervention. Oestrogen-only & combined HRT were not reported separately
Goldstajn, Marina Sprem, Mikus, Mislav, Ferrari, Filippo Alberto et al. (2022) Effects of transdermal versus oral hormone replacement therapy in postmenopause: a systematic review. Archives of gynecology and obstetrics	- Systematic review. The systematic review compared the effects of transdermal and oral administration route of oestrogens in HRT and did not include any meta-analysis. The systematic review cannot be included as whole, however the included studies list was checked for any relevant studies and where appropriate, these were included

Study	Reason for exclusion
Graff-Iversen, S, Hammar, N, Thelle, D S et al. (2004) Hormone therapy and mortality during a 14-year follow-up of 14 324 Norwegian women. Journal of internal medicine 256(5): 437-45	- Intervention. Oestrogen-only & combined HRT not reported separately
Greenspan, S.L.; Resnick, N.M.; Parker, R.A. (2005) The effect of hormone replacement on physical performance in community-dwelling elderly women. American Journal of Medicine 118(11): 1232-1239	- Intervention. Oestrogen-only & combined HRT not reported separately
Grodstein, F, Manson, J E, Colditz, G A et al. (2000) A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Annals of internal medicine 133(12): 933-41	- Outcomes. Relevant confounders not adjusted for: *Confounders only adjusted for results that do not differentiate between oestrogen-only or combined HRT*
Grodstein, F; Manson, J E; Stampfer, M J (2001) Postmenopausal hormone use and secondary prevention of coronary events in the nurses' health study. a prospective, observational study. Annals of internal medicine 135(1): 1-8	- Population. Does not match the review protocol: *Subgroup analysis of women with prior myocardial infarction*
Grodstein, F, Stampfer, M J, Falkeborn, M et al. (1999) Postmenopausal hormone therapy and risk of cardiovascular disease and hip fracture in a cohort of Swedish women. Epidemiology (Cambridge, Mass.) 10(5): 476-80	- Cohort already included: *Cohort included in Grodstein 2006 and Grodstein 2008*
Grodstein, F, Stampfer, M J, Manson, J E et al. (1996) Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. The New England journal of medicine 335(7): 453-61	- Cohort already included: *Cohort included in Grodstein 2006*
Gu, Haifeng, Zhao, Xiaohong, Zhao, Xiaoping et al. (2014) Risk of stroke in healthy postmenopausal women during and after hormone therapy: a meta-analysis. Menopause (New York, N.Y.) 21(11): 1204-10	- Systematic review. The systematic review included non-relevant studies and cannot be included as whole. The included studies list was checked for any relevant studies and where appropriate, these were included
Heckbert, S R, Weiss, N S, Koepsell, T D et al. (1997) Duration of estrogen replacement therapy in relation to the risk of incident myocardial infarction in postmenopausal women. Archives of internal medicine 157(12): 1330-6	- Intervention. Oestrogen-only & combined HRT were not reported separately
Hedblad, Bo, Merlo, Juan, Manjer, Jonas et al. (2002) Incidence of cardiovascular disease, cancer and death in postmenopausal women affirming use of hormone replacement therapy. Scandinavian journal of public health 30(1): 12-9	- Intervention. Oestrogen-only & combined HRT were not reported separately
Henderson, B E; Paganini-Hill, A; Ross, R K (1988) Estrogen replacement therapy and protection from acute myocardial infarction. American journal of obstetrics and gynecology 159(2): 312-7	- Intervention. Oestrogen-only & combined HRT not reported separately - Outcomes - relevant confounders not adjusted for: *Age adjusted only*
Hernan, Miguel A, Alonso, Alvaro, Logan, Roger et al. (2008) Observational studies analyzed like	- Cohort already included: *See Grodstein 2006, 2008*

Study	Reason for exclusion
randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology (Cambridge, Mass.) 19(6): 766-79	
Hernandez Avila, M; Walker, A M; Jick, H (1990) Use of replacement estrogens and the risk of myocardial infarction. Epidemiology (Cambridge, Mass.) 1(2): 128-33	- Outcomes. Relevant confounders not adjusted for
Hippisley-Cox, Julia, Pringle, Mike, Crown, Nicola et al. (2003) A case-control study on the effect of hormone replacement therapy on ischaemic heart disease. The British journal of general practice : the journal of the Royal College of General Practitioners 53(488): 191-6	- Comparison. Not placebo or no HRT
Hodis, Howard N, Mack, Wendy J, Azen, Stanley P et al. (2003) Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. The New England journal of medicine 349(6): 535-45	- Outcomes. Reported outcomes do not match the review protocols: *Study does not report primary outcomes*
Hodis, Howard N, Mack, Wendy J, Henderson, Victor W et al. (2016) Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. The New England journal of medicine 374(13): 1221-31	- Intervention. Oestrogen-only & combined HRT were not reported separately
Hodis, Howard N, Mack, Wendy J, Shoupe, Donna et al. (2015) Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause (New York, N.Y.) 22(4): 391-401	- Outcomes. Reported outcomes do not match the review protocols: *Baseline results only*
Honigberg, Michael C; Trinder, Mark; Natarajan, Pradeep (2022) Lipoprotein(a), Menopausal Hormone Therapy, and Risk of Coronary Heart Disease in Postmenopausal Individuals. JAMA cardiology 7(5): 565-568	- Study design. Comment on another publication
Huang, Alison J, Sawaya, George F, Vittinghoff, Eric et al. (2009) Hot flushes, coronary heart disease, and hormone therapy in postmenopausal women. Menopause (New York, N.Y.) 16(4): 639-43	- Cohort already included
Hunt, K; Vessey, M; McPherson, K (1990) Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. British journal of obstetrics and gynaecology 97(12): 1080-6	- Outcomes. Relevant confounders not adjusted for: *Comparison is with age standardised mortality rates*
Kaemmle, L M, Stadler, A, Janka, H et al. (2022) The impact of micronized progesterone on cardiovascular events - a systematic review. Climacteric : the journal of the International Menopause Society 25(4): 327-336	- Systematic review. The systematic review included non-relevant studies and cannot be included as whole. The included studies list was checked for any relevant studies and where appropriate, these were included

Study	Reason for exclusion
Karim, Roksana, Mack, Wendy J, Lobo, Roger A et al. (2005) Determinants of the effect of estrogen on the progression of subclinical atherosclerosis: Estrogen in the Prevention of Atherosclerosis Trial. Menopause (New York, N.Y.) 12(4): 366-73	- Outcomes. Reported outcomes do not match the review protocols: *Study does not report primary outcomes*
Karim, Roksana, Xu, Wenrui, Kono, Naoko et al. (2022) Effect of menopausal hormone therapy on arterial wall echomorphology: Results from the Early versus Late Intervention Trial with Estradiol (ELITE). Maturitas 162: 15-22	- Outcomes. Reported outcomes do not match the review protocols: *Study does not report any of the primary outcomes specified in the protocol*
Khan, MA, Hlatky, MA, Liu, MW et al. (2003) Effect of postmenopausal hormone therapy on coronary heart disease events after percutaneous transluminal coronary angioplasty. The American Journal of Cardiology 91(8): 989-991	- Cohort already included: *Reports results on the effect of HRT on CHD specifically after PTCA in the HERS trial.*
Kim, Ji-Eun, Chang, Jae-Hyuck, Jeong, Min-Ji et al. (2020) A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases. Scientific reports 10(1): 20631	- Systematic review. The systematic review included non-relevant studies and cannot be included as whole. The included studies list was checked for any relevant studies and where appropriate, these were included
Kim, Ji-Eun, Choi, Jaesung, Park, JooYong et al. (2021) Effects of menopausal hormone therapy on cardiovascular diseases and type 2 diabetes in middle-aged postmenopausal women: analysis of the Korea National Health Insurance Service Database. Menopause (New York, N.Y.) 28(11): 1225-1232	- Intervention. Oestrogen-only & combined HRT not reported separately: *Analysis by duration or recency of use is not reported by oestrogen-only / combined HRT*
Lakoski, Susan G, Liu, Yongmei, Brosnihan, K Bridget et al. (2008) Interleukin-10 concentration and coronary heart disease (CHD) event risk in the estrogen replacement and atherosclerosis (ERA) study. Atherosclerosis 197(1): 443-7	- Cohort already included: *ERA trial*
Lemaitre, Rozenn N, Heckbert, Susan R, Psaty, Bruce M et al. (2002) Hormone replacement therapy and associated risk of stroke in postmenopausal women. Archives of internal medicine 162(17): 1954-60	- Cohort already included: *See Lemaitre 2006*
Li, Cairu, Engstrom, Gunnar, Hedblad, Bo et al. (2006) Risk of stroke and hormone replacement therapy. A prospective cohort study. Maturitas 54(1): 11-8	- Intervention. HRT use not analysed according to duration or recency
Liu, Longjian, Klein, Liviu, Eaton, Charles et al. (2020) Menopausal Hormone Therapy and Risks of First Hospitalized Heart Failure and its Subtypes During the Intervention and Extended Postintervention Follow-up of the Women's Health Initiative Randomized Trials. Journal of cardiac failure 26(1): 2-12	- Outcomes. Reported outcomes do not match the review protocols
Lokkegaard, Ellen, Jovanovic, Zorana, Heitmann, Berit L et al. (2003) Increased risk of stroke in	- Cohort already included: *Cohort included in Lokkegaard 2017*

Study	Reason for exclusion
hypertensive women using hormone therapy: analyses based on the Danish Nurse Study. Archives of neurology 60(10): 1379-84	
Madika, Anne-Laure, MacDonald, Conor James, Fournier, Agnes et al. (2021) Menopausal hormone therapy and risk of incident hypertension: role of the route of estrogen administration and progestogens in the E3N cohort. Menopause (New York, N.Y.) 28(11): 1204-1208	- Conference abstract.
Magliano, Dianna J, Rogers, Sophie L, Abramson, Michael J et al. (2006) Hormone therapy and cardiovascular disease: a systematic review and meta-analysis. BJOG : an international journal of obstetrics and gynaecology 113(1): 5-14	- Study type. Comment on another publication
Manson, JoAnn E, Aragaki, Aaron K, Bassuk, Shari S et al. (2019) Menopausal Estrogen-Alone Therapy and Health Outcomes in Women With and Without Bilateral Oophorectomy: A Randomized Trial. Annals of internal medicine 171(6): 406-414	- Cohort already included: *Subgroup analysis of WHI trial by bilateral salpingo-oophorectomy*
Mares, Pierre, Chevallier, Thierry, Micheletti, Marie-Christine et al. (2008) Coronary heart disease and HRT in France: MISSION study prospective phase results. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 24(12): 696-700	- Intervention. Oestrogen-only & combined HRT not reported separately and HRT use not analysed according to duration or recency - Outcomes. Relevant confounders not adjusted for
Marjoribanks, Jane, Farquhar, Cindy, Roberts, Helen et al. (2017) Long-term hormone therapy for perimenopausal and postmenopausal women. The Cochrane database of systematic reviews 1: cd004143	- Systematic review. The systematic review included some studies that did not match the inclusion criteria for this review and cannot be included as whole. The included studies list was checked for any studies that did match the inclusion criteria and were individually included
Merz, C Noel Bairey, Olson, Marian B, McClure, Candace et al. (2010) A randomized controlled trial of low-dose hormone therapy on myocardial ischemia in postmenopausal women with no obstructive coronary artery disease: results from the National Institutes of Health/National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). American heart journal 159(6): 987e1-7	- Outcomes. Reported outcomes do not match the review protocols
Mikkola, Tomi S, Tuomikoski, Pauliina, Lyytinen, Heli et al. (2015) Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. Menopause (New York, N.Y.) 22(9): 976-83	- Comparison. Not placebo or no HRT: *Comparison is age standardised mortality rate*
Miller, Virginia M, Naftolin, Fredrick, Asthana, Sanjay et al. (2019) The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned?. Menopause (New York, N.Y.) 26(9): 1071-1084	- Cohort already included

Study	Reason for exclusion
Mishra, Shiva Raj, Waller, Michael, Chung, Hsin-Fang et al. (2021) Association of the length of oestrogen exposure with risk of incident stroke in postmenopausal women: Insights from a 20-year prospective study. International journal of cardiology 328: 206-214	- Intervention - reported interventions do not match the protocol: *Total oestrogen exposure*
Mohammed, Khaled, Abu Dabrh, Abd Moain, Benkhadra, Khalid et al. (2015) Oral vs Transdermal Estrogen Therapy and Vascular Events: A Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism 100(11): 4012-20	- Comparison. Not placebo or no HRT
Nelson, Heidi D, Walker, Miranda, Zakher, Bernadette et al. (2012) Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the U.S. Preventive Services Task Force recommendations. Annals of internal medicine 157(2): 104-13	- Systematic review. The systematic review assessed the effects of HRT for the primary prevention of chronic conditions, not HRT on menopausal symptoms. The systematic review cannot be included as whole, however the included studies list was checked for any relevant studies and where appropriate, these were included
Nevitt, M C, Felson, D T, Williams, E N et al. (2001) 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 and rheumatism 44(4): 811-8	- Outcomes. Reported outcomes do not match the review protocols
Newton, K.M., LaCroix, A.Z., McKnight, B. et al. (1997) Estrogen replacement therapy and prognosis after first myocardial infarction. American Journal of Epidemiology 145(3): 269-277	- Intervention. Oestrogen-only & combined HRT were not reported separately
Nie, Guangning, Yang, Xiaofei, Wang, Yangyang et al. (2022) The Effects of Menopause Hormone Therapy on Lipid Profile in Postmenopausal Women: A Systematic Review and Meta-Analysis. Frontiers in pharmacology 13: 850815	- Systematic review. The systematic review included some studies that did not match the inclusion criteria for this review and cannot be included as whole. The included studies list was checked for any studies that did match the inclusion criteria and were individually included
Nudy, Matthew; Chinchilli, Vernon M; Foy, Andrew J (2019) A systematic review and meta-regression analysis to examine the 'timing hypothesis' of hormone replacement therapy on mortality, coronary heart disease, and stroke. International journal of cardiology. Heart & vasculature 22: 123-131	- Systematic review. The systematic review included some studies that did not match the inclusion criteria for this review and cannot be included as whole. The included studies list was checked for any studies that did match the inclusion criteria and were individually included
Oliver-Williams, Clare, Glisic, Marija, Shahzad, Sara et al. (2019) The route of administration, timing, duration and dose of postmenopausal hormone therapy and cardiovascular outcomes in	- Systematic review. The systematic review included some studies that did not match the inclusion criteria for this review and cannot be included as whole. The included studies list was

Study	Reason for exclusion
women: a systematic review. Human reproduction update 25(2): 257-271	checked for any studies that did match the inclusion criteria and were individually included
Ott, Johannes; Egarter, Christian; Aguilera, Alex (2022) Dydrogesterone after 60 years: a glance at the safety profile. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 38(4): 279-287	- Study design. Not a systematic review, randomised controlled trial, or observational study
Ouyang, Pamela, Tardif, Jean-Claude, Herrington, David M et al. (2006) Randomized trial of hormone therapy in women after coronary bypass surgery. Evidence of differential effect of hormone therapy on angiographic progression of disease in saphenous vein grafts and native coronary arteries. Atherosclerosis 189(2): 375-86	- Intervention. Oestrogen-only & combined HRT not reported separately
Paganini-Hill, A; Ross, R K; Henderson, B E (1988) Postmenopausal oestrogen treatment and stroke: a prospective study. BMJ (Clinical research ed.) 297(6647): 519-22	- Intervention. HRT use not analysed according to duration or recency: *Compares ever verses never users*
Paoletti, Anna Maria, Cagnacci, Angelo, Di Carlo, Costantino et al. (2015) Clinical effect of hormonal replacement therapy with estradiol associated with noretisterone or drospirenone. A prospective randomized placebo controlled study. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 31(5): 384-7	- Intervention. HRT was not oestrogen-only, or combined oestrogen and progestogen
Peters, Sanne A E and Woodward, Mark (2021) Oestradiol and the risk of myocardial infarction in women: a cohort study of UK Biobank participants. International journal of epidemiology 50(4): 1241-1249	- Comparison. Not placebo or no HRT
Plu-Bureau, G. and Mounier-Vehier, C. (2021) Menopausal hormone therapy an cardiovascular risk. Postmenopausal women management: CNGOF and GEMVi clinical practice guidelines. Gynecologie Obstetrique Fertilite et Senologie 49(5): 438-447	- Comparison. Not placebo or no HRT
Poornima, Indu G, Mackey, Rachel H, Allison, Matthew A et al. (2017) Coronary Artery Calcification (CAC) and Post-Trial Cardiovascular Events and Mortality Within the Women's Health Initiative (WHI) Estrogen-Alone Trial. Journal of the American Heart Association 6(11)	- Cohort already included: *Subgroup analysis of WHI trial*
Pradhan, Aruna D, Manson, JoAnn E, Rossouw, Jacques E et al. (2002) Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. JAMA 288(8): 980-7	- Comparison. Not placebo or no HRT: *Compares low, intermediate and high inflammatory marker risk groups*

Study	Reason for exclusion
Prentice, Ross L, Aragaki, Aaron K, Chlebowski, Rowan T et al. (2021) Randomized Trial Evaluation of the Benefits and Risks of Menopausal Hormone Therapy Among Women 50-59 Years of Age. American journal of epidemiology 190(3): 365-375	- Cohort already included: *WHI age 50-59 subgroup*
Prentice, Ross L, Langer, Robert D, Stefanick, Marcia L et al. (2006) Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. American journal of epidemiology 163(7): 589-99	- Outcomes. Relevant confounders not adjusted for
Prentice, Ross L, Manson, Joann E, Langer, Robert D et al. (2009) Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. American journal of epidemiology 170(1): 12-23	- Cohort already included: *WHI data presented in a way which is not useable, and which has been extracted from other studies.*
Psaty, B M, Heckbert, S R, Atkins, D et al. (1994) The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. Archives of internal medicine 154(12): 1333-9	- Cohort already included: *Overlap with Lemaitre 2006*
Psaty, B M, Smith, N L, Lemaitre, R N et al. (2001) Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. JAMA 285(7): 906-13	- Intervention. Oestrogen-only & combined HRT not reported separately
Qureshi, Adnan I, Malik, Ahmed A, Saeed, Omar et al. (2016) Hormone replacement therapy and the risk of subarachnoid hemorrhage in postmenopausal women. Journal of neurosurgery 124(1): 45-50	- Cohort already included: *WHI observational study*
Renoux, Christel, Dell'aniello, Sophie, Garbe, Edeltraut et al. (2008) Hormone replacement therapy use and the risk of stroke. Maturitas 61(4): 305-9	- Cohort already included: *See Renoux 2010*
Salaminia, S., Mohsenzadeh, Y., Motedayen, M. et al. (2019) Hormone replacement therapy and postmenopausal cardiovascular events: A meta-analysis. Iranian Red Crescent Medical Journal 21(2): e82298	- Systematic review. The systematic review included some studies that did not match the inclusion criteria for this review and cannot be included as whole. The included studies list was checked for any studies that did match the inclusion criteria and were individually included
Salpeter, Shelley R, Walsh, Judith M E, Greyber, Elizabeth et al. (2006) Brief report: Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. Journal of general internal medicine 21(4): 363-6	- Systematic review. The systematic review included some studies that did not match the inclusion criteria for this review and cannot be included as whole. The included studies list was checked for any studies that did match the inclusion criteria and were individually included
Sanghvi, Mihir M, Aung, Nay, Cooper, Jackie A et al. (2018) The impact of menopausal hormone therapy (MHT) on cardiac structure and function:	- Outcomes. Reported outcomes do not match the review protocols

Study	Reason for exclusion
Insights from the UK Biobank imaging enhancement study. PloS one 13(3): e0194015	
Sare, Gillian M; Gray, Laura J; Bath, Philip M W (2008) Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. European heart journal 29(16): 2031-41	- Systematic review. The systematic review included some studies that did not match the inclusion criteria for this review and cannot be included as whole. The included studies list was checked for any studies that did match the inclusion criteria and were individually included
Schierbeck, LL, Rejnmark, L, Tofteng, CL et al. (2011) Hormone Replacement Treatment in Early Postmenopausal Women Reduces Cardiovascular Events - A Randomized Controlled Study. Circulation 124(21meetingabstracts): a11380	- Conference abstract.
Schierbeck, Louise Lind, Rejnmark, Lars, Tofteng, Charlotte Landbo et al. (2012) Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ (Clinical research ed.) 345: e6409	- Intervention. Oestrogen-only & combined HRT not reported separately
Shufelt, Chrisandra L, Johnson, B Delia, Berga, Sarah L et al. (2011) Timing of hormone therapy, type of menopause, and coronary disease in women: data from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. Menopause (New York, N.Y.) 18(9): 943-50	- Intervention. Oestrogen-only & combined HRT not reported separately
Shufelt, Chrisandra L, Merz, C Noel Bairey, Prentice, Ross L et al. (2014) Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study. Menopause (New York, N.Y.) 21(3): 260-6	- Comparison. Not placebo or no HRT
Sidney, S; Petitti, D B; Quesenberry, C P Jr (1997) Myocardial infarction and the use of estrogen and estrogen-progestogen in postmenopausal women. Annals of internal medicine 127(7): 501-8	- Study design. Observational study: data on HRT use not collected at time of prescription or before the outcome was known: *Cases with myocardial infarction were interviewed about their HRT use*
Simon, Joel A, Lin, Feng, Vittinghoff, Eric et al. (2006) The relation of postmenopausal hormone therapy to serum uric acid and the risk of coronary heart disease events: the Heart and Estrogen-Progestin Replacement Study (HERS). Annals of epidemiology 16(2): 138-45	- Comparison. Not placebo or no HRT: *Serum uric acid level as a risk factor for CHD*
Simony, Sofie Bay, Mortensen, Martin Bodtker, Langsted, Anne et al. (2022) Sex differences of lipoprotein(a) levels and associated risk of morbidity and mortality by age: The Copenhagen General Population Study. Atherosclerosis 355: 76-82	- Study design. Observational study: data on HRT use not collected at time of prescription or before the outcome was known
Sourander, L, Rajala, T, Raiha, I et al. (1998) Cardiovascular and cancer morbidity and mortality and sudden cardiac death in	- Intervention. Oestrogen-only & combined HRT not reported separately

Study	Reason for exclusion
postmenopausal women on oestrogen replacement therapy (ERT). Lancet (London, England) 352(9145): 1965-9	
Speroff, L (2001) Postmenopausal hormone therapy and primary prevention of cardiovascular disease -- Nurses' health study 20-year follow-up. Maturitas 38(3): 221-4	- Cohort already included
Stram, Daniel O, Liu, Yuan, Henderson, Katherine D et al. (2011) Age-specific effects of hormone therapy use on overall mortality and ischemic heart disease mortality among women in the California Teachers Study. Menopause (New York, N.Y.) 18(3): 253-61	- Intervention. Oestrogen-only & combined HRT not reported separately
Su, Irene H, Chen, Yu-Chun, Hwang, Wei-Ting et al. (2012) Risks and benefits of menopausal hormone therapy in postmenopausal Chinese women. Menopause (New York, N.Y.) 19(8): 931-41	- Intervention. HRT use not analysed according to duration or recency: *HRT duration ranged from 2 months to 10 years but all were analysed together*
Swica, Yael, Warren, Michelle P, Manson, JoAnn E et al. (2018) Effects of oral conjugated equine estrogens with or without medroxyprogesterone acetate on incident hypertension in the Women's Health Initiative hormone therapy trials. Menopause (New York, N.Y.) 25(7): 753-761	- Outcomes. Reported outcomes do not match the review protocols: *Study does not report any primary outcomes*
Toh, Sengwee, Hernandez-Diaz, Sonia, Logan, Roger et al. (2010) Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. Annals of internal medicine 152(4): 211-7	- Cohort already included: *Study uses WHI data to estimate the effect of oestrogen-plus-progestin hormone therapy on CHD risk.*
Tuomikoski, Pauliina, Salomaa, Veikko, Havulinna, Aki et al. (2016) Decreased mortality risk due to first acute coronary syndrome in women with postmenopausal hormone therapy use. Maturitas 94: 106-109	- Intervention. Oestrogen-only & combined HRT not reported separately
Varas-Lorenzo, C., Garcia-Rodriguez, L.A., Perez-Gutthann, S. et al. (2000) Hormone replacement therapy and incidence of acute myocardial infarction: A population-based nested case-control study. Circulation 101(22): 2572-2578	- Cohort already included: *Overlap with Kim 2006*
Venetkoski, Minttu, Savolainen-Peltonen, Hanna, Rahkola-Soisalo, Paivi et al. (2018) Increased cardiac and stroke death risk in the first year after discontinuation of postmenopausal hormone therapy. Menopause (New York, N.Y.) 25(4): 375-379	- Outcomes. Relevant confounders not adjusted for: *Comparison with age standardised mortality rate*
Vickers, Madge R, Martin, Jeannett, Meade, Tom W et al. (2007) The Women's international study of long-duration oestrogen after menopause (WISDOM): a randomised controlled trial. BMC women's health 7: 2	- Cohort already included

Study	Reason for exclusion
Weiner, Mark G, Barnhart, Kurt, Xie, Dawei et al. (2008) Hormone therapy and coronary heart disease in young women. Menopause (New York, N.Y.) 15(1): 86-93	- Intervention. HRT use not analysed according to duration or recency: *Ever versus never users*
Wharton, Whitney, Dowling, Maritza, Khosropour, Christine M et al. (2009) Cognitive benefits of hormone therapy: cardiovascular factors and healthy-user bias. Maturitas 64(3): 182-7	- Study design. Observational study: data on HRT use not collected at time of prescription or before the outcome was known
Wild, Robert A, Hovey, Kathleen M, Andrews, Christopher et al. (2021) Cardiovascular disease (CVD) risk scores, age, or years since menopause to predict cardiovascular disease in the Women's Health Initiative. Menopause (New York, N.Y.) 28(6): 610-618	- Comparison. Not placebo or no HRT
Wilson, P W; Garrison, R J; Castelli, W P (1985) Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study. The New England journal of medicine 313(17): 1038-43	- Intervention. Oestrogen-only & combined HRT not reported separately
Windler, Eberhard, Zyriax, Birgit-Christiane, Eidenmuller, Britta et al. (2007) Hormone replacement therapy and risk for coronary heart disease. Data from the CORA-study--a case-control study on women with incident coronary heart disease. Maturitas 57(3): 239-46	- Intervention. Oestrogen-only & combined HRT not reported separately
Wolf, P H, Madans, J H, Finucane, F F et al. (1991) Reduction of cardiovascular disease-related mortality among postmenopausal women who use hormones: evidence from a national cohort. American journal of obstetrics and gynecology 164(2): 489-94	- Intervention. Oestrogen-only & combined HRT not reported separately
Wong, Jorge A, Rexrode, Kathryn M, Sandhu, Roopinder K et al. (2017) Menopausal age, postmenopausal hormone therapy and incident atrial fibrillation. Heart (British Cardiac Society) 103(24): 1954-1961	- Outcomes. Reported outcomes do not match the review protocols
Xu, Zhiwei, Chung, Hsin-Fang, Dobson, Annette J et al. (2022) Menopause, hysterectomy, menopausal hormone therapy and cause-specific mortality: cohort study of UK Biobank participants. Human reproduction (Oxford, England) 37(9): 2175-2185	- Intervention. Oestrogen-only & combined HRT not reported separately
Yang, Dicheng, Li, Jing, Yuan, Zhongxiang et al. (2013) Effect of hormone replacement therapy on cardiovascular outcomes: a meta-analysis of randomized controlled trials. PloS one 8(5): e62329	- Systematic review. The systematic review included some studies that did not match the inclusion criteria for this review and cannot be included as whole. The included studies list was checked for any studies that did match the inclusion criteria and were individually included
Yoshida, Yilin, Chen, Zhipeng, Baudier, Robin L et al. (2022) Menopausal hormone therapy and risk of cardiovascular events in women with prediabetes or type 2 diabetes: A pooled analysis	- Intervention. Oestrogen-only & combined HRT not reported separately

Study	Reason for exclusion
of 2917 postmenopausal women. Atherosclerosis 344: 13-19	
Yoshikata, Remi, Myint, Khin Zay Yar, Ohta, Hiroaki et al. (2021) Effects of an equol-containing supplement on advanced glycation end products, visceral fat and climacteric symptoms in postmenopausal women: A randomized controlled trial. PloS one 16(9): e0257332	- Intervention. Oestrogen-only & combined HRT not reported separately
Zheng, Y., Zhang, H., Lu, W. et al. (2019) Estrogen replacement therapy is not a recommended therapy for postmenopausal women with coronary heart disease: A meta-analysis. Clinical and Experimental Obstetrics and Gynecology 46(2): 219-226	- Systematic review. The systematic review included non-relevant studies and cannot be included as whole. The included studies list was checked for any relevant studies and where appropriate, these were included
Zhong, Charlie, Voutsinas, Jenna, Willey, Joshua Z et al. (2020) Physical Activity, Hormone Therapy Use, and Stroke Risk among Women in the California Teachers Study Cohort. Neuroepidemiology 54(4): 320-325	- Comparison. Not placebo or no HRT

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

Further to the 3 research recommendations below, research recommendation 2 of the NICE guideline (on types of progestogens related to breast cancer, endometrial cancer and cardiovascular disease) is also relevant to this evidence review. The details can be found in appendix K of evidence review D.

K.1.1 Research recommendation

What is the impact of HRT on health outcomes for trans men and non-binary people registered female at birth (who are not taking cross-sex hormones as gender-affirming hormone therapy at the time of taking HRT or in the follow-up period) in relation to:

- Cardiovascular disease
- Stroke
- Breast, endometrial and ovarian cancer
- Dementia
- All-cause mortality.

Why this is important

The relative risks compared to benefits of HRT for trans men and non-binary people are poorly understood. Knowing the potential risks and benefits associated with hormone therapy allows individuals to make informed decisions about their healthcare. There is paucity of evidence for HRT in this group and it is important to have research that opens up the narrative of individual variations, side effects and risks.

Rationale for research recommendation

Table 31: Research recommendation rationale

Importance to 'patients' or the population	The relative risks compared to benefits of HRT for trans men and non-binary people are poorly understood, even though this group of patients is increasing.
Relevance to NICE guidance	There is limited evidence to guide the clinical care of trans-men and non-binary people in taking HRT. In particular, the relative risks vs benefit of HRT. This information is essential to inform future updates of key recommendations of this guideline.
Relevance to the NHS	The outcome would affect whether and for how long HRT is recommended for trans-men and non-binary people. If HRT was protective against long-term disease such as osteoporosis or CVD, this could reduce the amount of treatment needed for osteoporosis or cardiovascular disease. HRT for trans men and non-binary people is vital for informed decision-making, safety monitoring, evidence-based practices, improving overall health outcomes, addressing knowledge gaps, influencing policy and advocacy, considering mental health implications, and reducing health disparities.

National priorities	High– Menopause including HRT use is part of Department of Health & Social Care's Women's Health Strategy for England.
Current evidence base	Minimal long-term data
Equality considerations	Subgroups of people with or without gender affirming surgery (i.e. those without breasts, uterus, or ovaries)

HRT: Hormone replacement therapy

Modified PICO table

Table 32: Research recommendation modified PICO table

Population	Trans-men and non-binary people who were assigned female at birth and who are not currently taking cross-sex hormones as gender-affirming therapy at the time of taking HRT or in the follow-up period.

Intervention	• HRT*
	  ○ Oestrogen-only
	  ○ Combined oestrogen and progestogen
	  - Sequential combined
	  - Continuous combined
	  - Any combined
	* Regulated micronised progesterone are included but compounded micronised progesterone are excluded.

Comparator	Placebo treatment No HRT
Outcome	• Death from any cause • Cardiovascular disease • Incidence of breast cancer • Incidence of endometrial cancer • Incidence of ovarian cancer • Dementia
Study design	Observational study designs where data on HRT use are collected before the outcome of interest is known such as prospective cohort studies, nested case-control studies within prospective cohorts, and record linkage studies.
Timeframe	Long term
Additional information	Research in the perimenopause is particularly welcomed

HRT: Hormone replacement therapy

K.1.2 Research recommendation

What is the impact of HRT on health outcomes for people from minority ethnic family backgrounds in relation to:

- Cardiovascular disease
- Stroke
- Breast, endometrial and ovarian cancer
- Dementia
- All-cause mortality

Why this is important

The relative risks compared to benefits of HRT for people from minority ethnic family backgrounds are poorly understood. It is known that black women, particularly between the ages of 50-60 years, have in increased risk of stroke, and therefore may have potentially greater HRT risks. Evidence has also shown that that while HRT in white women reduced the risks of cardiovascular disease, this effect was not observed for black women. Knowing the potential risks and benefits associated with hormone therapy allows individuals to make informed decisions about their healthcare. There is paucity of evidence for HRT in this group and it is important to have research that opens up the narrative of individual variations, side effects and risks.

Rationale for research recommendation

Table 33: Research recommendation rationale

Importance to 'patients' or the population	The relative risks compared to benefits of HRT for people from minority ethnic family backgrounds are poorly understood and there are concerns that minority ethnic women may be at greater risk of some adverse effects of HRT such as stroke and CVD.
Relevance to NICE guidance	There is limited evidence to guide the clinical care of people from minority ethnic family backgrounds in taking HRT and managing menopause. In particular, the relative risks vs benefit of HRT. This information is essential to inform future updates of key recommendations of this guideline.
Relevance to the NHS	The outcome would affect whether and for how long HRT is recommended for people from minority ethnic family backgrounds. HRT usage for people from minority ethnic family backgrounds is vital for informed decision making, safety monitoring, evidence bases practices, improving overall health outcomes, addressing knowledge gaps, influencing policy and advocacy, considering mental health implications, and reducing health disparities.
National priorities	High– Menopause including HRT use is part of Department of Health & Social Care's Women's Health Strategy for England.
Current evidence base	Minimal short and long-term data
Equality considerations	Further research would address equality considerations particularly in the following groups, people: • with disabilities • from diverse races and ethnicities • from diverse socio-economic backgrounds

HRT: Hormone replacement therapy

Modified PICO table

Table 34: Research recommendation modified PICO table

Population	People from minority ethnic family backgrounds

Intervention	HRT* Oestrogen-only Combined oestrogen and progestogen Sequential combined Continuous combined Any combined * Regulated micronised progesterone are included but compounded micronised progesterone are excluded.
Comparator	Placebo treatment No HRT
Outcome	• Death from any cause • Cardiovascular disease • Incidence of breast cancer • Incidence of endometrial cancer • Incidence of ovarian cancer • Dementia
Study design	Observational study designs where data on HRT use are collected before the outcome of interest is known such as prospective cohort studies, nested case-control studies within prospective cohorts, randomised controlled trials and record linkage studies.
Timeframe	Short and long term
Additional information	Research in the perimenopause is particularly welcomed

K.1.3 Research recommendation

Does the person's age at menopause or the time between the person's menopause and their first use of HRT affect the long-term risk of coronary heart disease in people who take or have taken combined HRT? Why this is important

It is uncertain whether the timing of initiation of HRT (with respect to timing of menopause) affects the risk of CHD. Current evidence is conflicting about whether starting HRT within 10 years of menopause decreases future CHD or not. People considering or taking HRT need to be informed about whether timing of HRT use affects future CHD risk.

Rationale for research recommendation

Table 35: Research recommendation rationale

Importance to 'patients' or the population	It is uncertain whether any effect of HRT on future CHD depend on when HRT is started and stopped (timing). Women may wish to know whether timing of HRT use affects future CHD risk.
Relevance to NICE guidance	MHT is the most effective treatment for vasomotor symptoms. However, it is uncertain whether MHT also affects later CHD risk and how the timing of when HRT is started and stopped (with regard to timing of menopause)

	may affect this. This information is essential to inform future updates of key recommendations of this guideline.
Relevance to the NHS	The outcome would affect when and whether women choose to start and stop HRT .
National priorities	High– Menopause including HRT use is part of Department of Health & Social Care's Women's Health Strategy for England.
Current evidence base	Minimal short and long-term data
Equality considerations	The outcome of this research could impact on people who have menopause at a younger age.

Modified PICO table

Population	Women, non-binary, and trans people with menopause (including perimenopause and post-menopause). More research is particularly needed in people from ethnic minority backgrounds.

Intervention	• Oestrogen-only HRT
	• Combined oestrogen and progestogen HRT
	  ○ Sequential combined
	  ○ Continuous combined
	  ○ Any combined

Comparator	• Placebo treatment • No HRT
Outcome	• Coronary heart disease

Analysis of subgroups	• Evidence stratified in two layers first by:
	  ○ Current and past use
	  ○ Duration of use
	• then by:
	  - Age at first use of HRT
	  - Time since menopause at first use of HRT
	  - Equality groups (see Equality Impact Assessment form)

Study design	Observational study designs where data on HRT use are collected before the outcome of interest is known such as prospective cohort studies, nested case-control studies within prospective cohorts, randomised controlled trials and record linkage studies.
Timeframe	Short and long-term
Additional information	Research in the perimenopause is particularly welcomed

Appendix L Absolute risk tables and calculations

Absolute risk tables and calculations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on developing cardiovascular disease?

Absolute risks were calculated according to age group. For certain subgroups (age at first use; time since menopause at first use; constituent; ethnicity) it was not possible to calculate the absolute risks due to lack of information on their background risks.

Note: Some of the cells in the tables show a non-significant (NS) absolute number of cases highlighting that there is no important difference between HRT users and non-HRT users in terms of the outcome in question. Where NS is not written beside the absolute number of cases, this means that there is a statistically significant difference between the HRT users and non-HRT users. In some cases, the absolute number of cases are the same but are still regarded as statistically significant, this is due to the cases being presented as rounded to the nearly whole number, per 1000 cases.

Table 36: Number of coronary heart disease cases per 1000 people over a 5-year period with no use or current use of combined HRT in people who, if they used it, started HRT at 50, and used it for 5 years (randomised controlled trials)

HRT use	Number of cases
Non-HRT users	9
HRT users	10 (from 9 to 11) NS

NS means that the difference between the figure for HRT users and the corresponding figure for non-HRT users is non-significant.
All people included in the figures are aged 50 years or over.
Figures shown are number of cases per 1000 people.

Table 37: Number of coronary heart disease cases per 1000 people over a 5-year period with no use or current use of oestrogen-only HRT in people who, if they used it, started HRT at 50, and used it for 5 years (randomised controlled trials).

HRT use	Number of cases
Non-HRT users	9
HRT users	9 (from 7 to 11) NS

NS means that the difference between the figure for HRT users and the corresponding figure for non-HRT users is non-significant.
All people included in the figures are aged 50 years or over.
Figures shown are number of cases per 1000 people.

Table 38: Number of stroke cases per 1000 people over a 5-year period with no use or current use of combined or oestrogen-only HRT in people who, if they used it, started HRT at 50, with an unknown duration of use (observational studies and randomised controlled trials)

HRT use	Number of cases
Non-HRT users	3
Combined (oral) HRT users (RCT)	3 (from 3 to 4)
Combined (transdermal) HRT users (observational)	3 (from 2 to 4) NS

HRT use	Number of cases
Non-HRT users	3
Oestrogen-only (oral) HRT users (RCT)	4 (from 3 to 5)
Oestrogen-only (transdermal) HRT users (observational)	3 (from 2 to 3) NS

NS means that the difference between the figure for HRT users and the corresponding figure for non-HRT users is non-significant.
All people included in the figures are aged 50 years or over.
Figures shown are number of cases per 1000 people.

Calculations

Absolute risks for HRT users were calculated by applying the relevant risk ratios to the risk of stroke or coronary heart disease (CHD) in never users.

The rate of stroke or CHD incidence in never users of HRT was calculated by solving the following formula:

Incidence among all women in a given age range = [proportion of women who are current users × (RRcurrent × β)] + [proportion of never users × β]

Stroke

Where:

β = risk of stroke in never users

RRcurrent = The average stroke relative risk for HRT users versus never users [RR (current vs never users)] in the general population and is taken from the risks calculated in this review, assuming ¼ of HRT users use oestrogen-only and ¾ use combined HRT. This gives an average RR of 1.26.

CHD

Where:

β = risk of CHD in never users

RRcurrent = The average CHD relative risk for HRT users versus never users [RR (current vs never users)] in the general population and is taken from the risks calculated in this review, assuming ¼ of HRT users use oestrogen-only and ¾ use combined HRT. This gives an average RR of 1.03.

The proportion of women using HRT in each age band is estimated using NHS HRT data on Hormone Replacement Therapy in 2017 and dividing by the ONS census population figures for women in that age band for 2017.

The stroke and CHD 5-year incidence are calculated using first-time admission counts for women who belonged to the specified age group at their first-time admission in the year 2017. First-time admission is defined as first record of admission with any of the relevant ICD-10 codes for stroke or CHD in the Hospital Episode Statistics (HES) database, between April 2000 and time of admission.

Note: This means that patients with a relevant admission before 2000, or who were previously first admitted in a different country, will be erroneously classified as first-time admissions.

See Supplement 19 for calculations.

Note: Although there was both observational and RCT evidence available for stroke outcomes for oral route of administration, the risks applied to calculate the absolute numbers are taken from the RCT evidence as there is no risk of residual confounding. For the transdermal route of administration, the risks applied to calculate the absolute numbers are taken from the observational data as there was limited RCT data available.

Absolute risks using observational study data

Table 39: Number of coronary heart disease cases with no use and current use of combined HRT in people who, if they used it, started HRT at 50 with unknown duration of use

	Number of cases
Non-HRT users	9
HRT users	7 (from 5 to 8)

Table 40: Number of coronary heart disease cases with no use and current use of oestrogen-only HRT in people who, if they used it, started HRT at 50 with unknown duration of use

	Number of cases
Non-HRT users	9
HRT users	6 (from 5 to 7)