HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

Reassessment of menopausal hormone therapy

Assessment Report

28 May 2014

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01 BACKGROUND AND PURPOSE OF THE REASSESSMENT

The Transparency Committee (TC) of HAS assesses medicinal products that have obtained Marketing Authorisation (MA) when the company marketing them wishes them to be included on the list of refundable medicines (articles L.162-17 of the French Social Security Code and L.5123-2 of the French Public Health Code) or on request.

The TC is a scientific body composed of medical practitioners, pharmacists and specialists in methodology and epidemiology.
Its objectives are:

- to provide an opinion to ministers responsible for health and social security on the justification for reimbursement of medicinal products by social security and/or for their use in hospitals, with particular regard to their actual benefit (AB) and to the improvement in actual benefit (IAB) they are likely to offer compared with treatments that are already available;
- to contribute to the proper use of medicinal products by publishing relevant and independent scientific information on the products.

These objectives are defined in the French Social Security Code, in particular in articles R.163-2 to R.163-21, L.161-37, L.161-39 and L.161-41.
According to articles L. 162-17, L. 161-37, L.161-39, L. 161-41, L. 161-44, R. 163-2 to R. 163-21, R. 161-71, R. 161-76 and R. 161-85 of the French Social Security Code and articles L. 5123-2 and L. 5123-3 of the French Public Health Code, the opinions of the TC specify the actual benefit and improvement in actual benefit provided by the medicinal products.
This assessment is performed on the basis of a critical analysis of scientific data obtained through evidence based medicine and the opinion of experts, in accordance with the indications and dosages in the Marketing Authorisation.

01.1 History and background to the reassessment

Pursuant to article R.163-21 of the French Social Security Code, the Transparency Committee would like to reassess the actual benefit of all proprietary medicinal products indicated for hormone replacement therapy in menopause (oestrogen deficiency symptoms and prevention of post-menopausal osteoporosis), and in particular their long-term safety based on data from literature published since the last information point from the AFSSAPS [French Healthcare Product Safety Agency] (February 2008).

01.2 Summary of previous assessments

PROPRIETARY MEDICINAL PRODUCT Active ingredient/Route of administration	MOST RECENT OPINION	
	DATE	Actual Benefit
Oestradiol Transdermal administration		
CLIMARA 50 µg/24 h	11 May 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
DELIDOSE 0.5 mg 1 mg	18 November 2009 Renewal of inclusion	Substantial
DERMESTRIL 25 µg/24 h 50 µg/24 h 100 µg/24 h	16 December 2009 Renewal of inclusion	Substantial
DERMESTRIL SEPTEM 25 µg/24 h 50 µg/24 h 75 µg/24 h	16 December 2009 Renewal of inclusion	Substantial
ESTRADERM 25 µg/24 h	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
ESTRAPATCH 40 µg/24 h 60 µg/24 h 80 µg/24 h	28 March 2007 Renewal of inclusion	Substantial
ESTREVA 0.1%, gel	28 March 2007 Renewal of inclusion	Substantial
FEMSEPT 50 µg/24 h 75 µg/24 h 100 µg/24 h	6 April 2011 Renewal of inclusion	Unchanged [substantial] pending the reassessment of proprietary medicinal products indicated for hormone replacement therapy for oestrogen deficiency symptoms in post-menopausal women.
OESTRODOSE	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
OESTROGEL	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).

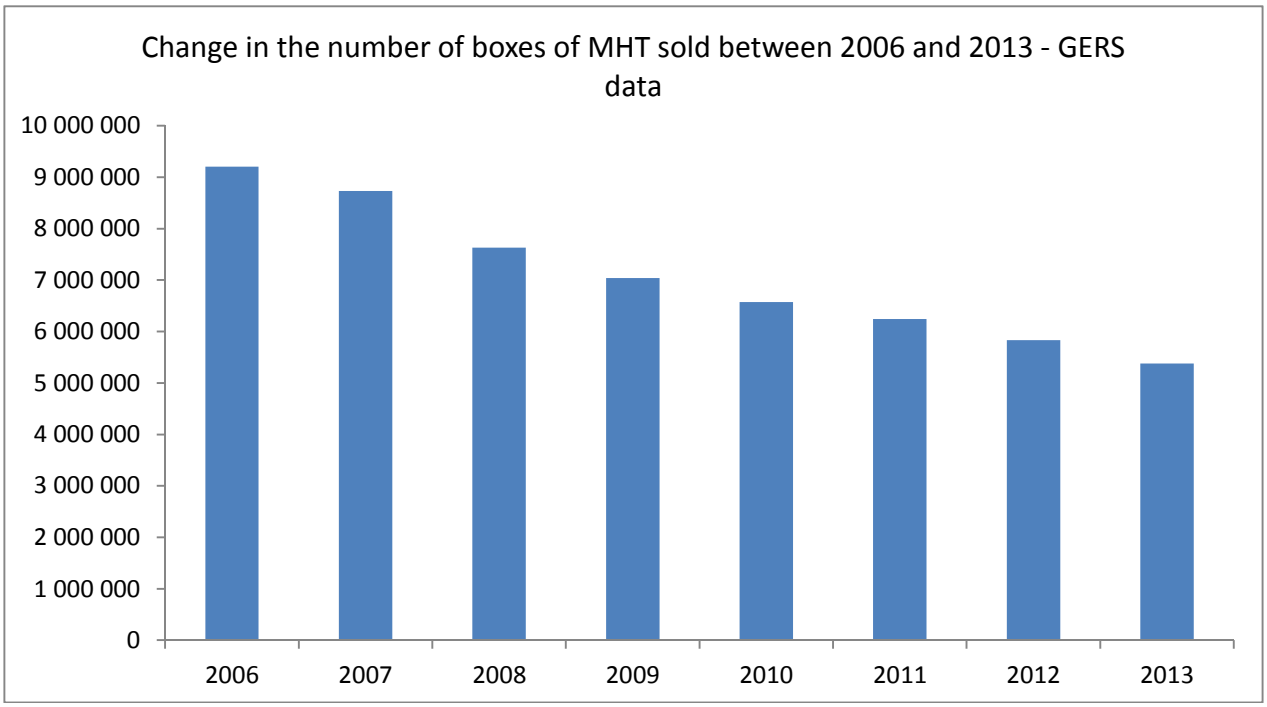
OESCLIM 25 µg/24 h 37.5 µg/24 h 50 µg/24 h	9 March 2011 Renewal of inclusion	Unchanged [substantial] pending the reassessment of proprietary medicinal products indicated for hormone replacement therapy for oestrogen deficiency symptoms in post-menopausal women.
THAIS 25 µg/24 h 50 µg/24 h 100 µg/24 h	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
THAISSEPT 25 µg/24 h 50 µg/24 h 75 µg/24 h	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
VIVELLEDOT 25 µg/24 h 37.5 µg/24 h 50 µg/24 h 75 µg/24 h 100 µg/24 h	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
Oral Oestrogens		
Oestradiol		
ESTREVA tablet 1.5 mg	28 March 2007 Renewal of inclusion	Substantial
OROMONE 1 mg 2 mg	8 July 2009 Renewal of inclusion	Substantial
PROVAMES 1 mg 2 mg	11 May 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
Oestriol PHYSIOGYNE 1 mg	17 March 2007 Renewal of inclusion	Moderate
Tibolone LIVIAL 2.5 mg	28 March 2001 Inclusion	Substantial
Combined HRT **Transdermal administration** **Oestradiol/levonorgestrel**		
FEMSEPTCOMBI 50 µg/10 µg	6 April 2011 Renewal of inclusion	Unchanged [substantial] pending the reassessment of proprietary medicinal products indicated for hormone replacement therapy for oestrogen deficiency symptoms in post-menopausal women.
FEMSEPTEVO 50 µg/7 µg	6 April 2011 Renewal of inclusion	Unchanged [substantial] pending the reassessment of proprietary medicinal products indicated for hormone

		replacement therapy for oestrogen deficiency symptoms in post-menopausal women.
Combined HRT Oral		
Oestradiol / norethisterone acetate		
ACTIVELLE 1 mg/0.5 mg	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
KLIOGEST 2 mg/1 mg	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
NOVOFEMME 1 mg/1 mg; 1 mg	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
TRISEQUENS 2 mg; 1 mg/2 mg; 1 mg	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
Oestradiol/gestodene AVADENE 1 mg/0.025 mg	18 April 2007 Renewal of inclusion	Substantial
Oestradiol/dydrogesterone CLIMASTON 1 mg/5 mg 1 mg/10 mg 2 mg/10 mg	9 March 2011 Renewal of inclusion	Unchanged [substantial] pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
Oestradiol valerate / cyproterone acetate CLIMENE 2 mg; 2 mg/1 mg	9 March 2011 Renewal of inclusion	Unchanged [substantial] in the MA indications, pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause (symptoms of oestrogen deficiency and prevention of post-menopausal osteoporosis).
Oestradiol valerate / dienogest CLIMODIENE 2 mg/ 2mg	18 July 2007 Renewal of inclusion	Substantial

Oestradiol valerate / medroxyprogesterone acetate DIVINA 2 mg/10 mg; 2 mg DUOVA 1 mg/2.5 mg 1 mg/5 mg 2 mg/5 mg	10 June 2009 Renewal of inclusion 10 June 2009 Renewal of inclusion	Substantial Substantial
Oestradiol / nomegestrol acetate NAEMIS 1.5 mg; 1.5 mg/3.75 mg	12 September 2007 Renewal of inclusion	Substantial
Progestogens		
Medrogestone COLPRONE	21 January 2009 Renewal of inclusion	Substantial
Dydrogesterone DUPHASTON	21 January 2009 Renewal of inclusion	Substantial
Nomegestrol acetate LUTENYL	21 January 2009 Renewal of inclusion	Substantial
Chlormadinone acetate LUTERAN	27 January 2010 Renewal of inclusion	Substantial
Progesterone MENAELLE UTROGESTAN	18 March 2009 Renewal of inclusion 28 April 2010 Renewal of inclusion	Substantial Substantial
Promegestone SURGESTONE	6 April 2011 Renewal of inclusion	Substantial in the MA indications, except for the indication "menopause (in addition to an oestrogen treatment)" for which the Committee is undecided pending a reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause. .

02 SALES DATA

According to the GERS [Group for the development and production of statistics] data regarding the proprietary medicinal products indicated for menopausal hormone therapy; the annual number of boxes sold has regularly reduced between 2006 and 2013:



2006: 9,208,372
2007: 8,734,052
2008: 7,630,706
2009: 7,038,007
2010: 6,574,847
2011: 6,242,055
2012: 5,834,057
2013: 5,378,751

These data do not include the sale of progestogen-only HRT which is only prescribed for menopausal hormone therapy in combination with an oestrogen.

03 CLINICALLY RELEVANT COMPARATORS

03.1 Medicinal products

3.1.1 Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in post-menopausal women.

NAME (INN) *Company*	Same TC* Yes/No	Indication	Date of opinion	Actual Benefit	Reimbursement Yes/No
ABUFENE (beta-alanine) *BOUCHARA - RECORDATI*	No	For use in menopausal hot flushes	06/04/2011	Insufficient	No

*therapeutic category

◗ Conclusion

The ABUFENE proprietary medicinal product, "the efficacy of which does not seem to be different from that of a placebo" (opinion dated 6 April 2011) is not a relevant comparator of menopausal hormone therapies.

There is no relevant comparator in this indication.

3.1.2 Prevention of post-menopausal osteoporosis in women at high risk of osteoporotic fracture and with intolerance or contraindication to the other treatments indicated for the prevention of osteoporosis.

◗ Conclusion

There is no relevant comparator in this indication

04 LITERATURE SEARCH

04.1 Data submitted by the pharmaceutical companies

The distributors were asked to supply HAS with all the clinical data that would enable AB reassessment of the proprietary medicinal products indicated for hormone replacement therapy in menopause.
The data provided by the companies specifically concerning the efficacy and/or safety of their proprietary medicinal product(s) and published after their last inclusion renewal are summarised in section 04.
The data concerning the efficacy and safety of hormone replacement therapy in menopause but not specifically studying their proprietary medicinal product(s) have been included in the literature review according to the same selection criteria as the data from the literature search.

04.2 Sources of data identified in the literature

Searches focused on the subjects and study types defined in agreement with the project manager and were limited to publications written in English and French.

The search period was from January 2008 to March 2012.

The following sources were consulted:
for international literature: the Medline database
the Cochrane Library;
websites publishing guidelines and technological or economic assessment reports;
websites of learned societies competent in the field being studied;

Systematic monitoring in Medline was performed until October 2013 with the following equation:
(Hormone Replacement Therapy OR "Estrogen Replacement Therapy)[Mesh] AND Postmenopause[Mesh]

This search was supplemented with the bibliography provided by the experts and companies.

04.3 Strategy and results of the literature search

Study type / subject		**Period**	**Number of references**
	Terms used		
Psychotherapy			
- Recommendations		01/2008 – 03/201	44
Step 1	(Breast Neoplasms[Mesh:noexp] OR Ovarian Neoplasms[Mesh:noexp] OR Colorectal Neoplasms[Mesh:noexp] OR Lung Neoplasms[Mesh:noexp] OR Esophageal Neoplasms[Mesh] OR Skin Neoplasms[Mesh:noexp] OR Osteoporosis[Mesh:noexp] OR Endometrial Neoplasms[Mesh:noexp] OR Diabetes Mellitus[Mesh] OR Stomach Neoplasms[Mesh] OR Cognition Disorders[Mesh] OR Endometrial Hyperplasia[Mesh] OR Central Nervous System Neoplasms[Mesh] OR Asthma[Mesh] OR Depression[Mesh] OR Depressive Disorder[Mesh:noexp] OR Mortality[Mesh:noexp] OR Stroke[Mesh] OR Myocardial Infarction[Mesh] OR Lithiasis[Mesh] OR Fibrocystic Breast Disease[Mesh] OR Venous Thromboembolism[Mesh] OR Urinary Incontinence[Mesh] OR Menopause[Mesh] OR Menopause, Premature[Mesh] OR Premenopause[Mesh] OR Perimenopause[MeSH Terms] OR Postmenopause[Mesh]) AND (Hormone Replacement Therapy[Mesh:noexp] OR Estrogen Replacement Therapy[Mesh] OR postmenopausal hormone		

	therapies[tiab] OR Women's Health Initiative[ti])		
AND			
Step 2	Guidelines as topic[mesh terms] OR health planning guidelines[MeSH Terms] OR recommendation*[title] OR guideline*[title] OR practice guideline[publication type] OR guideline[Publication Type] OR Consensus Development Conferences as topic[mesh terms] OR Consensus Development Conferences, NIH as topic[MeSH Terms] OR Consensus Development Conference[publication type] OR Consensus Development Conference, NIH[Publication Type] OR Practice Guidelines as topic[MeSH]		
- Meta-analyses and systematic reviews		01/2008 03/2012	32
Step 1			
AND			
Step 3	meta-analysis as topic[mesh terms] OR metaanalysis[title] OR meta-analysis[title] OR meta analysis[title] OR meta-analysis[Publication Type] OR systematic review[title/abstract] OR systematic overview[TIAB] OR systematic literature review[TIAB] OR cochrane database syst rev[TA]		
- Controlled studies		01/2008 03/2012	201
Step 1			
AND			
Step 4	Controlled Clinical Trial[Publication Type] OR Controlled Clinical Trials as topic[MeSH] OR random*[title] OR randomized controlled trials as topic[mesh terms] OR random allocation[mesh terms] OR double-blind method[mesh terms] OR single-blind method[mesh terms] OR randomized controlled trial[Publication Type] OR cross-over studies[mesh terms]		
- Controlled studies - adverse effects		01/2008 03/2012	66
Step 5	(Perimenopause[MeSH Terms] OR Postmenopause[Mesh]) AND (Hormone Replacement Therapy /adverse effects[Mesh] OR Estrogen Replacement Therapy /adverse effects[Mesh])		
AND			
Step 4	Controlled Clinical Trial[Publication Type] OR Controlled Clinical Trials as topic[MeSH] OR random*[title] OR randomized controlled trials as topic[mesh terms] OR random allocation[mesh terms] OR double-blind method[mesh terms] OR single-blind method[mesh terms] OR randomized controlled trial[Publication Type] OR cross-over studies[mesh terms]		
- Prospective studies		01/2008 03/2012	130
Step 6	(Perimenopause[MeSH Terms] OR Postmenopause[Mesh]) AND (Hormone Replacement Therapy[Mesh] OR Estrogen Replacement Therapy[Mesh])		
AND			
Step 4	cohort studies[MeSH] OR follow-up studies[MeSH] OR prospective studies[MeSH] OR cohort study[Title] OR cohort studies[Title]		

04.4 Selection of studies

The following publications were not taken into account:

- Abstracts
- Publications before 2008
- Case series
- Retrospective studies
- Studies focusing on interim endpoints
- Studies not including an analysis based on whether or not menopausal hormone therapy was taken.
- Non-randomised comparative clinical studies or clinical studies only including intra-group comparisons.

A level of evidence was allocated to considered studies according to the ANAES [National Health Accreditation and Assessment Agency] literature analysis guide (appendix 4)

05 DATA SUBMITTED BY THE COMPANIES

05.1 Efficacy

DELIDOSE (oestradiol)

The company submitted two publications of clinical studies[1,2]

- The first study compared the efficacy of three daily doses of gel (1 mg, 0.5 mg and 0.25 mg; only the first two doses are included in the MA dosage) with a placebo on the change in frequency and intensity of hot flushes after 12 weeks of treatment in post-menopausal women.
  In total, 495 women with moderate to severe vasomotor symptoms were included, 488 of which (having provided data collected for at least 4 days) were included in the efficacy analysis.
  The analysis concluded that there was a significant reduction in the frequency and intensity of the hot flushes after 12 weeks of treatment compared with the placebo for each of the studied doses.
- The second study is a post-hoc analysis of the previous study, based on age and whether or not there was a history of an oophorectomy or a hysterectomy. It was not taken into account.

CLIMASTON (oestradiol /dydrogesterone)

The company submitted a clinical study report[3] and its publication[4] and a second clinical study publication[5] the results of which will not be taken into account:

- The first study has already been taken into account in the previous Transparency Committee opinion concerning CLIMASTON.

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[1] Hedrick R.E., Ackerman RT, Koltun WD, Halvorsen MB, Lambrecht L.J. transdermal estradiol gel 0,1% for the treatment of vasomotor symptoms in postmenopausal women. Menopause. 2009; 16: 132-40

[2] Hedrick R.E., Ackerman RT, Koltun WD, Halvorsen MB. Estradiol gel 0,1% relieves vasomotor symptoms independent of age, ovarian status, or uterine satuts. Menopause. 2010; 17: 1-7

[3] A randomized, placebo controlled, double blind, multinational study to demonstrate efficacy in continuous combined 0,5 mg estradiol and 2,5 mg dydrogesterone in the treatment of vasomotors symptoms in postmenopausal women in comparison to placebo over 3 months and to investigate the bleeding pattern over a double blind treatment period of one year compared with continuous combined 1 mg estradiol and 5 mg dydrogestérone. Clinical study report S102.3.119.

[4] Stevenson JC, Durand G, kahler E, Pertynski T. Oral ultra-low dose continuous combined hormone replacement therapy with 0,5 mg 17β-oestradiol and 2,5 mg dydrogesterone for the treatment of vasomotor symptoms: results from a double-blind, controlled study. Maturitas. 2010; 67: 227-32.

[5] Bergeron C, Nogales FF, Rechberger T, Tatarchjuk T, Zipfel L. Ultra-low dose continuous combined hormone replacement therapy with 0,5 mg 17β-oestradiol and 2,5 mg dydrogesterone : protection of the endometrium and amenorrhea rate. Maturitas. 2010;66: 201-5

- The second study only involved a dosage of CLIMASTON not marketed in France and has not been the subject of a Transparency Committee opinion.

OESTROGEL, OESTRODOSE, THAIS, THAISSEPT (oestradiol)
The company submitted five publications of clinical studies using oestradiol administered as a gel or transdermal device, four of which were not selected[6,7,8,9] (name of the transdermal device proprietary medicinal product not specified or other than those listed in this opinion, retrospective studies, studies focused on interim endpoints).
A randomised, single-blind study in two parallel groups (n=38) compared the effect of a 6-month treatment with tibolone (LIVIAL) 2.5 mg/day or transcutaneous oestradiol (OESTROGEL) 1.5 mg (2.5 g of gel)/day on quality of life.[10] There was a significantly greater reduction of the MRS (Menopause Rating Scale) in the group treated with tibolone than in the group treated with oestradiol.

UTROGESTAN (progesterone)
The company provided seven publications concerning the use of oral or vaginal progesterone.[11,12,13,14,15,16,17] These were not included because there are retrospective studies, abstracts, studies having evaluated a dosage not included in the MA, with an unspecified number of patients per treatment group or studies focusing on interim endpoints or the use without MA.

The companies did not submit a new clinical study for the other proprietary medicinal products included in this reassessment.

[6] Kroft J, Klostermann NR, Moody JR, Taerk E, Wolfman W. A novel regimen of combination transdermal estrogen and intermittent vaginally administered progesterone for relief of menopausal symptoms. Gynecol Endocrinol 2010;26(12):902-908.
[7] Di Carlo C, Tommaselli GA, Gargano V, Savoia F, Bifulco G, Nappi C. Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns. Climacteric 2010;13(5):442-446.
[8] Murkes D, Conner P, Leifland K et al. Effects of percutaneous estradiol-oral progesterone versus oral conjugated equine estrogens-medroxyprogesterone acetate on breast cell proliferation and bcl-2 protein in healthy women. Fertil Steril 2011;95(3):1188-1191.
[9] Cuadros JL, Fernandez-Alonso AM, Chedraui P, Cuadros AM, Sabatel RM, Perez-Lopez FR. Metabolic and hormonal parameters in post-menopausal women 10 years after transdermal oestradiol treatment, alone or combined to micronized oral progesterone. Gynecol Endocrinol 2011;27(3):156-162.
[10] Bhattacharya SM, Jha A. Effects of transdermal estradiol gel and oral tibolone on health-related quality of life after surgical menopause. Int J Gynaecol Obstet 2010;110(3):213-216.
[11] Kroft J, Klostermann NR, Moody JR, Taerk E, Wolfman W. A novel regimen of combination transdermal estrogen and intermittent vaginally administered progesterone for relief of menopausal symptoms. Gynecol Endocrinol 2010;26(12):902-908.
[12] Di Carlo C, Tommaselli GA, Gargano V, Savoia F, Bifulco G, Nappi C. Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns. Climacteric 2010;13(5):442-446.
[13] Murkes D, Conner P, Leifland K et al. Effects of percutaneous estradiol-oral progesterone versus oral conjugated equine estrogens-medroxyprogesterone acetate on breast cell proliferation and bcl-2 protein in healthy women. Fertil Steril 2011;95(3):1188-1191.
[14] Cuadros JL, Fernandez-Alonso AM, Chedraui P, Cuadros AM, Sabatel RM, Perez-Lopez FR. Metabolic and hormonal parameters in post-menopausal women 10 years after transdermal oestradiol treatment, alone or combined to micronized oral progesterone. Gynecol Endocrinol 2011;27(3):156-162.
[15] Prior JC, Hitchcock CI.Progesterone for vasomotors symptoms: a 12-week randomized, masked placebo-controlled trial in healthy, normal-weight women 1-10 years since final menstrual flow. Abstract ENDO 2010
[16] Schüssler P, Kluge M, Yassouridis A, Dressler M, Held K, Zihl J, Steiger A. Progesterone reduces wakefulness in sleep EEG and has no effect on cognition in healthy postmenopausal women. Psychoneuroendocrinology. 2008; 33: 1124-31.
[17] Caufriez A, Leproult R, L'Hermite-Balériaux M, Kerkhofs M, Copinschi G. Progesterone prevents sleep disturbances and modulates GH, TSH and melatonin secretion in postmenopausal women. J Clin Endocrinol Metab. 2011; 96

05.2 Safety

DELIDOSE1 (oestradiol)
- the most common adverse events (mentioned by at least 5% of patients in at least one treatment group) were metrorrhagia, mastalgia and vaginal mycosis. One serious adverse event was considered to be treatment-related: a postoperative pulmonary embolism.
- the most common adverse events were metrorrhagia (7%) and bleeding of uterine origin (6.5%). The frequency of adverse events according to the dosage used was not specified.

ESTRAPATCH, (oestradiol)
The company submitted an amendment to the SPC for the ESTRAPATCH proprietary medicinal products (see appendix).
The amendments concerned the following paragraphs:
- Therapeutic indications
- Posology and method of administration
- Contraindications
- Special warnings and precautions for use
- Interaction with other medicinal products and other forms of interaction
- Undesirable effects

PHYSIOGINE (oestriol)
The company submitted a publication concerning the risk of breast cancer on oestrogen-only HRT.[18] This publication was prior to 2008 so was not included in the literature review concerning hormone replacement therapy in menopause.
This Finnish cohort study included women over 50 years of age having bought an oestrogen-only menopausal therapy at least once (oral, transdermal or vaginal) between 1994 and 2001. They were identified from the national registry of medical reimbursements. Women who were treated for less than 6 months or who used conjugated equine oestrogen were excluded from the analysis.
The cases of breast cancer were identified from the Finnish cancer registry.
The results were expressed as a standardised incidence ratio (SIR) (number of observed cases/number of expected cases calculated from the incidence in the general population per 5-year age group for the same observation period).
The risk was significantly increased for the users of oral or transdermal oestradiol.
The risk was not significantly increased in the population of women treated with oral oestriol. The SIRs were:
- 1.07 [95% CI: 0.86; 1.32] if used for less than 5 years (n=3717)
- 1.41 [95% CI: 0.80; 2.28] if used for more than 5 years (n=1367)

The companies did not submit a new clinical study for the other proprietary medicinal products included in this reassessment.

[18] Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen only therapy. Obstet Gynecol 2006;108:1354-1360

06 THERAPEUTIC USE

The Committee recommends:
- Carefully considering the benefit of hormone therapy relative to the symptoms and their impact on patient quality of life.
- Complying with contraindications when prescribing these therapies, in particular concerning the risk of thromboembolism and breast cancer.
These treatments will be prescribed according to AFSSAPS guidelines (see appendix), in particular:
- before initiating or reinstituting HRT, a complete clinical and gynaecological examination (including an analysis of the family history) should be performed. Regular breast examinations should be performed according to current guidelines (palpation, mammography, ultrasound, etc.) and adapted in accordance with the individual case.
- at the start of treatment, patients must be given all relevant information enabling an appropriate and informed prescription. Thus, patients must be informed of the risks inherent to the treatment. In addition, the treatment should be reassessed regularly, at least once a year, taking into account changes in the benefit/risk ratio. The treatment may be temporarily suspended during this reassessment in order to verify the persistence of the menopausal syndrome and its severity.

Menopausal disorders
There is no reimbursable medicinal product indicated in the treatment of oestrogen deficiency signs in post-menopausal women other than oestrogen-only or combined menopausal hormone therapies.
These therapies will be prescribed at the minimum effective dose, for the shortest possible duration, when the menopausal symptoms experienced by the patient are sufficiently troublesome to impair her quality of life.

Prevention of post-menopausal osteoporosis
In the prevention of post-menopausal osteoporosis, oestrogen-only or combined HRT are indicated in women with an increased osteoporotic fracture risk and who have intolerance or contraindication to the other treatments indicated for the prevention of osteoporosis.
They are recommended in cases of menopausal disorders and recent menopause, after a minor fracture or if there is a low T-score, if there is intolerance to or failure of other treatments.[19,20]

Premature menopause
When these treatments are prescribed for congenital or acquired premature menopause:
- the dose of oestrogen must be sufficient to alleviate the oestrogen deficiency and prevent the associated risk of osteoporosis,
- temporary annual suspension of treatment is not necessary.

Oestrogen-progesterone combinations and progestogens indicated in menopausal hormonal therapy in combination with an oestrogen are recommended in women with an intact uterus to prevent the risk of endometrial hyperplasia following oestrogen-only HRT.[21].

[19] Briot K, Cortet B, Thomas T et al. 2012 update of French guidelines for the pharmacological treatment of postmenopausal osteoporosis. Joint Bone Spine 2012;79:304-13
[20] Briot K. Traitement de l'ostéoporosepostménopausique : comment utiliser les nouvelles recommandations françaises ? Mise au point. La lettre du rhumatologue. 2013; 395: 18-22.
[21] Furness S, Roberts H, Marjoribanks J *et al.* Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review). Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD000402. DOI: 10.1002/14651858.CD000402.pub3.

07 REMINDER OF THE AFSSAPS UPDATES

Menopausal hormone therapy (MHT) has been the subject of several updates and guidelines from AFSSAPS[1,2,3,4] between 2003 and 2008. These publications are mainly based on the results of the HERS[5,6] and WHI[7,8,9,10,11,12,13,14,15,16] randomised studies and the MWS[17,18], E3N[19] and ESTHER[20,21,22] epidemiological studies.

07.1 Point d'étape - July 2006

This update was based on a review of literature published between 2002 (first results of the WHI study) and 2006 (see appendix 1).

[1] Actualisation des recommandations sur le traitement hormonal substitutif - Communiqué de synthèse - AFSSAPS, 3 December 2003.
[2] AFSSAPS/ANAES report - Traitements hormonaux substitutifs de la ménopause - 11 May 2004.
[3] AFSSAPS "Mise au point sur le traitement hormonal de la ménopause THM " Point d'étape – June 2006.
[4] AFSSAPS - Traitement hormonal de la ménopause (THM) - Point d'information - February 2008.
[5] Hulley S. et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary disease in postmenopausal women (HERS I). JAMA, 1998, 280 : 605-613
[6] Hulley S et al. Non cardiovascular disease outcomes during 6,8 years of hormone therapy (HERS II). JAMA, 2002; 288: 58-66
[7] Writing group for the Women's Health Initiative investigators. "Risks and benefits of estrogen plus progestin in healthy post menopausal women". JAMA 2002 ; 288 : 321-33.
[8] Cauley J et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density. JAMA 2003 ; 290 : 1729-38
[9] Chlebowski RT et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women (WHI). JAMA 2003 ; 289 : 3243-53
[10] Anderson G.L. et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 2003 ; 290 : 1739-48
[11] Schumaker S.A. et al. Estrogen plus Progestin and the incidence of dementia and mild cognitive impairment in postmenopausal Women: The Women's Health Initiative Memory Study. JAMA 2003 ; 289 : 2651-62
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[18] Million Women Study Collaborators. Endometrial cancer and hormone-replacement in the Million Women Study. Lancet. 2005, 365 : 1543-51.
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[22] Canonico M et al. Hormone therapy and venous thromboembolism among post menopausal women. Impact of the route of administration and progestogens: the ESTHER study. Circulation 2007; 115 : 840-845.

07.2 Point d'information - February 2008

This updating of the progress report from July 2006 was based on reanalysis of the WHI randomised study[23] and the new data from three epidemiological studies: MWS (Million Women Study)[24], NIH-AARP Diet and health study[25] (cohort of retired people from the National Institute of Health) and E3N[26] (see appendix 2).

07.3 EMA - January 2010

In January 2010, the pharmacovigilance working party of the EMA published an SPC revision for the oestrogen-based proprietary medicinal products, alone or in combination with progestogens, indicated in MHT (see appendix 3)

[23] Rossouw JE et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA, 2007 ; 297 : 1465-77

[24] Beral V et al. Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet, 2007; 369 : 1703-10

[25] Lacey J.V. et al. Menopausal hormone therapy and ovarian cancer risk in the national institutes of health-AARP diet and health study cohort. J of the Natl Cancer Inst, 2006; 98: 1397-1405

[26] Fournier A et al. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat , 2008 ; 107(1) : 103-11

08 ANALYSIS OF DATA FROM THE LITERATURE PUBLISHED SINCE THE LAST PROGRESS REPORT BY THE AFSSAPS IN 2008

08.1 Overall analyses (studying several criteria: cardiovascular risk, cancers, fractures, death etc.)

Oestrogen-only HRT

- WHI randomised study - oestrogen-only HRT - post-treatment follow-up - 2011[27] (level 1 evidence for the first double-blind section of the study, level 2 evidence for the follow-up phase after treatment discontinuation)

The randomised versus placebo phase was prematurely stopped after an average of 7.1 years of treatment due to an increased stroke risk. Patient monitoring was implemented. The results of this publication focus on a mean post-treatment follow-up of 10.7 years.

The double-blind phase included 10,739 women who had had a hysterectomy aged between 50 and 79 years. Amongst them, 7645 (78%) consented to participate in the post-treatment monitoring phase; 3778 of whom received oestrogen and 3867 received the placebo. There was no significant difference concerning the baseline characteristics between the two groups.

The main results of these two phases and from the entire duration of the study are shown in *Table 1*.

Table 1: main results (treatment and follow-up) from the oestrogen-only WHI study

	Treatment/placebo relative risk [95% CI]		
	Double-blind (treatment)*	Follow-up	Double-blind + follow-up
- Coronary heart disease‡	0.95 [0.78; 1.15]	0.97 [0.75; 1.25]	0.95 [0.82; 1.11]
- Death from coronary heart disease	0.98 [0.70; 1.39]	0.84 [0.56; 1.27]	0.92 [0.71; 1.20]
- Myocardial infarction	0.98 [0.79; 1.21]	1.09 [0.81; 1.47]	1.01 [0.85; 1.20]
- Bypasses/angioplasties	0.93 [0.79; 1.11]	1.14 [0.88; 1.46]	0.99 [0.86; 1.14]
- Strokes	1.36 [1.08; 1.71]	0.89 [0.64; 1.24]	1.19 [0.98; 1.43]
- Deep vein thromboses	1.47 [1.06; 2.05]	0.63 [0.41; 0.98]	1.09 [0.84; 1.41]
- Pulmonary embolisms	1.37 [0.90; 2.07]	0.98 [0.62; 1.55]	1.18 [0.87; 1.60]
- Thromboembolic accidents §	1.32 [0.99; 1.75]	0.72 [0.51; 1.03]	1.05 [0.84; 1.31]
All cardiovascular diseases	1.11 [1.01; 1.23]	0.93 [0.79; 1.10]	1.06 [0.98; 1.15]
- Invasive breast cancer	0.79 [0.61; 1.02]	0.75 [0.51; 1.09]	0.77 [0.62; 0.95]
- Colorectal cancer	1.15 [0.81; 1.64]	1.01 [0.58; 1.79]	1.11 [0.82; 1.50]
All cancers	0.94 [0.82; 1.08]	0.93 [0.77; 1.13]	0.94 [0.84; 1.05]
Hip fractures	0.67 [0.46; 0.96]	1.27 [0.88; 1.82]	0.92 [0.71; 1.18]
Death from any cause	1.04 [0.89; 1.22]	1.00 [0.84; 1.18]	1.02 [0.91; 1.15]
Overall index ||	1.03 [0.93; 1.14]	1.02 [0.89; 1.16]	1.03 [0.95; 1.11]

*: results already published in 2004
‡: death and myocardial infarction
§: deep vein thrombosis/pulmonary embolism
||: index summarising the benefit-risk ratio including the primary efficacy endpoints of the study: coronary heart diseases and breast cancers, plus strokes, pulmonary embolisms, colorectal cancers, hip fractures and death from other causes.

The stroke and deep vein thrombosis risk significantly increased on treatment compared with the placebo during the double-blind phase but there was no longer any significant difference between the groups during the follow-up phase.

The risk of invasive breast cancer was significantly lower in the treated group throughout the duration of the study.

27 LaCroix A *et al.* Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy. JAMA 2011; 305: 1305-14

Reduction of the hip fracture risk observed in the treated group was not maintained during the follow-up phase.
The risks of death from any cause and the overall index of chronic diseases were not different between the treated group and the placebo group for any of the study phases.
The analyses per age group revealed a significant difference in risk according to the age groups for four risks:

- in the group of women aged 50 to 59 years at the start of the study, those on treatment had a lower risk of coronary heart disease than those on the placebo: RR = 0.59 [0.38; 0.90], myocardial infarction: RR = 0.54 [0.34; 0.86], deaths from any cause: RR = 0.73 [0.53; 1.00].
- in the group of women aged 70 to 79 years at the start of the study, those on treatment had a higher risk of colorectal cancer than those on the placebo: RR = 1.83 [1.08; 3.12] and for the overall index: RR = 1.15 [1.01; 1.32].

- WHI randomised study - oestrogen-only HRT - post-treatment follow-up - 2013[28] - (level of evidence 2)

This publication gave the results after a median post-treatment follow-up of 6.6 years and a median total follow-up of 13 years.
The main results (only the statistically significant results are detailed) are shown in *Table* 2:

Table 2: main results (double-blind and follow-up) from the oestrogen-only WHI study:

	Treatment/placebo relative risk [95% CI]	
	Follow-up	Double-blind + follow-up
- Coronary heart disease	ns	ns
- Death from coronary heart disease	--	ns
- Myocardial infarction	--	ns
- Bypasses/angioplasties	--	ns
- Strokes	--	ns
- Deep vein thromboses	--	ns
- Pulmonary embolisms	--	ns
All cardiovascular diseases	--	ns
- Invasive breast cancer	ns	0.79 [0.65; 0.97]
- Colorectal cancer	--	ns
- Lung cancer	--	ns
- All cancers	--	ns
- Death from cancer	--	ns
Hip fractures	--	ns
Death from any cause	ns	ns
Overall index*	ns	ns

*: ||: index summarising the benefit-risk ratio including the primary efficacy endpoints of the study: coronary heart diseases and breast cancers, plus strokes, pulmonary embolisms, colorectal cancers, hip fractures and death from other causes.
ns: not significant.

Oestrogen-only and combined HRT

- Post-hoc analysis of the two WHI randomised studies - 2009[29]: results in women having started the treatment shortly after their menopause (level 2 evidence).

This analysis compared the risk of coronary heart disease, stroke, thromboembolic accident, breast cancer, endometrial cancer, colorectal cancer, all cancers, hip fracture, death and overall index (see footnote on the table page) in women having started MHT less than 5 years after menopause with those having started later, in the population of the two controlled WHI studies: equine oestrogen-only and equine oestrogen + medroxyprogesterone acetate.

28 Manson JA *et al.* Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. JAMA; 2013;310: 1353-68.
29 Prentice R.L *et al*. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. AM.J.Epidemiol. 2009; 170: 12-23.

The presented results are those observed at the end of the double-blind phase in each study, corresponding to a mean treatment duration of 7.1 years for the study with oestrogen-only and 5.6 years for the study with combined HRT. The results (only the statistically significant results are detailed) are shown in *Table 3:*

Table 3: main results from the post-hoc analysis of the interventional WHI studies:

	Relative Risk [95% CI]			
	CEO only / placebo		CEO + MPA / placebo	
Time between menopause and start of treatment	< 5 years	> 5 years	< 5 years	> 5 years
- Strokes	ns	1.64 [1.12; 2.41]§	ns	ns
- Venous thromboembolic accidents	1.71 [1.12; 2.6]‡	ns	2.26 [1.00; 5.1]§ 1.78 [1.05; 3.02]‡	2.59 [1.81; 3.71]§ ns
Invasive breast cancers	ns	ns	1.77 [1.07; 2.93]§* 2.06 [1.30; 3.27]‡	ns
Invasive colorectal cancer	ns	ns	0.35 [0.13; 0.94]‡	ns
All invasive cancers	1.72 [1.00; 2.94]§	0.48 [0.27; 0.84]‡	ns	ns
- Hip fractures	0.54 [0.30; 0.99]‡	ns	0.25 [0.09; 0.74]‡	ns
- Overall index ||	1.22 [1.04; 1.43]‡	ns	ns	ns

CEO: conjugated equine oestrogen;
MPA: medroxyprogesterone acetate;
ns: not significant;
‡: women already treated before their inclusion in the WHI studies;
§: women who had never been treated before their inclusion in the WHI studies; ||: index summarising the benefit-risk ratio including the two primary endpoints of the study: coronary artery diseases and breast cancers, plus strokes, pulmonary embolisms, endometrial cancers, colorectal cancers, hip fractures and death from other causes.
* it should be noted that there is a significant interaction (p=0.03) between the time of treatment initiation after menopause and the risk of invasive breast cancer on combined HRT.

- Cochrane systematic review of randomised studies - 2012[30] (level 2 evidence).

This systematic review included randomised versus placebo studies for a treatment duration at least equal to 1 year. Seventy percent of data have been extracted from the two WHI interventional studies and the HERS study. The reported results are mainly from post-hoc analyses of the WHI studies. The majority of participants were American women with comorbidities; the mean age was over 60 years in the majority of the studies. The meta-analyses of published data concerned the oestrogen-only and the combined HRT separately for the different studied risks:

On oestrogen-only HRT, it was concluded that there is a statistically significant increase of the following risks:

- Thromboembolic accident. The risk was higher during the first 2 years: RR = 2.22 [1.12; 4.39] and then reduced: RR = 1.32 [1.00; 1.74] at 7.1 years. The risk was then no longer increased: RR = 1.05 [0.84; 1.31] at 10.7 years. These results are only based on the oestrogen-only WHI study.
- stroke RR = 1.34 [1.07; 1.68] at 7.1 years (WHI study).
- gallstones (meta-analysis of 3 studies, in which the weight of the WHI study was preponderant): RR = 1.75 [1.40; 2.19].
- mild cognitive impairment or probable dementia at 5.2 years (WHI study: composite endpoint, women aged over 65 years): RR = 1.36 [1.01; 1.84].

After 7.1 years of follow-up (WHI study), there was no increased risk of breast cancer RR = 0.79 [0.61; 1.01] or coronary accidents (infraction or death of cardiac origin) RR = 0.78 [0.61; 1.13]. The fracture risk (all clinical fractures) was significantly reduced at 7.1 years: RR = 0.73 [0.65; 0.80] (WHI study).

30 Marjoribanks J, Farqhar C, Roberts H, Lethaby Al. Long term hormone therapy for perimenopausal and posmenopausal women. Cochrane database of systematic reviews 2012, Issue 7.

On combined HRT, it was concluded that there is a statistically significant increase of the following risks:

- thromboembolic accident (WHI). The risk was highest at 1 year: RR = 3.59 [1.95; 6.61] at 2 years: 2.98 [1.88; 4.71], at 7.9 years: 1.65 [1.32; 2.05].
- coronary accident (infarction and death of cardiac origin). In these analyses, the weight of the WHI study was preponderant. A significantly increased risk was revealed on combined HRT as a primary prevention : RR = 1.89 [1.15; 3.10] at 1 year (two studies including WHI), 1.45 [1.07; 1.98] at 3 years two studies including WHI). The risk was not significantly increased at 5.6 years RR = 1.22 [0.98; 1.52] (WHI).
- stroke.
  The risk on combined HRT was significantly increased after 3 years of treatment (WHI): RR = 1.47 [1.02; 2.11], at 5.6 years of follow-up (WHI) RR = 1.38 [1.08; 1.75] and at 7.9 years: RR = 1.29 [1.06; 1.56]
- breast cancer (WHI study): the risk was not significantly increased compared with the placebo during the 4 first years of follow-up. The risk was significantly increased at 5.6 years of follow-up: RR = 1.26 [1.02; 1.56] and at 7.9 years: RR = 1.27 [1.07; 1.52]
- death following breast cancer: RR = 1.98 [1.00; 3.95] at 11 years of follow-up.
- probable dementia in women aged over 65 years: RR = 1.97 [1.16; 3.33] (WHI study) at 4.2 years.
- gallstones: (meta-analysis of four studies, including the WHI study): RR = 1.55 [1.29; 1.86].
- death following lung cancer RR = 1.74 [1.19; 2.57] (WHI study) at a mean follow-up of 8 years.

It was concluded that there is a statistically significant reduction of the risk of colon cancer at 5.6 years: RR = 0.64 [0.44; 0.91]. The risks were no longer significantly different at 7.1 years of follow-up: RR = 0.76 [0.57; 1.01] (WHI study).
The fracture risk (all clinical fractures) was significantly reduced at 5.6 years RR = 0.78 [0.71; 0.86] and at 7.9 years RR = 0.82 [0.76; 0.89] (WHI study).

There was no evidence of an increase of the following risks on oestrogen-only or combined HRT:

- death from any cause,
- death following coronary heart disease,
- transient ischaemic accidents
- death from stroke, breast cancer, endometrial cancer, ovarian cancer, any cause.
- lung cancer, endometrial cancer, ovarian cancer

Combined HRT

- WHI randomised study - conjugated equine oestrogen 0.625 mg/day + medroxyprogesterone acetate with 2 years of post-treatment follow-up - 2008 [31] (level 1 evidence for the double-blind treatment vs placebo period, level 2 evidence for the follow-up period):

After the treatment phase of the WHI study, the results of which were published in 2002, 8506 patients were included in the treated group and 8102 in the placebo group. Treatment administration was prematurely stopped after a mean duration of participation in the study of 5.6 years due to an overall index in favour of excessive risk compared with the benefits of the treatment (cf *Table 1*). Patients' mean age at inclusion was 63.6 years. During the post-intervention phase, corresponding to the period between the premature discontinuation of treatments and the initially planned end of the study, which is a mean follow-up of 2.4 years, the patients underwent follow-up as planned in the study protocol. During this phase, follow-up included 8052 patients in the treated group and 7678 in the placebo group.
The main results of these two phases are shown in *Table 4.*

31 Heiss G et al. health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA. 2008; 299: 1036 -1045

Table 4: results of the WHI CEO + MPS WHI study, double-blind and follow-up phases

	Relative Risk [95% CI]	
	Double-blind phase treatment/placebo*	Follow-up treatment/placebo
- Coronary heart disease‡	1.22 [0.99; 1.51]	0.95 [0.73; 1.26]
- Bypasses/angioplasties	1.00 [0.82; 1.21]	1.04 [0.81; 1.35]
- Strokes	1.34 [1.05; 1.71]	1.16 [0.83; 1.61]
- Thromboembolic accidents §	1.98 [1.52; 2.59]	0.95 [0.63; 1.44]
All cardiovascular diseases	1.13 [1.02; 1.25]	1.04 [0.89; 1.21]
- Invasive breast cancers	1.26 [1.02; 1.55]	1.27 [0.91; 1.78]
- Endometrial cancers	0.81 [0.48; 1.35]	0.75 [0.40-1.43]
- Colorectal cancer	0.62 [0.43; 0.89]	1.08 [0.66; 1.77]
All cancers	1.03 [0.92; 1.15]	1.24 [1.04; 1.48]
Osteoporotic fractures		
- Hip	0.67 [0.47; 0.95]	0.92 [0.64; 1.34]
- Vertebral	0.68 [0.48; 0.96]	0.96 [0.64; 1.44]
- Other	0.75 [0.68; 0.83]	0.87 [0.74; 1.03]
Death from any cause	0.97 [0.81; 1.16]	1.15 [0.95; 1.39]
Overall index ||	1.12 [1.02; 1.24]	1.11 [0.97; 1.27]

*: results already published in 2004
‡: death and myocardial infarction;
§: deep vein thromboses/pulmonary embolisms;
||: index summarising the benefit-risk ratio including the two primary efficacy endpoints of the study: coronary heart diseases and breast cancers, plus strokes, pulmonary embolisms, endometrial cancers, colorectal cancers, hip fractures and death from other causes.

During the follow-up phase, the risks of stroke, thromboembolic accident, cardiovascular diseases, invasive breast cancer and the overall index were no longer significantly different between groups. The risk concerning the "all cancers" endpoint became significantly higher in the previously treated group compared with the placebo group.
The risks of death from any cause were not different between groups during either of the two study phases.

- WHI randomised study - conjugated equine oestrogen 0.625 mg/day + medroxyprogesterone acetate - post-treatment follow-up - 2013[28] - (level 2 evidence)

This analysis gives the results for a median post-treatment follow-up of 8.2 years and a median total follow-up of 13.2 years.
The main results (only the statistically significant results are detailed) are shown in *Table 5:*
Table 5: main results (double-blind and follow-up) from the CEO + MPA WHI study:

	Relative Risk [95% CI]	
	Follow-up treatment/placebo	Double-blind + follow-up treatment/placebo
- Coronary heart disease	ns	ns
- Death from coronary heart disease	--	ns
- Myocardial infarction	--	ns
- Bypasses/angioplasties	--	ns
- Strokes	--	1.16 [1.00; 1.35]
- Deep vein thromboses	--	1.24 [1.01; 1.53]
- Pulmonary embolisms	--	1.26 [1.00; 1.59]
All cardiovascular diseases	--	1.08 [1.00; 1.15]
- Invasive breast cancer	1.32 [1.08; 1.61]	1.28 [1.11; 1.48]
- Colorectal cancer	--	ns
- Lung cancer	--	ns
- Endometrial cancer		0.67 [0.49 0.91]
- Ovarian cancer	--	ns
- All cancers	--	ns
- Death from cancer	--	ns
Hip fractures	--	0.81 [0.68 0.97]
Death from any cause	ns	ns
Overall index*	ns	1.06 [1.00; 1.13]

||: index summarising the benefit-risk ratio including the primary efficacy endpoints of the study: coronary heart diseases and breast cancers, plus strokes, pulmonary embolisms, colorectal cancers, hip fractures and death from other causes

- Cohort study (UGPRD - United Kingdom) - 2008[32] (level 3 evidence).

This study performed from the United Kingdom's General Practice Research Database studied the coronary risk on combined HRT based on conjugated equine oestrogen and norgestrel in women younger than those included in the WHI study: aged between 50 and 55 years and in women aged over 55 years. The inclusion and non-inclusion criteria in the analysis were the same as those for the WHI study. The untreated women were matched to the treated women at a ratio of 2:1. The participants were considered as treated if they were using MHT at the time of their inclusion into the study. Inclusions took place between 1990 and 1995, the study finished in 1999. In total, 20,654 treated women, 10,454 of which finished the study and 30,102 untreated women, 13,766 of which finished the study were included in the group of women aged 50 to 55 years; 13,658 treated women and 37,730 untreated women were included in the group of women aged over 55 years. It should be noted that the menopausal status of the included women was not known. The statistically significant results are shown in *Table 6*.

Table 6: results from the UGPRD cohort study

	Relative Risk [95% CI]	
	50 to 55 years treated/untreated	> 55 years treated/untreated
Stroke	1.52 [1.11; 2.08]	ns
Deep vein thrombosis	1.65 [1.42; 1.93]	1.58 [1.38; 1.80]
Thromboembolic events	1.63 [1.41; 1.89]	1.55 [1.37; 1.75]
Breast cancer	1.52 [1.29; 1.78]	1.67 [1.43; 1.95]
Colorectal cancer	ns	0.56 [0.35; 0.87]
All cancers	1.27 [1.13; 1.42]	1.19 [1.07; 1.32]
Hip fracture	0.41 [0.19; 0.88]	ns
Death	0.76 [0.63; 0.91]	0.75 [0.65; 0.86]

No difference was revealed for the risk of myocardial infarction and pulmonary embolism between untreated women and treated women, regardless of the age group.

08.2 Mortality from any cause

Oestrogen-only and combined HRT

- Cohort study (France) - mortality from any cause - 2010[33] (level 4 evidence).

This cohort study was performed using data from the health and retirement scheme for independent workers in the Provence Alps region. Eligible women were aged between 60 and 69 years and must have had at least one medicinal product reimbursement in 2001. Women with or having had breast or uterine cancer were not included. The inclusions took place in May 2002 and involved a random sample of 1200 women meeting the inclusion criteria. The data collection start date was 1 January 2001 and the data collection end date was 1 January 2009. At inclusion, the mean age of the participants was 64.7 years, 277 women (23.1%) were being treated with MHT and 923 (76.9%) were not; amongst them, 174 were former users, 480 had never used MHT and for 269, this information was not known. During the study, only deaths were collected. The continued use of MHT, duration of use of MHT and the causes of death are not known.

On the data collection end date, 33 women (2.8%) were lost to view and 50 had died (4.2%).

The relative risk of death, adjusted for "the factors associated with MHT administration which could also influence mortality", compared with non-users was 1.07 [0.45; 2.5] for the users and 1.26 [0.54; 2.93] for the former users.

32 Weiner M.G. *et al.* Hormone therapy and coronary heart disease in young women. Menopause. 2008; 1: 86-93

33 Ha-Vinh et al. Caractéristiques individuelles et mortalité associées au traitement hormonal substitutif de la ménopause: étude d'une cohorte française de femmes d'âge compris entre 60 et 69 ans. J Gyn Obst Biol Reprod. 2010; 39: 453-465

- Cohort study (California Teachers Study - USA) - mortality from any cause - 2011[34] (level 2 evidence).

The California Teachers Study (CTS), initiated in 1995-1996 included 133,479 working and retired female teachers and administration personnel, recruited through a State of California pension fund who completed a questionnaire sent by email. The cohort was monitored annually for the diagnosis of cancers, death and address changes.

In total, 71,237 women were included in this study which aimed to study death from any cause and death due to ischaemic cardiomyopathy. Deaths and their causes were identified annually from the registries. Information about MHT (ongoing, previous or not used) and the type of treatment (oestrogen with or without progestogens) was collected from the inclusion questionnaire and updated using a questionnaire from May 2000. Data collection stopped on 31 December 2004; the follow-up duration was calculated from the date of the initial questionnaire until death or database lock. The Cox model considered the age at the time of the questionnaire, the use of MHT and their interaction. The analysis was adjusted for BMI, tobacco use, alcohol consumption, physical activity, total calorie and fat intake, protein and cholesterol during the year preceding the inclusion questionnaire, history of diabetes, arterial hypertension, myocardial infarction or heart disease, skin cancers, strokes, type of MHT (none, oestrogen-only, combined, use of two types of medicinal products), its duration of use, age at the start of treatment and time between the onset of menopause and initiation of treatment.

The risk of death from any cause was significantly lower in treated women than in untreated women: RR = 0.83 [0.79; 0.89]. There was a very significant trend for the relative risk to increase with the increasing age group at inclusion ($p<0.0001$). On analysis per age group, the risk was significantly lower in treated women than in untreated women for those aged 36 to 59 years: RR = 0.54 [0.46; 0.62] and 60 to 64 years: RR = 0.65 [0.54; 0.77]. For the following age groups: 65-69, 70-74, 75-84 and 85-94, the risk was not significantly different.

- Meta-analysis - mortality from any cause - 2009[35,36] (level 2 evidence).

The aim of this meta-analysis of published data was to assess the mortality from any cause in post-menopausal women treated with oestrogen-only or combined HRT, with an average age of less than 60 years. The literature search focused on the period from 1996 - January 2008. It searched randomised controlled studies which lasted at least 6 months, assessed a hormone replacement therapy and mentioned at least one death as well as prospective cohort studies studying the adjusted relative risk of mortality on MHT.

In total, 19 randomised studies and 8 observational studies were included in the analysis (in which the weight of the WHI study was preponderant).

In the observational studies, 212,171 women underwent a mean follow-up of 13.8 years. In the randomised studies, 7052 women were included in the treated groups and 7594 in the control groups and follow-up was from 1 to 6.8 years. The treatments involved were conjugated equine oestrogens, oral esterified oestradiol, transdermal oestradiol, alone or combined with a progestogen, taken continuously or cyclically.

For the women aged 50 to 59 years included in the oestrogen-only WHI study who were mistakenly counted twice in the 2009 publication [35], the authors published a rectification [36]. According to this, the new odds ratio calculation concerning the mortality associated with hormone replacement therapy compared with a placebo or no treatment was unchanged: 0.72 [0.62; 0.82]. The authors concluded that the results of their meta-analysis indicated a lower total mortality in treated younger post-menopausal women (under 60 years) compared with women of the same age who are untreated or receiving a placebo.

34 Stram D.O. Age-specific effects of hormone therapy use on overall mortality and ischemic heart disease mortality among women in the California Teachers Study.Menopause. 2011; 3: 253-61

35 Salpeter RS *et al.* Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. Am J Med. 2009 Nov;122(11):1016-1022.e1

36 Cornu C *et al.* Women were included twice in a meta-analysis. Am J Med. 2011 Sep;124(9):e17; author reply e19.

08.3 Mammary conditions

8.3.1 Benign proliferative breast diseases

Oestrogen-only HRT

- Post-hoc analysis of the interventional WHI study comparing an oestrogen treatment: oral CEO, 0.625 mg, (n= 5310) with a placebo, (n= 5429) - 2008[37] (level 2 evidence).

This analysis studied the incidence of benign breast conditions diagnosed from histological analysis of biopsies, for a mean follow-up duration of 6.9 years. The relative risk for all benign conditions was 2.11 [1.58; 2.81]. It was 2.34 [1.71; 3.20] for the conditions without atypia and 1.12 [0.53; 2.40] for atypical hyperplasia out of only 33 cases.

Oestrogen-only and combined HRT

- Cohort study including all the women included in the randomised WHI studies (MHT, diet change and calcium + vitamin D supplementation) - 2009[38] (level 2 evidence).

This analysis studied the incidence of benign breast conditions diagnosed from biopsies or fine needle aspirations in the patients included in these randomised studies.
The analysis was adjusted for age at inclusion, ethnicity, place of residence, randomisation group, frequency of physical examinations and mammograms. Risk analysis in women having discontinued MHT was also adjusted for treatment duration.
In total, 68,132 post-menopausal women were included for a mean follow-up of 7.8 years. Out of the biopsies or fine needle aspirations performed, 4225 underwent centralised reading to look for benign epithelial proliferative lesions and 1792 incident cases of benign epithelial proliferative lesions were diagnosed, 1498 without atypia and 294 with atypia.
The risk of benign proliferative epithelial lesion was significantly increased in women using MHT (combined or oestrogen-only) compared with those who had never used it: RR = 2.13 [1.89; 2.40]; it was increased for the lesions without atypia RR = 2.23 [1.95; 2.54] and with atypia: RR = 1.71 [1.28; 2.27]. The risk increased with the treatment duration, more rapidly on combined HRT than on oestrogen-only HRT.
If MHT was discontinued, the risk was no longer different from that of untreated women from 5 years of interruption.

Combined HRT

- Post-hoc analysis of the interventional WHI study comparing combined HRT: oral CEO, 0.625 mg + medroxyprogesterone acetate, 2.5 mg (n = 8506) with a placebo, (n= 8102) - 2008[39] (level 2 evidence).

This analysis studied the incidence of benign breast conditions diagnosed from histological analysis of biopsies, for a mean follow-up duration of 5.5 years. The relative risk for all benign conditions was 1.74 [1.35; 2.25]. It was 2.00 [1.50; 2.66] for the conditions without atypia and 0.76 [0.38; 1.52] for atypical hyperplasia out of only 36 cases.

8.3.2 Breast cancer

Incidence/mortality

Oestrogen-only HRT

- WHI interventional study (oestrogen-only) with post-treatment follow-up - 2012[40] (level 1 evidence for the first period, level 2 evidence for the follow-up period)

37 Rohan T.E. *et al*. Conjugated equine estrogen and risk of benign proliferative breast disease: a randomised controlled trial. J.Natl Cancer Inst. 2008; 100: 563-571.
38 Cui Y. *et al*. Menstrual and reproductive history, postmenopausal hormone use, and risk of benign proliferative epithelial disorders of the breast: a cohort study. 2009. 114; 113-120
39 Rohan T.E. *et al*. Estrogen plus progestin and risk of Benign proliferative breast disease. Cancer Epidemiol Biomarkers Prev. 2008; 17:2337-2343.

This new analysis of the CEO WHI study studied the incidence of breast cancers and mortality from breast cancer in the study population after a median duration of 5.9 (2.5-7.3) years of treatment and a total median follow-up duration of 11.8 years (9.1 to 12.9 years). At the start of the study, 5310 women were included in the treated group and 5429 in the placebo group; 3778 women from the treated group and 3867 from the placebo group who did not develop breast cancer were monitored during the post-intervention phase (time between treatment discontinuation and the initially planned end of the study) and the study extension phase (from the planned end of the study until 2009).
Three intention-to-treat analyses were performed and involved the treatment phase, the follow-up phase without treatment and the entire study. For the treatment phase analysis, the data were censored on the date of death, last follow-up or end of treatment. ; for the entire analysis, the data was censored on the date of death or last follow-up.
For the entire study, the oestrogen-only HRT was associated with a lower annual incidence of invasive breast cancer compared with the placebo: 0.27% versus 0.35%, HR = 0.77 [0.62-0.95], with no difference between the treatment phase and the follow-up phase. In the subgroup analyses, there was a significant interaction with family history of breast cancer and personal history of benign breast conditions. The risk was not reduced in women with these histories. Deaths due to breast cancer and death from any cause after breast cancer were fewer in the treated group: HR=0.37 [0.13; 0.91] and HR=0.62 [0.39; 0.97] respectively. There was no significant risk difference between the women having started treatment more or less than 5 years after menopause.

- Post-hoc analysis of the interventional and observational WHI studies (oestrogen-only HRT) - 2008[41] (level 2 evidence).

The interventional study did not reveal an increased incidence of breast cancers in oestrogen-only HRT cases versus placebo: RR = 0.80 [0.62; 1.04] for a mean treatment duration of 7.1 years.
The observational WHI study is a prospective cohort which included women not eligible for the interventional study or not wanting to participate in it.
This post-hoc analysis compared the incidence of breast cancers on oestrogen-only HRT in the interventional study (conjugated equine oestrogen, n = 4493; placebo, n = 4596) excluding women for whom the age of menopause onset or the existence of HRT prior to the study was not documented and in the corresponding population of the observational cohort (CEO n = 9336; without MHT, n = 8101) for a follow-up duration equivalent to 7.1 years.
After adjustment for the use of a hormone therapy before inclusion, the risk of breast cancer was higher in the observational study than in the interventional study with a relative risk ratio of 1.43 [0.91; 2.26]; after additional adjustment for the time between the start of menopause and the start of treatment, the relative risk ratio between the two studies was 1.07 [0.60; 1.93]. This disappearance of the results difference between the two studies after adjustment for the time between menopause and treatment initiation suggests a difference in the risk of breast cancer depending on the time between menopause and the initiation of oestrogen-only HRT, but the low number of women having started oestrogen-only HRT less than 5 years after menopause in this study does not enable a conclusion to be drawn.

Oestrogen-only and combined HRT

- Cohort study (Italy) - 2008[42] (level 2 evidence).

This cohort was formed from the Lombardy health service database. The population concerned were women aged 50 to 75 years having had a least one prescription for MHT (oral, vaginal or transdermal oestrogen, alone or combined with a progestogen) between 1998 and 2000. The follow-up continued until 2005. The treatments administered during the follow-up were identified

40 Anderson G.L. conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hytsterectomy: extended follow-up of the Women's health Initiative randomised placebo-controlled trial. The Lancet Oncology. 2012: DOI: 10.1016/S1470-2045
41 Prentice R *et al*. Conjugated equine estrogens and breast cancer risk in the Women's Health Intiative clinical trial and observational study. Am J Epidemiol. 2008 ; 167: 1407-15
42 Corrao G et al. Menopause hormone replacement therapy and cancer risk : an italian record linkage investigation. Annals of oncology. 2008; 19: 150-155

from the regional prescription database. The hospitalisations for cancer were identified from the regional hospitalisation database. Women having had an MHT prescription before the start of follow-up, having been hospitalised for cancer or monitored for less than 6 months were excluded. In total, 73,505 women were included for a follow-up of 471,612 women-years, 93,638 of which were exposed to MHT. More than 88% of women started their oestrogen therapy using transdermal administration. Women having been treated for less than 6 months formed the reference group.
On the overall analysis, the risk of cancer was not increased in women treated for 6 months or longer.
On the analysis based on the duration and for all the treatments, the risk of breast cancer was significantly increased from 13 months of use: RR = 1.19 [1.01; 1.40] for 13 to 24 months, RR = 1.34 [1.13; 1.58] for 25 months or longer. There was a significant trend for the risk to increase with treatment duration ($p<0.04$).
The risk was significantly increased from a duration of 25 months in cases of transdermal treatment RR = 1.27 [1.07; 1.51] and from a duration of 13 months for the oral treatments RR = 1.63 [1.08; 2.45] for 13 to 24 months and RR = 2.14 [1.43; 3.21]. The risks in cases of oral treatment and transdermal treatment were significantly different. For the two types of treatment, there was a significant trend for the risk to increase with treatment duration.

- Cohort study (EPIC - Europe) - 2011[43] (level 3 evidence).

This prospective cohort (European Prospective Investigation into Cancer and nutrition) involved 23 centres in 10 European countries having included a total of around 370,000 women recruited between 1992 and 2000.
The data from the E3N cohort were included in this study, only taking into account the information on the use of MHT collected at inclusion from the subjects; data concerning the previous use of MHT were not taken into account. Women for whom information on the use of MHT was not available and those with cancer at the time of recruitment were not included. Only post-menopausal women (bilateral oophorectomy, no menstrual period for at least 12 months or aged 55 years and over) at the time of their recruitment in the cohort were included in this analysis; this was a total of 133,744 women in 8 European countries.
Depending on the country, the incident cancers were identified from the cancer registries, data from national health insurance files, contact with the participants or their family; mortality data were obtained from the death records. Participant follow-up was from inclusion until diagnosis of cancer (apart from skin cancers other than melanomas), their death, emigration or the end of study follow-up, the date of which was different depending on the country.
Progestogens were divided into two groups for analysis: progesterone derivatives and testosterone derivatives. Two administration regimens were identified for combined HRT: sequential (progestogen administered 10 to 14 days per month) and continuous (oestrogen + progestogen administered every day).
The relative risks specific to each country were estimated according to the Cox model using the type of menopause, BMI, use of oral contraceptives, number of pregnancies to full-term, age at first pregnancy, age at first menstrual period and alcohol consumption as variables. The analysis was stratified by the centre and age at inclusion. Sensitivity analyses concerning the age at menopause, history of benign breast disease, physical activity and history of breast cancer in first-degree relatives were performed.
The follow-up covered 1,153,747 person-years, which is a mean duration of 8.6 years.
Compared with the absence of treatment, the use of oestrogen-only HRT at the time of inclusion was associated with increased risk: RR = 1.42 [1.23; 1.64], as was the use of combined HRT: RR = 1.77 [1.40; 2.24] with significant heterogeneity of the relative risks between countries for the two types of treatments; the risk was also significantly higher with combined HRT than with oestrogen-only. There was no change in risk according to the BMI.

43 Bakken K, Fournier A *et al.* Menopausal hormone therapy and breast cancer risk : impact of different treatments. The European Prospective Investigation into Cancer and nutrition. Int J Cancer. 2010 ; 128 : 144-56

The relative risk increased with the duration of use. With oestrogen-only HRT, the RR was between 1.01 [0.7; 1.46] for use ≤ 1 year and 1.72 [1.15; 2.57] for > 10 years. With combined HRT, it was between 1.44 [1.09; 1.89] for use ≤ 1 year and 1.98 [1.12; 3.50] for > 10 years.
For the users of oestrogen-only HRT, the risk was not significantly different between the use of equine conjugated oestrogen or oestradiol nor between oral or transcutaneous oestrogen administration.
For the users of combined HRT, the risk was higher with continuous treatment than with sequential treatment RR = 1.43 [1.19; 1.72]. No significant difference was revealed between the testosterone derivatives and the progesterone derivatives; this comparison was only possible for the sequential regimens.

- Cohort study (Million Women Study - United Kingdom) - 2011[44] (level 2 evidence).

The participants of this cohort (1.3 million women) were recruited from the breast cancer screening programme organised by the National Health Service between May 1996 and December 2001. The information concerning incident cancers and deaths were provided by the National Health Service registries. The information concerning the tumour characteristics were obtained from the cancer registries, clinical data, data from study questionnaires and histopathology reports.
This analysis performed on the cohort involved women having undergone natural menopause, oophorectomy or who were over 53 years of age when the age of menopause was unknown. Women with invasive cancer (excluding skin cancers apart from melanomas) or in situ breast cancer at the time of inclusion or for whom information on possible hormone therapy is missing were not included in the analysis.
The number of women-years was calculated from the date of patient recruitment, the date of menopause or from the age of 53 years, until the date of notification of breast cancer, death, 48 months after the last completed questionnaire for the study or 31 December 2002. The participants completed two questionnaires: one at inclusion and one 3 years later, in particular to update the data concerning the use of a MHT. At the time of the database lock, 2/3 of participants had received the 2nd questionnaire and the response rate was 65%.
In total, the analysis included 1,129,025 women who provided data collected prospectively and concerning the use of MHT and the risk factors for breast cancer. The median age at inclusion was 56.6 years. The follow-up duration was 4.05 million women-years during which 15,759 incident breast cancer cases were recorded.
The relative risk of breast cancer was significantly higher in women having interrupted MHT. RR = 1.08 [1.04; 1.12] and in women on treatment: RR = 1.68 [1.64; 1.72] than in those never having received MHT.
Amongst women on treatment, the relative risk was 1.38 [1.32; 1.44] for those treated with oestrogen-only HRT and 1.96 [1.90; 2.02] for those on combined HRT.
The risk increased with the duration of use for oestrogen-only HRT and for combined HRT.

- Nested case-control study (UGPRD - United Kingdom) - 2008[45] (level 3 evidence).

This study, performed from the United Kingdom's General Practice Research Database which represents around 8% of the British population, studied the risk of breast cancer on MHT.
Invasive breast cancers (n = 6347) occurring in women aged 50 to 75 years between 1 January 1998 and 31 December 2004 (n = 502,820) were identified. For each case, five controls were selected (n = 31,516). They were matched for the year of birth, the general practitioner consulted and the year of entry into the UGPRD. The cases and the controls with a history of breast cancer before 50 years of age were not included in the study.
Prescriptions for MHT were identified from the patients' medical records. Exposure to MHT during the 2 years prior to the data collection end date was not taken into account.

44 Beral V *et al.* Breast cancer risk in relation to the interval between menopause and starting hormone therapy. JNCI; 2011:4: 296-304
45 Opatrny L *et al* . Hormone replacement therapy use and variations in the risk of breast cancer. BJOG 2008; 2: 169-75

The analysis was adjusted for personal history of endometrial cancer, hysterectomy, oophorectomy, oral contraceptives, obesity, tobacco use, alcohol consumption, and family history of breast cancer.
The included women had a mean age of 61 years and had been monitored for around 7 years.
Women treated with oestrogen-only HRT: OR = 0.97 [0.86; 1.09] or with tibolone: OR = 0.86 [0.65; 1.13] did not have a significantly increased risk compared with women who had never been treated, unlike the women treated with combined HRT: OR = 1.33 [1.23; 1.44].
Women having used combined HRT including transdermal oestrogen did not have a significantly increased risk of cancer: OR = 1.08 [0.81; 1.43] in contrast to those treated with oral oestrogen: OR = 1.38 [1.27; 1.49].
Women having used a combined HRT, including a progesterone derivative, had a slightly higher risk than those having used a testosterone derivative: OR = 1.53 [1.22; 1.92] versus OR = 1.29 [1.18; 1.40].
In both cases, it was not specified if the risks were significantly different.

- Case-control study (France) [46] - 2013 (level 3 evidence).

This study was performed in two regions: Côte d'Or and Ille-et-Vilaine.
It included incident in situ and invasive cancers diagnosed between April 2005 and March 2007 and occurring in women aged 25 to 75 years living in one of the two regions involved. The cases were recruited in the regional cancer centre as well as in other public or private hospitals in each region.
The controls were women with no history of breast cancer, recruited in the general population from a telephone list, matched on age (10-year age groups) and the study zone. Quotas were applied to the socioeconomic status of the controls in order to reflect the distribution by socioeconomic level of the general population.
This analysis only included women considered as post-menopausal: no menstrual period for 1 year or more, bilateral oophorectomy, women having started MHT before their menstrual periods stopped, women having had a hysterectomy aged 50 years and over. A total of 739 cases and 816 controls were included.
The data were collected using a questionnaire completed during a meeting. The data concerning MHT included the start and end dates of use and the name of the products used. The participants were considered as being treated if they were treated or had discontinued treatment for less than 1 year at the time of the meeting or the diagnosis of cancer. The analyses were adjusted for age and zone of study, age at the first menstrual period, parity, age at first pregnancy carried to full-term, duration of breastfeeding, use of oral contraceptives, history of benign breast disease, existence of family history of breast cancer and BMI.
Risk was not significantly increased for all the women using oestrogen-only or combined HRT nor for women having discontinued the treatment.
The risk was not significantly increased in users of tibolone.
There was a significantly increased risk in women having been treated with combined HRT for 4 or more years: OR = 1.55 [1.02; 2.36].
There was no increased risk in women using oestrogen in combination with micronised progesterone: OR = 0.80 [0.44; 1.43]. The risk was significantly increased in women using oestrogen combined with a synthetic progestogen: OR = 1.72 [1.11; 2.65]; there was a significant trend for the risk to increase with treatment duration. The risk for the testosterone derivatives was: OR = 3.35 [1.07; 10.4] and for the progesterone derivatives: OR = 1.57 [0.99; 2.49].

- Case-control study (Finland) [47] - 2010 (level 3 evidence).

From the Finnish cancer registry, this study identified women aged 50 to 62 years with breast cancer diagnosed between 1995 and 2007 (n = 9956). For each case, three controls were selected in the Finnish population registry, matched on age; age at menopause, menopausal

[46] Cordina-Duverger E *et al* .Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France. PLOS ONE www plosone.org. 2013. 11; e78016
47 Lyytinen H *et al* . A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as well. Int J Cancer. 2010 ; 126 : 483-89

status and BMI were not known. The use of a hormone therapy was established from the national registry of medical reimbursements.
There was no observed increase of the cancer risk (n = 991 cancers) for the oestrogen-only HRT (oral or transdermal oestradiol): OR = 1.01 [0.93-1.09].
The cancer risk (n = 1731) was increased with combined HRT: OR = 1.36 [1.27-1.46], same for the treatment durations less than 3 years for norethisterone and levonorgestrel and for durations longer than 3 years with medroxyprogesterone acetate. The risk was not increased with dydrogesterone.
The cancer risk (n = 473) was increased with the combination of oestrogen and a coil releasing levonorgestrel: OR = 2.07 [1.78-2.41].

- Case-control study (Germany)[48] - 2008 (level 3 evidence).

This study performed in two regions in Germany, included cases of histologically confirmed invasive and in situ cancers from the cancer registry and the hospital admissions registries between 2001 and 2005. The controls were selected at random from the population registries and matched on the year of birth and region. A questionnaire was sent to participants in particular concerning the use of MHT. In total, 3464 cases and 6657 controls were included in the analysis.
The risk of invasive cancer was significantly increased in the users being treated: OR = 1.73 [1.55-1.94], but not in those having discontinued treatment.
The risk was significantly increased on combined HRT: OR = 1.99 [1.77-2.23] but not on oestrogen-only HRT or progestogen-only HRT. The risk was higher on continuous combined HRT: OR = 2.10 [1.85-2.38] than on cyclical HRT OR = 1.64 [1.39-1.93]. There was a significant trend for the risk to increase with treatment duration.
The risk was significantly higher with continuous HRT containing norethisterone or levonorgestrel: OR = 2.27 [1.98-2.62] than with those containing progesterone derivatives: OR = 1.47 [1.12-1.97], p = 0.003.

Combined HRT

- WHI interventional study (combined HRT) with post-treatment follow-up - 2010[49] (level 1 evidence for the first period, level 2 evidence for the follow-up period)

This new analysis of the CEO + MPA WHI study studied the incidence of breast cancers and mortality from breast cancer in the study population after a median duration of 5.6 ± 1.3 years of treatment and a total median follow-up duration of 11 ± 2.7 years. At the start of the study, 8506 women were included in the treated group and 8102 in the placebo group; 8506 women from the treated group and 7682 from the placebo were monitored during the post-intervention phase (time between treatment discontinuation and the initially planned end of the study); 6545 women in the treated group and 6243 women in the placebo group participated in the study extension phase (from the end of the post-intervention phase until 2009). An intention-to-treat analysis was performed and involved all the women included in the study, censoring the data from those having refused to participate in the extension phase follow-up. The incidence of breast cancer (RR: 1.25 [1.07; 1.46], breast cancer with lymph node involvement (RR: 1.78 [1.23 ; 2.58], the incidence of deaths directly attributable to breast cancer (RR: 1.96 [1.00; 4.04], and deaths from any cause occurring after a diagnosis of breast cancer (RR: 1.57 [1.01; 2.48]) were higher in the treated group. There was no difference in the histology or the receptor sub-types for the cancers occurring on treatment or placebo.

- Observational WHI study - 2013[50] (level 2 evidence).

This study included women who were not eligible or not interested in participating in the clinical study. In total, 41,449 post-menopausal women participated, 25,328 of whom were untreated and 16,121 women treated with combined HRT.

48 Flesh-Janis D *et al*. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. Int.J.Cancer. 2008;123:933-41
49 Chlebowski R. *et al*. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010; 304 : 1684-92
50 Chlebowski R.T. *et al.* Estrogen plus progestin and breast cancer incidence and mortality in the women's health initiative observational study. JNCI; 2013. 105: 526-34

After a mean follow-up of 11.3 ± 3.1 years, 2,236 invasive cancers were diagnosed. The women on combined HRT had already been treated for an average of 5.3 years before their entry into the study. The analyses were stratified by age group and adjusted for ethnicity, BMI, level of education, tobacco use, alcohol consumption, physical activity, family history, Gail score and existence of an oophorectomy.
The risk of invasive breast cancer was significantly higher in treated women: HR = 1.55 [1.41; 1.70]. The risk of death from breast cancer was not significantly increased: HR = 1.32 [0.90; 1.93], but the risk of death from any cause after breast cancer was significantly increased in treated women: HR = 1.65 [1.29; 2.12].

- Cohort study (Finland) - 2009[51] (level 3 evidence).

This study was performed from the Finnish medical reimbursement registry and the Finnish cancer registry. All women over 50 years of age, having bought combined HRT for a duration of at least 6 months between 1994 and 2005 were included; total of 221,551 women. The expected number cancers was calculated from the incidence of breast cancer in the total Finnish population during the same observation period. Oestrogen therapies included oral oestradiol (1 or 2 mg/day), transdermal oestradiol (25 to 100 µg/day) or oestradiol gel (0.5 to 1.5 mg) combined with a continuous or sequential progestogen (10 to 14 days every 1 to 3 months). The most commonly used progestogens were norethisterone acetate (43%), medroxyprogesterone (30%) and dydrogesterone (12%). For women whose exposure was considered to be known precisely (having started their treatment at least 1 year after opening of the registry or having used the treatment for at least 10 years since the opening of the registry), totalling 136,213 women, the standardised incidence ratio was 1.05 [0.97-1.11] for 6 months to 3 years of use, 1.31 [1.20-1.42] for 3 to 5 years, 1.72 [1.58-1.89] for 5 to 10 years and 2.07 [1.84-2.30] for 10 years or more. The standardised incidence ratio was higher on continuous combined HRT than on sequential HRT (1.24 versus 1.42 for 3 to 5 years, 1.78 versus 2.44 for 5 to 10 years). The standardised incidence ratio was higher on norethisterone than on medroxyprogesterone and dydrogesterone (1.34 versus 1.27 versus 1.22 for 3 to 5 years; 2.03 versus 1.64 versus 1.13 for 5 to 10 years). The increased standardised incidence ratio for the treatments using dydrogesterone was not statistically significant for any treatment duration but the number of treated women was low compared with the other two progestogens. There was no difference based on the oestrogen route of administration.

Tibolone

- Randomised study versus placebo of women having undergone surgery for breast cancer (contraindicated situation in the MA) and having hot flushes[52] - 2009 (level 1 evidence).

The primary efficacy endpoint for this study was the risk of breast cancer recurrence on treatment with tibolone at a dose of 2.5 mg/day.
A total of 3098 women were included in the analysis. For a median follow-up of 3.1 years, the relative risk of breast cancer was significantly higher in the women treated with tibolone: RR = 1.40 [1.14; 1.70].

- Cohort study (Million Women Study - United Kingdom) - 2011[44] (level 2 evidence).

For the women on tibolone treatment, the risk was not different to that observed with oestrogen-only or combined HRT: RR = 1.38 [1.25-1.52].

- Placebo-controlled study[53] - 2008 (level 2 evidence).

The objective of this study was to demonstrate the effect of tibolone treatment (1.25 mg/) on bone density and fracture risk. In total, 4,538 women aged between 60 and 85 years were included.
There was a reduced risk of invasive breast cancer in the treated group: HR = 0.32 [0.13; 0.80].

51 Lyytinen *H et al* : Breast Cancer Risk in Postmenopausal Women Using Estradiol-Progestogen Therapy. Obstetrics & gynecology, 2009:113, 1, 65-73
52 Kennemans P, Bundred N Foidart JM et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double blind, randomised, non-inferiority trial. Lancet Oncol 2009 Feb;10(2):135-46. doi: 10.1016/S1470-2045(08)70341-3. Epub 2009 Jan 23.
53 Cummings SR, Ettinger B, Delmas PD et al. The effects of tibolone in older postmenopausal women. NEJM. 2008: 359: 697-708

The study was stopped after 34 months of treatment (median duration) due to an increased risk of strokes in the treated group.
It should be noted that the dosage used in the study was half of what is shown in the tibolone MA (2.5 mg/day).

- Case-control study (Germany)[48] - 2008 (level 3 evidence).

The risk of invasive cancer was not significantly increased on tibolone.

Time between menopause and start of treatment

Oestrogen-only and combined HRT

- Cohort study (Million Women Study - United Kingdom) - 2011[44] (level 2 evidence).

The risk was significantly increased if the treatment was started less than 5 years after menopause compared with if it was started 5 or more years after menopause. It was 1.43 [1.36; 1.49] versus 1.05 [0.89; 1.23] for oestrogen-only HRT and 2.04 [1.97; 2.12] versus 1.53 [1.38; 1.69] for combined HRT. The mean treatment duration was longer when treatment was started early after menopause; however, the risk was higher in this case, whether the treatment duration was less than or more than 5 years.
The standardised incidence ratio in women aged 50 to 59 years was 0.30% [0.29; 0.31] for women who had never been treated; for women treated with oestrogen-only HRT, it was 0.43% [0.42; 0.45] if the treatment was started less than 5 years after menopause and insignificantly different compared with that of untreated women who started treatment 5 or more years after menopause: 0.32% [0.27; 0.37]. In women treated with combined HRT, the standardised incidence ratio was 0.61% [0.59; 0.64] and 0.46% [0.41; 0.51].
In women having discontinued treatment, the incidence rate reduced rapidly during the 2 years following interruption and the risk was then similar to that of women who had never been treated: 0.99 [0.93; 1.05].
The incidence rate increased with the BMI in women who had never been treated. The increased risk of breast cancer was proportionally higher in thin women: RR = 1.65 [1.53; 1.78] than in women who were overweight or obese: RR = 1.22 [1.13; 1.31] for women being treated compared with untreated women. For these two categories defined by the BMI, the risk was statistically higher if treatment started less than 5 years after menopause; the risk was not increased for women who were overweight or obese having started oestrogen-only HRT 5 years or more after menopause.
The authors concluded that the risk of breast cancer was higher in the users of combined HRT than oestrogen-only HRT and if the hormone therapy was started shortly after menopause.

Combined HRT

- Post-hoc analysis of the interventional and observational WHI studies (combined HRT) - 2008[54] (level 2 evidence).

This post-hoc analysis of the interventional study combined with the observational study aimed to study the influence of treatment prior to inclusion in the studies and the influence of the time between onset of menopause and the initiation of MHT on the risk of breast cancer.
This analysis was based on 16,608 women included in the interventional study and a corresponding subcohort from the observational study including 32,084 women, 25,328 of whom were not treated at inclusion and 6756 had identical treatment to that of the interventional study. The duration of follow-up was 5.5 years.
In the randomised study, for women not having taken MHT prior to inclusion, the risk of breast cancer on combined HRT compared with the placebo was significantly different (p=0.02) in women having started treatment within the 5 years following menopause (HR 1.77 (95% CI 1.07-2.93) and more the 5 years after menopause (HR 0.99 (0.74-1.31).
The combined analysis of both studies also concluded that there is an even higher risk when the treatment was started earlier after menopause, but the number of women having started combined

54 Prentice R *et al*. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. Am J Epidemiol. 2008 ; 167: 1207-16

HRT during the 5 years following menopause was low. The risk also increased with the treatment duration.

- Cohort study (E3N - France) - 2009[55] (level 2 evidence).

The Etude Epidémiologique des Femmes de la Mutuelle Générale de l'Education Nationale (an epidemiological study of women run by MGEN [General cooperative of national education]) is a prospective cohort study initiated in 1990 that included 98,995 women who are members of the MGEN, born between 1925 and 1950. The participants have been completing a biannual self-administered questionnaire since 1990.
This E3N cohort analysis looked for a relationship between the risk of breast cancer and the time between the date of menopause and the initiation of combined HRT ≤ 3 years or > 3 years. The oestrogen therapies were almost exclusively oestradiol, the most commonly used progestogens were progesterone and dydrogesterone; the other progestogens were mainly nomegestrol acetate and promegestone, followed by chlormadinone, norethisterone, medroxyprogesterone and cyproterone. The study focused on women whose age at the onset of menopause and age at the start of treatment were known and for whom follow-up data were available. The diagnosis of cancer was reported by the patients on the questionnaires sent twice yearly and in several cases, recorded from MGEN files or in the National database of causes of death, then confirmed by obtaining histopathology reports. Since the risk of breast cancer was not significantly increased in women having discontinued MHT for more than 1 year, regardless of the time between menopause and the start of treatment, the following analyses only concern data from women being treated or having discontinued treatment for at least 1 year. Between 1992 and 2005, 1726 invasive cancers were diagnosed out of 53,310 monitored women, with a mean follow-up duration of 8.1 years. The relative risks were analysed for the treatment durations ≤ 2 years, 2 to 5 years, 5 to 10 years and > 10 years.
For treatments including progesterone, the risk was not significantly increased if treatment was started ≤ 3 years after menopause and lasted less than 5 years and if treatment started > 3 years after menopause, regardless of duration. Conversely, the relative risks were significantly increased for treatment started ≤ 3 years after menopause and having lasted more than 5 years: RR = 1.47 [1.11; 1.95] for 5 to 10 years and RR = 1.92 [1.34; 2.74] for longer than 10 years. The increased risk depending on length of use was significant: p=0.002.
For treatments containing dydrogesterone, only the relative risk for treatments started > 3 years after menopause and having lasted between 5 and 10 years was statistically significant: RR = 1.77 [1.02; 3.09]
For treatments containing other progestogens (nomegestrol, promegestone, cyproterone acetate, chlormadinone, norethisterone, medroxyprogesterone, medrogestone), analysed together, if treatment was started ≤ 3 years after menopause, the relative risks were significantly increased regardless of the treatment duration. If treatment was started > 3 years after menopause, the relative risks were significant from 2 years of treatment.

Tibolone

- Cohort study (Million Women Study - United Kingdom) - 2011[44] (level 2 evidence).

The results with tibolone were similar to those from other treatments, however, with no significant difference between the risks: RR = 1.49 [1.33; 1.67] for the treatments started < 5 years after menopause and RR = 1.16 [0.92; 1.47] if the treatment was started ≥ 5 years after menopause.

Type of breast cancer

Oestrogen-only and combined HRT

- Cohort study (CPS II - USA) - 2009[56] (level 2 evidence).

55 Fournier A et al. estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment intiation influence risk. J Clin Oncol 2009; 27: 5138-43
56 Calle E. *et al*. postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype. Cancer. 2009. 936-944

This analysis focusing on the CPS II nutrition cohort aimed to study the relationship between the use of MHT (oestrogen-only or combined) and the risk of incident invasive lobular and ductal breast cancer.
The CPS II Nutrition cohort was initiated in 1992 and was formed by inviting members aged 50 to 74 years on this date, from the CPS II mortality prospective cohort initiated in 1982 by the American Cancer Society, to participate. The subjects who consented, completed a self-administered questionnaire and were included on the date of the questionnaire. The participants completed the questionnaires in 1997, 1999, 2001 and 2003. The incident cancers were identified either from the questionnaires and validated using medical records or cancer registries, or from cancer registries or death certificates. Information on the histological nature of the cancers was obtained from medical records or the cancer registries; mixed cancers were classified as lobular cancers. Information on the use of MHT was obtained from questionnaires. Data collection stopped on 30 June 2005. The analysis was adjusted for age, age at menopause, type of menopause, existence of a hysterectomy, mammogram, BMI and level of education.
In total, 68,369 post-menopausal women were included in the analysis; 3199 cases of incident invasive cancer were diagnosed, 1821 of which were ductal cancers and 471 were lobular cancers.
On oestrogen-only HRT, the relative risk of ductal cancer was not increased in the total population regardless of the treatment duration; however, this risk was increased in women whose BMI was < 25: RR = 1.28 [1.03; 1.60]. The relative risk of lobular cancer was 1.30 [0.94; 1.78], it was significantly increased from a duration of use of 10 years: RR = 1.59 [1.07; 2.35] for 10 to 19 years and RR = 1.58 [1.01; 2.47] for > 20 years.
On combined HRT, the risk of ductal cancer: RR = 1.75 [1.53; 2.01]; and lobular cancer: RR = 2.12 [1.62; 2.77] was significantly increased; for the two histological types, the risk was significant increased from a duration of use of 2 to 3 years.
The former users of combined HRT whose treatment duration was 5 years or more had an increased risk of ductal cancer during the 2 years following discontinuation: RR = 2.38 [1.50; 3.78]; the risk of lobular cancer was not increased.

- Post-hoc analysis of the interventional (level 2 evidence) and observational[57] (level 3 evidence) WHI studies - USA - 2013

These analyses concerning the risk of intraductal cancer involved 16,276 women included in the CEO + MPA study and 10,187 women included in the CEO-only study for the interventional studies.
The women included in the observational studies had participated in patient selection for the WHI studies but could not be included or refused to participate. From these, two subcohorts were defined: one corresponding to the CEO + MPA study and included women with an intact uterus, 30,421 taking the same treatment as that of the study and 23,926 not using hormone therapy at inclusion, the other corresponded to the CEO-only study and included women who had had a hysterectomy, 9462 taking the same treatment as that of the study and 9195 not taking treatment at inclusion. All these women must have had a mammogram within the 2 previous years and not have a history of cancer.
The CEO + MPA treatment period of the study was interrupted in 2002 after a mean duration of participation of 5.6 years and that of the CEO-only study was interrupted in 2004 after a mean participation duration of 7.1 years. Participant follow-up lasted until 30 September 2010.
In the interventional CEO + MPA study, the risk of intraductal cancer was not significantly increased during the interventional phase: RR = 1.29 [0.83; 2.02] nor during the post-treatment follow-up: RR = 1.23 [0.91; 1.64]. In the observational study, the risk was significantly increased: RR = 1.65 [1.25; 2.19] after adjustment for age, ethnicity, level of education, family history, Gail score, age at first menstrual period, parity, age at first childbirth, use of oral contraceptives, BMI, cigarette use, alcohol consumption, physical activity and history of an oophorectomy. There was not a significant trend for the risk to increase with treatment duration.
There was no significant change in risk on oestrogen-only HRT in the interventional study or the observational study.

57 Luo J *et al.* Effects of menopausal hormone therapy on ductal carcinoma in situ of the breast. Breast cancer res treat. 2013; 137: 915-25

- Cohort study (EPIC) - Europe[58] - 2012 (level 3 evidence).

This analysis aimed to study a possible association between the presence of hormone receptors in the tumour with BMI and a possible interaction of MHT.
Information on the use of HRT was collected at the time of inclusion: present or past use, name of proprietary medicinal products, oestrogen-only or combined HRT, sequential or continuous, age at start and duration of use.
The participants were recruited between 1992 and 2000 and data collection stopped between 2005 and 2010 depending on the centre.
Out of the 144,223 post-menopausal women included, 54.7% had never used MHT.
The analysis was stratified by the centre and age. In comparison to women who had never used MHT, the post-menopausal women using MHT at inclusion had a significantly increased risk for OR (oestrogen receptor)-PR (progesterone receptor)- tumours (Hazard ratio = 1.30 [1.05; 1.62] and for OR+PR+ tumours (HR = 1.74 [1.56; 1.95] p<0.001. The risk was significantly lower for the OR-PR- tumours than for the OR+PR+ tumours (p=0.035).

- Case-control study - USA - 2012[59] - (level 3 evidence)

This study aimed to evaluate the relationship between the menopausal hormone therapy regardless of its type and the occurrence of ductal in situ cancer. It was included in the meta-analysis of Ni. The incident cases were recorded amongst the women residing in Connecticut, aged at least 20 years and having had their diagnosis between 1994 and 1998. The cases were identified from the Yale University Cancer Centre and the Connecticut tumour registry. The diagnoses were confirmed by reviewing histopathology reports.
The controls were women living in Connecticut, selected randomly from a telephone list and matched on age. The pre-menopausal women (case or control) with a history of breast cancer or an unknown biopsy result were excluded.
Information on the medical history and the treatments were obtained through a telephone interview.
The analyses included 576 cases and 603 controls. They were adjusted for age, number of pregnancies, age at first childbirth, duration of menopause, family history of breast cancer, history of a breast biopsy or a mammogram. No relationship was revealed between taking oestrogen-only or combined MHT and the risk of ductal in situ cancer. The risk was also not changed by the treatment duration.

- Meta-analysis - 2012[60] - (level 3 evidence)

This publication with meta-analyses of published data aimed to assess the risk of in situ breast cancer on MHT.

  - Oestrogen-only HRT

    Five case-control studies and two cohort studies were included in the analysis. The tests were in favour of a publication bias and heterogeneity between studies. A random effects model analysis concluded that there is a significantly increased risk with current or previous use of MHT: RR = 1.25 [1.01; 1.55].
    After stratification on the study type, the risk was significantly higher in the case-control studies but not in the cohort studies.

  - Combined HRT

    Three case-control studies and one cohort study were included in the analysis. The tests were in favour of a publication bias and heterogeneity between studies.
    A random effects model analysis concluded that there is not an increased risk with current or previous use of MHT: RR = 1.55 [0.95; 2.51]. The risk was significantly increased when the treatment lasted > 5 years. RR = 1.37 [1.07; 1.75].

58 Ritte R, *et al*. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. Beast cancer research.2012:14:R16
59 Calvocoresi l, Stove MH, Carter D, Claus E B. Postmenopausal hormone therapy and ductal carcinoma in situ: a population-based case control study. Cancer epidemiol. 2012.36; 161-168
60 Ni X, et al. Postmenopausal hormone therapy is associated with in situ breast cancer risk. Asian Pac J Cancer Prev. 2012 ;13:3917-25

Combined HRT

- Cohort study (E3N - France) - 2008[61] (level 2 evidence).

This analysis focusing on the E3N cohort aimed to search for a possible relationship between the type of MHT and the risk of invasive breast cancer according to the histological type.

The cases of cancer were identified from patient declarations and for a small number from insurance files or information on deaths. The histopathological reports giving information on the histological type and the presence of hormone receptors were obtained for 96% of incident cancer cases which were classified as ductal, lobular (including mixed cancers, ductal and lobular) or others.

In total, 2355 primary invasive cancers were diagnosed for a follow-up of 653,125 person-years; for 2265 a histopathological report was available and for 1792, the hormone receptor status was known.

The analyses were adjusted for the time since menopause, age at first menstrual period, parity and age at first pregnancy carried to full-term, breastfeeding, age at menopause, type of menopause, personal history of benign breast disease, family history of breast cancer, height, BMI, physical activity, previous mammograms, place of residence at inclusion, period of inclusion, use of oral contraceptives, use of progesterone-only HRT during pre-menopause, year of birth.

The risk of breast cancer for ongoing or previous use of any kind of MHT was significantly increased compared with untreated women.

The risk of lobular cancer was significantly increased in women treated with oestrogen + dydrogesterone: RR = 1.7 [1.1; 2.6] and with oestrogen + progestogen other than progesterone or dydrogesterone: RR = 2.0 [1.5; 2.7], but not increased in women taking an oestrogen + progesterone combination, with significant heterogeneity between the treatments.

The risk of mixed ductal and lobular cancer was also increased for these treatments: RR = 3.8 [1.2; 12] with oestrogen + dydrogesterone and RR = 3.9 [1.6; 9.5] with oestrogen + progestogen other than progesterone or dydrogesterone, with no heterogeneity between the types of treatments.

The risk of ductal cancer was significantly increased in women treated with oestrogen + progestogen other than progesterone or dydrogesterone: RR = 1.6 [1.3; 1.6], unlike treatments with oestrogen + progesterone and oestrogen + dydrogesterone, with significant heterogeneity between the treatments.

The risk of OR+ cancer was increased for ongoing or previous use of any kind of MHT: RR = 1.4 [1.2; 1.6] for PR+ cancers and RR = 1.7 [1.3; 2.2] for PR- cancers. It was significantly increased for PR+ cancers in cases of oestrogen-only HRT: 1.5 [1.0; 2.1] and for the treatments with oestrogen + progestogen other than progesterone and dydrogesterone in cases of PR+ cancer: RR = 1.8 [1.5; 2.1] and PR-: RR = 2.6 [1.9; 3.5].

There was no increased risk of OR+ or - cancer with treatment combining oestrogen with progesterone or dydrogesterone. There was significant heterogeneity between the types of treatments for the OR+ PR+ and OR+ PR- cancers

There was a significant trend for the risk to increase with duration of treatment combining an oestrogen with progesterone for OR+/PR- cancers.

08.4 Venous thromboembolic risk

Oestrogen-only and combined HRT

- Cohort study (Million Women Study - United Kingdom)[62] - 2012 (level 2 evidence)

This analysis focused on the first diagnoses, after inclusion in the cohort, of pulmonary embolism or deep vein thrombosis at admission into hospital or as a cause of death. Follow-up started in 1997 and was completed at the end of 2002 or 48 months after the last information on the use of MHT. The analysis was stratified by geographical region and socioeconomic status. It was

61 Fournier A; *et al*. Use of Different Postmenopausal Hormone Therapies and Risk of Histology- and Hormone Receptor–Defined Invasive Breast Cancer. JCO 2008 ; 8: 1260-68.

62 Sweetland S. *et al.* Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J THromb Haemost. 2012 Sept 10 Epub

adjusted for age and BMI. Smoking, alcohol consumption, physical activity, use of oral contraceptives, history of a hysterectomy, myocardial infarction, heart failure, inflammatory bowel disease, respiratory failure, stroke or varicose veins have no influence on the results.
In total, 1,058,259 post-menopausal women were included in the analysis for a total follow-up of 3.3 million women-years.
Compared with women never having taken MHT, women having discontinued the treatment did not have an increased thromboembolic risk: RR = 0.95 [0.84; 1.08] and the risk did not change depending on the length of time since discontinuation.
The risk was significantly increased for all women being treated: RR = 1.59 [1.45; 1.75].
It was higher for women treated with oral oestrogens combined with a progestogen: RR = 2.07 [1.86; 2.32] than for women treated with oral oestrogen-only HRT: RR = 1.42 [1.22; 1.66].
Amongst the users of oral oestrogens combined with a progestogen, the risk was significantly higher ($p<0.0007$) with the combinations containing medroxyprogesterone RR = 2.67 [2.25; 3.17] than with those containing other progestogens (norethisterone or norgestrel): RR = 1.91 [1.69; 2.17].
On oral treatment, the risk was two times higher during the first 2 years than during subsequent treatment ($p<0.0006$).
The risk was not increased with transdermal oestrogen-only therapies: RR = 0.82 [0.64; 1.06] nor with transdermal oestrogens combined with a progestogen: RR = 1.06 [0.68; 1.65], however, in this case, with a larger confidence interval.

- Cohort study (LITE - USA) - 2010[63] (level 2 evidence).

The Longitudinal Investigation of Thromboembolism Etiology study aimed to study the thromboembolic risk in post-menopausal women based on the present exposure to MHT (oral oestrogen with or without combined progestogen) in pooled populations of two cohorts (ARIC and CHS) initiated in 1987-1989 and 1989-1990 respectively.
The diagnosis of deep vein thrombosis or pulmonary embolism had to be validated through imaging diagnostic tests read by two doctors. The cases were classified as idiopathic or secondary (associated with cancer, major trauma, surgery, immobilisation).
Median follow-up duration was 13.1 years for the ARIC cohort and 11.7 years for the CHS cohort.
In total, 190 cases were identified, 84 of which were idiopathic and 106 secondary.
The analysis of thromboembolic accident risk was adjusted for age, BMI, existence of diabetes and the factor VIII measurement.
The thromboembolic accident risk was statistically higher in women on oral oestrogen-only or combined HRT: RR = 1.60 [1.06; 2.36]; this risk was higher for the idiopathic thromboembolic accidents RR = 2.40 [1.40; 4.12] than for the secondary ones: RR = 1.08 [0.63; 1.85], without information on the significance of this difference between the relative risks.

- Nested case-control study (GPRD - United Kingdom) - 2010[64] (level 3 evidence).

This study was performed using the United Kingdom's General Practice Research Database which contains data from around 6 million patients, collected from general practitioners. Women with a history of thromboembolic accident before 50 years of age or at inclusion in the cohort were excluded. Information about MHT prescriptions during the year preceding the date of the event for the patients and for the controls were obtained from the patients' electronic medical records. The incidence rate ratios were adjusted for age, BMI and thromboembolic accident risk factors.
The cases of thromboembolic accidents (n = 23,505) occurring in women aged 50 to 79 years between 1 January 1987 and 1 March 2008 (n = 955,582) were identified. For each case, up to 10 controls were selected (n = 231,562). They were matched on age, general practitioner consulted and the year of the first consultation.

63 Ohira T *et al*. Reproductive history, hormone replacement and incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology. Br.J. Haematol. 2010. 149: 606-612.
64 Renoux C. et al. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost. 2010; 8: 979-86

The adjusted incidence rate ratio for the thromboembolic accidents compared with the absence of treatment was not increased on transdermal oestrogen with or without combined progestogen: RR = 1.01 [0.89; 1.16] and 0.96 [0.77; 1.20] and did not vary with the oestrogen dose.
The adjusted incidence rate ratio for thromboembolic accidents was increased on oral oestrogen with or without combined progestogen: RR = 1.49 [1.37; 1.63] and 1.54 [1.44; 1.65] and increased with the dose of oestrogens administered. The increased risk on oral treatment was greater during the first year of use and disappeared after 4 months of treatment discontinuation.

- Meta-analysis - 2008[65] (level 2 evidence)

This publication with meta-analyses of published data aimed to assess the risk of coronary heart disease (myocardial infarction, sudden death of cardiac origin, unstable angina), venous thromboembolic accident (deep vein thrombosis, pulmonary embolism, cerebral venous thrombosis) and stroke (including transient ischaemic attack) on MHT during randomised studies versus placebo or versus absence of treatment.

  - One meta-analysis concerning the venous thromboembolic risk included 22 randomised studies, including the two WHI studies. This risk was significantly increased on MHT: odds ratio = 2.05 [1.44; 2.92].
  - An analysis indirectly compared the effect of oestrogen-only HRT (6 studies) to that of oestrogen + progestogen HRT (12 studies). It revealed a significantly increased risk on combined HRT: OR = 2.02 [1.39; 2.92].
  - Subanalyses did not reveal any difference according to the type of oestrogen (conjugated or oestradiol), the route of administration of the oestrogens (transdermal with very few cases or oral) or the age group (over or under 60 years of age).
  - An analysis concerning the effect of MHT on the severity of venous thromboembolic accidents included three studies with three levels of severity (fatal thromboembolic accident, non-fatal thromboembolic accident, no thromboembolic accident): it did not reveal any significant effect on the severity (OR = 2.57 [0.73; 9.01]).

- Systematic review and meta-analysis of published data - 2008[66]
  - An analysis including nine randomised studies versus placebo (including the two WHI studies) confirmed the increased risk of thromboembolic disease on oral oestrogen HRTs: OR = 2.1 [1.4; 3.1] (level 1 evidence).
  - The risk of venous thrombosis and pulmonary embolism on oral oestrogen HRT was studied from seven case-control studies and one cohort study. Compared with untreated women, the risk of an initial thromboembolic episode was significantly increased: OR = 2.5 [1.9; 3.4]. The risk was significantly higher during the 1st year of treatment: OR = 4.0 [2.9; 5.7] than for treatments taken for longer than 1 year: OR = 2.1 [1.3; 3.8], p = 0.046. It was similar for the oral oestrogen-only or combined HRT: OR = 2.2 [1.6; 3.0] versus OR = 2.0 [2.0; 3.2] (level 3 evidence).
  - An analysis including four case-control studies assessed the risk of venous thrombosis and pulmonary embolism on transdermal oestrogen therapy. Compared with untreated women, the risk of an initial thromboembolic episode was not significantly increased: OR = 1.2 [0.9; 1.7] (level 3 evidence).
  - The effect of a thrombogenic mutation was studied in an analysis including four case-control studies and the two WHI studies. In the untreated women, the presence of a factor V Leiden or prothrombin G20210 A mutation increases the risk of thrombosis compared with non-carriers of the mutation: OR = 3.3 [2.6; 4.1]. The combination of the presence of a mutation and the administration of oral oestrogens with or without progestogen further increased the risk compared with untreated women with no mutation: OR = 8 [5.4; 11.9] (level 3 evidence).

65 Sare G *et al*. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. Eur heart J. 2008; 29: 2031-41

66 Canonico M et al. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008; 31: 1227-31

- The thromboembolic risk in overweight or obese patients (BMI > 25) was studied in a meta-analysis including one case-control study and the two WHI studies. Compared with untreated women with a normal weight, the women whose BMI was > 25 treated with oral oestrogens with or without progestogen had a higher risk OR = 5.4 [2.9; 10.0] than the untreated women. 2.6 [2.1; 3.3] (level 3 evidence).

- Systematic review and meta-analysis of published data - 2010.[67]

This publication is an update of a previous publication [66]. It included four additional cohort studies published since 2008. The authors also excluded four randomised studies included in the previous publication in which recurrences of thromboembolic accidents were recorded without sufficient information on the first thrombotic episode in order to limit the analysis to the risk of the first thromboembolic accident.

- A meta-analysis including the same seven case-control studies as in the previous publication studied the thromboembolic risk on oral oestrogen HRT. Compared with untreated women, the risk of an initial thromboembolic episode was significantly increased: OR = 2.1 [1.7; 2.6] (level 3 evidence).
- A meta-analysis including five cohort studies (the references of which are [63, 64, 68]) studied the thromboembolic risk on oral oestrogen therapy with or without combined progestogen. Compared with untreated women, the risk of an initial thromboembolic episode was significantly increased: OR = 1.4 [1.3; 1.5] (level 2 evidence).
- A meta-analysis including six randomised studies (all included in the previous publication) studied the thromboembolic risk on oral oestrogen therapy with or without combined progestogen versus placebo. It confirmed the increased risk of an initial thromboembolic episode on oral oestrogen HRTs: OR = 2.4 [1.9; 3.0] (level 1 evidence).
- A meta-analysis including four case-control studies and two cohort studies (the references of which are[64, 68]) studied the venous thromboembolic risk on transdermal oestrogen therapy with or without combined progestogen. Compared with untreated women, the risk of an initial thromboembolic episode was not significantly increased: OR = 1.0 [0.9; 1.1] (level 3 evidence).

Combined HRT

- Cohort study (E3N - France) - 2010[68] (level 2 evidence).

This analysis focusing on the E3N cohort aimed to study the thromboembolic risk on MHT depending on the oestrogen route of administration and the type of combined progestogen. The studied endpoint was the occurrence of an initial episode of idiopathic pulmonary embolism or deep vein thrombosis of the lower limbs (in the absence of cancer, surgery, immobilisation or trauma). The thromboembolic accidents reported by the participants had to be validated by imaging diagnostic tests with centralised reading. The cases of fatal pulmonary embolism were identified on death certificates by the Centre of Epidemiology on the medical causes of death (INSERM [National Institute of Health and Medical Research]) using the ICD-10 codes.

The patients participated in follow-up until the date of diagnosis, death, diagnosis of cancer other than basal-cell skin cancer, the last completed questionnaire or July 2005.

The final analysis focused on 80,308 post-menopausal women amongst whom 549 documented initial idiopathic thromboembolic accidents were diagnosed, 134 of which were pulmonary embolism and 415 deep vein thrombosis.

The analysis was adjusted for BMI, parity, level of education and the period (before or after 2003, to take into account the changes in MHT use after publication of the WHI study).

The mean age of the participants at inclusion was 54 years and the mean follow-up was 10.1 years.

67 Olié V *et al*. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. Current opin hematol; 2010; 17; 457-463

68 Canonico m *et al.* Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism : results from the E3N Cohort study. Arterioscler Thromb Vasc Biol. 2010;30: 340-345

The thrombotic risk was similar in women having never been treated (reference group) and those having discontinued their treatment.
Compared with the absence of treatment, oral oestrogens were associated with an increased thrombotic risk: RR = 1.7 [1.1; 2.8], unlike transdermal oestrogens: RR = 1.1 [0.8; 1.8]. In addition, amongst the treated women, the risk linked to oral oestrogens was significantly increased compared with transdermal oestrogens: RR = 1.5 [1.1; 2.0].
An additional analysis including 65 validated cases (including 38 fatal cases of pulmonary embolism) but with no available information on the risk factors produced similar results.
No significantly increased thrombotic risk was revealed on treatment combined with micronised progestogen: RR = 0.9 [0.6; 1.5], pregnane derivatives (dydrogesterone, medrogestone, chlormadinone acetate, cyproterone, medroxyprogesterone): RR = 1.3 [0.9; 2.0], and nortestosterone derivatives (norethisterone acetate): RR = 1.4 [0.7; 2.4] (however, with a lower number of presented cases than for the other progestogen categories).
The treatments combined with norpregnane derivatives (nomegestrol acetate and promegestone) were associated with a significantly increased risk: RR = 1.8 [1.2; 2.7].

08.5 Ischaemic cardiomyopathy

Oestrogen-only and combined HRT

- Open randomised study (Denmark) - 2012 (level 2 evidence)[69]

This study aimed to evaluatethe effect of MHT as a primary prevention of osteoporotic fractures. The occurrence of cardiovascular disease or cancer were pre-specified safety endpoints.
The primary endpoint of this analysis was composite: occurrence of death or hospitalisation for myocardial infarction or heart failure. The secondary endpoints were the isolated components of the primary endpoint or hospitalisation for stroke. The other safety endpoints were the occurrence of death or breast cancer or another cancer and hospitalisation for pulmonary embolism or deep vein thrombosis.
The included women were in good health, recently post-menopausal and aged 45 to 58 years.
Women with an intact uterus received sequential oral treatment: 2 mg oestradiol for 12 days, 2 mg oestradiol and 1 mg norethisterone acetate for 10 days and 1 mg oestradiol for 6 days. Women who had had a hysterectomy (n=95) received 2 mg of oestradiol per day. The study, which should have lasted for 20 years, was interrupted after 10 years due to publication of the WHI study results and the patients were advised to discontinue the treatment. They were then monitored through national registries providing information about death and contact with hospitals. Whether or not the treatment was continued during the follow-up period is not known.
The intention-to-treat analyses were performed at treatment discontinuation and 6 years of follow-up. No lost to view occurred.
In all, 502 women were included in the treated group and 504 in the untreated group. Their mean age was 50 years and they had been post-menopausal for 7 months.
At 10 years of treatment, the risk was significantly lower in the treated group for the primary efficacy endpoint (death, hospitalisation for myocardial infarction or heart failure): OR = 0.48 [0.26; 0.87]. There was no significant difference between the groups for each of the primary endpoint components taken separately, nor for the occurrence of cancer regardless of the type, breast cancer, stroke, or thromboembolic accident.
After a total of 16 years of follow-up, the risk was significantly lower in the treated group for the primary efficacy endpoint: OR = 0.61 [0.39; 0.94]. There was no significant difference between the groups for each of the primary endpoint components taken separately, nor for the occurrence of cancer regardless of the type, breast cancer, stroke, or thromboembolic accident.

69 Schierbeck L *et al*. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 2012; 345:e6409 doi: 10.1136

- Post-hoc analysis of the GUSTO-III study (USA) - 2010[70] (level 3 evidence).

This randomised study aimed to compare the efficacy of two thrombolytic treatments during the acute phase of myocardial infarction. The primary efficacy endpoint was mortality. The use of menopausal hormone therapy made up part of the data collected at the start of the study, without details concerning the duration of use, the type and doses of medicinal products used. This post-hoc analysis aimed to look for a possible influence of MHT on mortality rate after an infarction. The patients were included between 1995 and 1997; 4124 women of whom 3791 were post-menopausal; 10% of them were taking MHT.

The non-adjusted mortality rate was significantly lower in the women receiving MHT. However, after adjustment for the risk factors, existence of MHT was not a significant predictive factor of mortality.

- Cohort study (CTS - USA) - 2011[34] (level 2 evidence).

In this analysis of the CTS cohort performed at the same time as the study on mortality from any cause, the overall risk of death from ischaemic cardiomyopathy was significantly lower in women treated with MHT than in untreated women: RR = 0.84 [0.74; 0.95]. There was a very significant trend for the risk to increase with increasing age at inclusion (p=0.008). On analysis per age group, the risk was significantly lower in treated women than in untreated women aged 36 to 59 years: RR=0.38 [0.22; 0.67] and 60 to 64 years: RR = 0.53 [0.3; 0.93]. For the following age groups: 65-69, 70-74, 75-84 and 85-94, the risk was not significantly different.

- Cohort study (Denmark)[71] - 2012 (level 2 evidence)

This cohort study based on registries included all the Danish women aged 51 to 70 years between January 1995 and December 2001. Women having had cardiovascular disease or hormone-dependent cancer before inclusion were excluded from the analysis. In total, 698,098 women were included for a follow-up of 2,952,635 women-years. Exposure to MHT and the type of MHT throughout the duration of the study was documented from the national registry of prescriptions. The occurrence of an initial myocardial infarction was documented from the national registry of patients (hospitalisations) and from the national registry of causes of death. During the follow-up period, 4947 infarctions were identified.

The analysis was adjusted for age, calendar year, level of education, geographical region, existence of antiarrhythmic treatment, antihypertensives, treatment for diabetes or hyperlipidaemia. The menopausal status of the women was not known, in particular for women in the reference group who had never been treated.

The risk of a myocardial infarction was not significantly increased in treated women: RR = 1.03 [0.95; 1.11]. The risk was significantly reduced in women having discontinued treatment: RR = 0.81 [0.71; 0.93]. On analysis per age group, the risk was significantly increased in treated women aged 51 to 54 years: RR = 1.24 [1.02; 1.51], and significantly reduced in women aged 60 to 69 years having discontinued treatment; it was unchanged in the other age groups.

The risk was increased with continuous combined HRT: RR = 1.35 [1.18; 1.53], contrary to cyclical combined HRT: RR = 0.92 [0.81; 1.05], the two risks were significantly different (p<0.001).

The risk was reduced with transdermal oestrogen therapy: RR = 0.62 [0.42; 0.93] and significantly lower than the risk observed with oral oestrogen therapy (p<0.04). There was no difference in the risk between the oral and transdermal route for combined HRT. The vaginal oestrogen therapies were associated with a significantly reduced risk: RR = 0.56 [0.44; 0.71].

The risk did not change depending on the oestrogen dose, nor depending on the type of the progestogen (norethisterone, medroxyprogesterone or levonorgestrel).

- Systematic review - 2008[65] (level 2 evidence)

70 Tackett A. *et al*. Hormone replacement therapy among postmenopausal women presenting with acute myocardial infarction: insights from the GUSTO II trial. Am.Heart J. 2010; 160: 678-84.

71 Lokkegaard E. *et a*l. Hormone therapy and risk of myocardial infarction : a national register study. European Heart Journal;2008; 29: 2660-8

This publication aimed to assess the risk of coronary heart disease (myocardial infarction, sudden death of cardiac origin, unstable angina), thromboembolic accident (deep vein thrombosis, pulmonary embolism, cerebral venous thrombosis) and stroke (including transient ischaemic attack) on MHT during randomised studies versus placebo or versus absence of treatment.

- A meta-analysis concerning the coronary heart disease risk included 20 randomised studies, including the two WHI studies. This risk was not significantly increased on MHT: odds ratio = 1.00 [0.9; 1.11].
- An analysis compared the effect of oestrogen-only HRT (7 studies) to that of oestrogen + progestogen HRT (16 studies). No significant difference was revealed between the two types of treatment: OR = 1.16 [0.85; 1.53].
- Subanalyses did not reveal any risk difference according to the type of oestrogen (conjugated or oestradiol), its route of administration or the age group (over or under 60 years of age).
- Two analyses concerned the effect of MHT on the severity of the coronary heart disease: one included 5 studies covering 4 severity levels (fatal infarction, non-fatal infarction, unstable angina, no infarction), the other included 15 studies covering 3 severity levels (fatal infarction, non-fatal infarction, no infarction). None revealed a significant effect of MHT on the severity of the coronary heart disease: OR=1 [0.85; 1.17] and 1.04 [0.93; 1.17] respectively.

Combined HRT

- Post-hoc analysis of the combined HRT WHI study - 2010[72] (level 2 evidence).

This analysis aimed to assess the risk of coronary heart disease on equine oestrogen + medroxyprogesterone acetate HRT depending on its duration and time of initiation after menopause, compared with the placebo group. The analyses were adjusted for treatment adherence. The results are presented in *Table 7*.

Table 7: risk of coronary heart disease*

Duration of use	2 first years after inclusion	8 years
All patients	2.36 [1.55; 3.62]	1.69 [0.98; 2.89]
Duration of menopause at inclusion		
- < 10 years	1.29 [0.52; 3.18]	0.64 [0.21; 1.99]
- ≥ 10 years	2.82 [1.73; 4.60]	2.22 [1.20; 4.11]
Age at inclusion		
- 50-59 years	2.69 [1.14; 6.36]	1.47 [0.57; 3.77]
- ≥ 60 years	2.30 [1.43; 3.72]	1.76 [0.97; 3.19]

*: myocardial infarction with hospitalisation, silent infraction identified on ECG and death due to coronary heart disease.

The authors concluded that the risk of coronary heart disease was not reduced for the first 2 years of treatment, including for women having started treatment less than 10 years after menopause. A possible cardioprotective effect of the treatment in women having started treatment less than 10 years after menopause only became apparent after 6 years of use (crossing of the survival curves without coronary heart disease of the placebo and treated groups).

Tibolone

- Cohort study (Denmark)[71] - 2012 (level 2 evidence)

The risk of myocardial infarction on tibolone was not significantly altered: RR = 0.80 [0.54; 1.20].

08.6 Strokes

Oestrogen-only and combined HRT

- Cohort study (Nurse's Health Study - USA) - 2008[73] (level 2 evidence).

72 Toh S *et al.* Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear ?. Annals of internal medicine 2010; 152:211-217

73 Grodstein F *et al.* Postmenopausal hormone therapy and stroke. Arch. Int. Med. 2008; 168: 861-66

This cohort, initiated in 1976, included 121,700 American nurses aged 30 to 55 years having answered a postal questionnaire. Follow-up questionnaires were then sent to them every 2 years, with a response rate of at least 90% each time.
This analysis aimed to study the relationship between MHT and occurrence of fatal or non-fatal CVA, the cases of which were recorded between 1976 and 2004. Only CVAs verified on medical records were taken into account. The analysis was adjusted for age, BMI, cigarette use, history of hypertension, diabetes and hypercholesterolaemia, and family history of myocardial infarction before the age of 60.
Compared with women who had never used MHT, the women being treated with oestrogen-only HRT had a higher risk of CVA: RR= 1.39 [1.18; 1.63], as did the women treated with combined HRT: 1.27 [1.04; 1.56].
The time between the start of menopause and the initiation of treatment does not appear to influence the risk. For oestrogen-only HRT, the RR was 1.20 [1.06; 1.58] for the treatments started close to menopause and 1.31 [1.06; 1.63] for treatments started ≥ 10 years after menopause. For combined HRT, the RR was 1.22 [0.95; 1.55] and 1.18 [0.87; 1.60] respectively.
The CVA risk increased significantly ($p<0.001$) with the dose of oestrogens: the risk was not increased for women taking 0.3 mg/day: RR= 0.93 [0.62; 1.40] while it was significant for those taking 0.625 mg/day: RR= 1.54 [1.31; 1.81] and 1.25 mg/day: RR = 1.62 [1.23; 2.14].

- Nested case-control study (UGPRD - United Kingdom) - 2010[74] (level 3 evidence).

This study performed from the United Kingdom's General Practice Research Database studied the risk of stroke depending on the oestrogen route of administration.
The initial stroke cases (n = 15,710) occurring in women aged 50 to 79 years between 1 January 1987 and 1 March 2008 (n = 870,286) were identified. For each case, up to four controls were selected (n = 59,958). They were matched on age, general practitioner consulted and the year of the first consultation.
The MHT prescriptions during the year preceding the date of the event for the patients and for the controls were identified from the patients' electronic medical records.
The incidence rate ratios were adjusted for age, BMI, stroke risk factors, use of aspirin or NSAIDs, history of a hysterectomy or an oophorectomy.
The annual incidence of strokes in the cohort was 2.85/1000.
The incidence rate ratio on transdermal oestrogen therapy with or without progestogen compared with the absence of treatment was 0.95 [0.75; 1.20]. The stroke risk was not increased for the low-dose transdermal oestrogens (≤ 50 µg): rate ratio was 0.81 [0.62; 1.05]. The risk was increased with higher doses (> 50 µg): rate ratio = 1.89 [1.15; 3.11]. The publication does not mention if the risk difference between the two doses was significant.
The oral therapy users had a higher incidence rate than the non-users: rate ratio: 1.28 [1.15; 1.42]. The incidence rate ratio for the low-dose oral HRT (≤ 0.625 CEO or 2 mg oestradiol) was 1.25 [1.12; 1.40] and for the higher doses (> 0.625 CEO or 2 mg oestradiol) 1.48 [1.16; 1.90]. The direct comparison of the transdermal and oral administration routes revealed a lower stroke risk on transdermal treatment than on oral treatment (rate ratio: 0.74 (0.58-0.95)

- Systematic review 2008[65] (level 2 evidence).

This publication aimed to assess the risk of coronary heart disease (myocardial infarction, sudden death of cardiac origin, unstable angina), thromboembolic accident (deep vein thrombosis, pulmonary embolism, cerebral venous thrombosis) and stroke (including transient ischaemic attack) on MHT during randomised studies versus placebo or versus absence of treatment.

- An analysis indirectly compared the effect of oestrogen-only HRT (8 studies) to that of oestrogen + progestogen HRT (14 studies). No significant difference was revealed between the two types of treatment: OR = 0.93 [0.70; 1.22].
- An analysis concerning the stroke risk included 18 randomised studies, including the two WHI studies. This risk was significantly increased on MHT: odds ratio = 1.32 [1.14; 1.53].

74 Renoux C. *et al.* transdermal and oral hormone replacement therapy and the risk of stroke : a nested case-control study. 2010 Jun 3;340:c2519. doi: 10.1136/bmj.c2519.

- Two analyses concerned the MHT effect on the severity of strokes. One included 4 studies with 4 severity levels (fatal CVA, non-fatal CVA, transient ischaemic attack, no CVA): no significant effect was revealed on the severity (OR = 1.10 [0.91; 1.33]). The other included 10 studies with 3 levels of severity (fatal CVA, non-fatal CVA, no CVA): the severity was significantly higher on MHT: OR = 1.31 [1.12; 1.54].
- Subanalyses did not reveal any difference according to the type of oestrogen (conjugated or oestradiol), the route of administration of the oestrogens or the age group (over or under 60 years of age).

Tibolone

- Placebo-controlled study[53] (level 2 evidence)

The objective of this study was to demonstrate the effect of tibolone treatment on bone density and fracture risk. In total, 4,538 women aged between 60 and 85 years were included. It should be noted that the dosage used in this study was half of that shown in the tibolone MA (2.5 mg/day).
The study was stopped after 34 months of treatment (median duration) despite a reduction in the risk of vertebral and non-vertebral fractures, due to an increased risk of strokes in the treated group: RR = 2.19 [1.14; 4.23].

08.7 Cognitive function

Oestrogen-only HRT

- Placebo-controlled study - 2008[75] (level 2 evidence)

This controlled, randomised, double-blind study with low numbers, evaluated the effect of 2 mg/day of oral oestradiol (n = 34) versus placebo (n= 31) for 12 weeks on cognitive function and menopausal symptoms in post-menopausal women aged 48 to 65 years without cognitive impairment or depression. There was no difference between groups for the psychometric tests or for the Hamilton Rating Scale for Depression. The only result which was statistically different between groups was reduction of the menopausal symptoms measured using the Greene scale.

- Controlled study - 2011[76] (level 2 evidence)

This controlled, randomised, double-blind study with low numbers evaluated the effect of conjugated equine oestrogen 0.625 mg mg/day (n = 27) versus placebo (n=32) for 6 months on the verbal memory of post-menopausal women having had a hysterectomy. The mean age of the included women was 50 ± 3.2 (43 to 56 years). No clinically significant improvement of verbal memory was revealed on oestrogens compared with placebo.

- Placebo-controlled study - WHISCA oestrogen-only - 2009[77] (level 1 evidence)

This study involved some of the patients from the WHI study included in the WHIMS study (Women's Health Initiative Memory Study) and having undergone a more detailed annual cognitive assessment (Women's Health Initiative Study of Cognitive Aging: WHISCA). These patients were aged 65 to 79 years at inclusion in the WHI study and had no signs of dementia. The WHISCA study started after the WHI study randomisation. The patients involved had therefore undergone their initial WHISCA study tests 1.1 to 5.6 years after the start of their treatment (mean of 3 years). The aim of this analysis was to study the effect of oestrogen-only HRT versus placebo.
In total, 886 women consented to participate in this study, 434 on active treatment (CEO) and 452 on placebo; 326 women in the treated group and 325 in the placebo group had the four annual assessments planned. The women included in the treated group had worse results than the placebo group for the mental rotation test during the initial study tests which were after 3 years of treatment. This difference was then increased during the following 2.7 years of treatment. Overall, there was no significant difference concerning cognitive function between the groups.

75 Marinho R. *et al.* Effect of estradiol on the cognitive function of postmenopausal women. Maturitas 2008; 60: 230-4
76 Gorenstein C. *et al.* Estrogen replacement therapy and cognitive functions in healthy postmenopausal women: a randomized trial. Arch Womens Ment Health. 2011; 14: 367-373
77 Resnick S.M. *et al.* Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. J Clin Endocrinol Metab. 2009; 11: 4152-4161

- Cross-sectional study - 2011 (level 4 evidence)[78]

This study with low numbers compared the effect of oestradiol (n = 43) and conjugated equine oestrogen (n = 25) on cognition in women treated for at least 1 year and aged 49 to 68 years. The studied areas were attention, verbal memory, working memory, visual memory, and spatial ability.
The patients had no cognitive disorder and had risk factors for Alzheimer's disease (history in a first-degree relative, presence of APOE ε4 allele, history of depression or bipolar disorder, hypothyroidism).
The patients treated with oestradiol had significantly better results for verbal memory.

Oestrogen-only and combined HRT

- Oestrogen-only and combined HRT WHISCA study with post-treatment follow-up[79] (level 1 evidence for the first period, level 2 evidence for the follow-up period).

This publication included results recorded during the WHISCA study and up to 5 years of follow-up after this study. In total, 2304 women consented to participate in this study, 1125 on active treatment (CEO or CEO + MPA) and 1179 on placebo; 955 women in the treated group and 978 in the placebo group participated in post-treatment follow-up; on the date when data collection stopped, 601 women from the treated group and 612 from the placebo group had had one test in 18 months. For the women in the CEO + MPA study, the mean duration of treatment was 5 years and the mean duration of follow-up after treatment was 4 years. For the women in the CEO study, the mean duration of treatment was 6.6 years and the mean duration of follow-up after treatment was 2.4 years.
The authors concluded that in the treated groups, a slight reduction in cognitive function was observed which persisted after treatment discontinuation with differences which were small, undetectable or without clinical significance on an individual level.

- Placebo-controlled study - 2011 (level 4 evidence)[80]

This comparative, randomised, double-blind study with low numbers aimed to study the efficacy of MHT in post-menopausal women with mild to moderate Alzheimer's disease.
The 43 patients were divided into five groups: 1) transdermal oestradiol 50 µg/day + placebo, 2) transdermal oestradiol 50 µg + MPA 2.5 mg/day, 3) transdermal oestradiol 100 µg/day + placebo, 4) transdermal oestradiol 100 µg/day + MPA 2.5 mg/day, 5) placebo patch + placebo tablet.
The study should have lasted for 1 year. However, due to a study withdrawal rate of 49% by this date, the results were examined after 3 months of treatment.
The comparison of treated groups as a whole compared with the placebo group (n=8) concluded that there was a significant improvement of visual memory and semantic memory.

- Cohort study - USA - 2008[81] (level 2 evidence)

The participants were recruited from amongst the members of a Californian health insurance plan, aged at least 75 years in 1988 and having been affiliated continuously since 1992. The electronic prescription data were used to identify the users and non-users of MHT. The users were defined as having had at least one prescription recorded each year between 1992 and 1998. The non-users were defined as not having had any prescription during the same period and were matched on age and code number with the MHT users. Only the women having answered a telephone questionnaire and not having dementia at inclusion in 1999 were included. They then had an annual telephone interview until the end of the study (31 December 2003), their death or a

78 Wroolie T. *et al.* Difference in verbal memory performance in postmenopausal women receiving hormone therapy: 17β-estradiol versus conjugated equine estrogens. Am. J Geriatr. Psychiatry; 2011: 19: 792-802
79 Espeland M.A. *et al.* Long-term effects of conjugated equine estrogen therapies on domain-specific cognitive function : results from the Women's Health Initiative Study of Cognitive Aging Extension. J Am Geriatr Soc. 2010; 58: 1263-71
80 Wharton W. *et al.* Short- term hormone therapy with transdermal estradiol improves cognition for postmenopausal women with Alzheimer's disease: results of a randomized controlled trial. Journal of Alzheimer disease. 2011; 26: 495-505
81 Petiti DB, Crooks VC, Chiu V *et al.* Incidence of dementia in long – term hormone users. Am J Epidemiol..2008; 167: 692-700

diagnosis of dementia. In total, 2906 women were included (mean age at the start of the study was 78.7 ± 3.2 years), 1519 of which were users. The mean duration of treatment at inclusion was 30.5 years for the users of oestrogen-only HRT and 23.2 years for combined HRT; the most commonly used treatments were equine oestrogens and medroxyprogesterone acetate.
After adjustment for age, level of education and medical history, relative risk of dementia was not significantly increased in treated women; it was 1.23 [0.94; 1.59] in oestrogen-only HRT users and 1.34 [0.95; 1.89] in users of combined HRT.

- Cohort study (KPNC - USA) - 2011[82] (level 2 evidence).

This cohort includes women members of a health system, the Kaiser Permanent Medical Care Program of Northern California, who have participated in regular health assessments between 1964 and 1973 while they were aged 40 to 55 years.
This analysis only included women having declared to be post-menopausal during follow-up, still members of the health system in 1994 and not having being diagnosed with dementia before 1999, which totalled 5504 women. The women were considered to be taking MHT if they declared that they were taking a hormone therapy, while they were not taking thyroid hormones and did not report endocrine disease. From 1994 to 1998, the MHT prescriptions were identified from a pharmaceutical database. All treatments were included apart from topical vaginal treatments. Women having had two prescriptions or more between 1994 and 1998 were considered as long-term users.
The dementia diagnoses were collected from medical records, including Alzheimer's disease and vascular dementia between 1999 and 2008, while the participants were aged from 75 to 84 years at the time of diagnosis. Women having had a diagnosis before 1999 were not included in the analysis.
The analysis was adjusted for age, level of education, ethnicity, BMI at 50 years of age, number of children, existence of diabetes, hypertension, hyperlipidaemia, stroke. 27% of participants (n=1524) had had a diagnosis of dementia between 1999 and 2008 at a median age of 80.4 years.
The use of MHT only around the age of 50 was associated with a reduction in the relative risk of dementia: RR= 0.74 [0.58; 0.94] compared with women having never used MHT. Conversely, the late use of MHT was associated with an increased risk: RR = 1.48 [1.10; 1.98].
A sensitivity analysis was stratified by existence of a CVA, these being highly predictive of dementia and previous studies having concluded that there is an increased risk of CVA on MHT. However, in the case of late use of MHT, the relative risk of dementia was significantly increased in women having had a CVA: RR = 1.63 [1.16; 2.31] while it was not in women never having had a CVA: RR = 1.15 [0.64; 2.05]. Women having used MHT during the two periods did not have an increased risk compared with women who had never used it.

- Cohort study (LAW study - Australia) 2010[83] (level 2 evidence).

The women included in this analysis were participating in a cohort, the Longitudinal Assessment of Ageing in Women Study, residing in an urban community and aged 40 to 80 years. The women having been treated for at least 1 year during the observation period were considered as users, separating those having started their treatment ≤ or > 3 years after menopause.
Each woman answered psychometric tests during two examinations 5 years apart: Mini-Mental State, National Reading Adult Test and Wechsler Memory Scale version 3. A change of ≥ 10% of a test score was considered to be clinically significant.
The analysis was adjusted for age, BMI, physical activity, cigarette use and alcohol consumption.
In total, 410 women were included, 213 of whom had never taken MHT, 197 having started treatment ≤ 3 years after menopause and 39 having started > 3 years after menopause.
Only women treated with oestrogen-only HRT and having started their treatment within 3 years following menopause (n=68) had a significantly reduced risk of MMS score modification: RR= 0.28 [0.08; 0.97] (significant difference compared with the other groups p =0.005).

82 Whitmer R. *et al*. Timing of hormone therapy and dementia : the critical window theory revisited. Ann Neurol. 2011; 69: 163-169
83 Khoo S. *et al*. Postmenopausal hormone therapy and cognition : effects of timing and treatment type. Climacteric. 2010; 13: 259-64

Women treated with combined HRT and having started their treatment within 3 years following menopause (n=90) had a significantly increased risk of WMS score modification: RR= 3.44 [1.21; 9.81] (significant difference compared with the other groups p =0.005).

- Cochrane systematic review - 2008[84] (level 1 evidence).

This systematic review of published data aimed to study the effect of MHT: oestrogen-only or combined with progestogens, compared with a placebo during randomised, double-blind studies concerning cognitive function of post-menopausal women and involving treatment of at least 2 weeks. In total, 16 studies (including the two WHI studies) having included 10,114 women were selected; the meta-analyses did not reveal prevention of cognitive function decline after 4 or 5 years of treatment with oestrogen-only or combined HRT: OR=1.34 [0.95; 1.9] and OR = 1.05 [0.72; 1.17] respectively. According to the analyses focusing on the effect of treatment over time, the oestrogen-only and combined HRTs did not maintain or improve cognitive function and could even have a negative effect on this endpoint (mean weighted difference = -0.45 [-0.99; 0.09] and = 0.16 [-0.58; 0.26] respectively at the end of follow-up). The negative effect was revealed for oestrogen-only HRT after 1 year and for combined HRT after 3 and 4 years. The results of smaller studies on the effect on individual cognitive domains for the most part did not provide any evidence of benefit.

- Cochrane systematic review - 2009[85] (level 1 evidence).

This systematic review aimed to study the effect of MHT: oestrogen-only or combined with progestogens, compared with a placebo during randomised, double-blind studies concerning cognitive function of post-menopausal women with dementia and involving treatment of at least 2 weeks. A total of seven studies having included 351 women were selected.
The results of the meta-analyses of published data were discordant according to the endpoints, the treatment durations and the doses used. This review did not enable a conclusion to be drawn on the usefulness of MHT in post-menopausal women with dementia.

- Systematic review - 2010[86] (level 4 evidence).

This systematic review of published data aimed to study the effect of MHT on the maintenance of cognitive function in post-menopausal women. It included 38 randomised studies including the two WHI studies. The analyses taking into account all the tests performed in all the studies did not reveal any influence of the menopausal therapies on cognitive function.
It did not reveal an influence of age at the start of treatment or time between menopause and treatment initiation, contrary to its duration: positive effects were noted, especially in the short studies (> 4 months) while negative effects were noted in the long studies and with combined HRT, especially including medroxyprogesterone acetate.

Combined HRT

- Placebo-controlled study - 2011 (level 4 evidence)[87]

This randomised, double-blind study with three groups of low numbers compared the effect on cognition of conjugated equine oestrogen + placebo (n=7), + medroxyprogesterone (n=9), + micronised progesterone (n=8) combinations administered for 12 weeks in post-menopausal women. The studied areas were mood, verbal memory, working memory, and spatial ability.
There was a significant reduction of verbal memory in the CEO + MPA group. The patients treated with CEO + MPA had significantly better results than the other groups for working memory.

84 Lethaby A *et al.* Hormone replacement therapy for cognitive function in postmenopausal women. Cochrane database of systematic review 2008, Issue 1
85 Hogervorst E. *et al*. Hormone replacement therapy to maintain cognitive function in women with dementia. Cochrane database of systematic review 2009, Issue 1
86 Hogervorst E *et al*. .Sex steroids to maintain cognitive function in women after the menopause: a meta-analyse of treatments trials. Maturitas. 2010; 66: 56-71
87 Sherwin *et al.* Differential effects of estrogen and micronized progesterone or medroxyprogesterone acetate on cognition in postmenopausal women. Fertility and Sterility;2011; 96: 399-403

08.8 Osteoporotic fractures

Oestrogen-only and combined HRT

- Cohort study (E3N - France) - 2011[88] (level 2 evidence).

This analysis of the E3N cohort focused on women presenting an osteoporotic fracture (low-energy fracture apart from fractures of the ribs, fingers and face, and occurring after menopause). Women having had several fractures were recorded for a single site according to the following hierarchy: femoral neck, vertebra, shoulder, leg, foot, ankle, wrist and arm. A series of analyses were performed on all the osteoporotic fractures and another on the wrist, vertebral and femoral neck fractures, considered as severe osteoporotic fractures.

The participants contributed to follow-up from the date of their inclusion or menopause until the occurrence of an osteoporotic fracture, the date of the most recent questionnaire or a diagnosis of any form of cancer.

In total, 5589 fractures occurring in a population of 78,182 women totalling a follow-up of 808,525 women-years were included in the analysis; amongst these fractures, 2235 were severe osteoporotic fractures.

A significant reduction of the osteoporotic fracture risk: HR=0.78 [0.73; 0.83] and severe osteoporotic fracture risk: HR=0.70 [0.63; 0.77] was observed in women being treated compared with those who had never been treated. There was a significant difference (p=0.03) of the osteoporotic fracture risk depending on the route of administration in women being treated: HR=0.69 [0.63; 0.77] for oral administration and HR=0.78 [0.72; 0.83] for transdermal administration. No significant difference in risk was found depending on the route of administration for severe osteoporotic fractures.

In women having discontinued treatment, the reduction of the risk persisted for the 5 years following discontinuation for severe osteoporotic fractures: HR=0.85 [0.73; 0.99]. There was an inverse relationship between the fracture risk and the treatment duration; this relationship was significant for women being treated and for women having discontinued treatment for 5 years or more; the women having used the treatment for at least 5 years and having interrupted MHT for 5 years or more preserved a significant reduction of the risk of a severe osteoporotic fracture compared with women who had never been treated: HR=0.83 [0.69; 0.99].

There was no significant difference in the fracture risk depending on the route of administration (oral or transdermal) in women having discontinued treatment.

Tibolone

Placebo-controlled study[53] (level 1 evidence)

The main objective of this study was to demonstrate the effect of tibolone treatment (1.25 mg/day, which is half the dose shown in the tibolone MA) on bone density and fracture risk. The included women were aged 60 to 85 years and had a T-score less than or equal to -2.5 at the hips or lumbar vertebrae, or less than or equal to -2 in cases of radiologically confirmed vertebral fracture. In total, 4538 patients were included.

The study was stopped after 34 months of treatment (median duration) due to an increased risk of strokes in the treated group.

At the end of treatment there was a significant reduction of the vertebral fracture risk (HR =0.55 [0.41; 0.74] and non-vertebral fracture risk (HR=0.74 [0.58; 0.93]).

08.9 Quality of life - Menopausal symptoms

Oestrogen-only HRT

- Placebo-controlled study - sexuality - 2008[89] (level 2 evidence).

This randomised, controlled, double-blind study comparing the effect of a patch providing 14 µg/day of oestradiol (n=208) with a placebo (n=209) for 2 years had as a secondary endpoint the

88 Engel P. et al. Risk of osteoporotic fractures after discontinuation of menopausal hormone therapy: results from the E3N cohort.Am.J.Epidemiol. 2011; 174: 12-21

89 Huang A *et al.* The effect of ultralow dose trandermal estradiol on sexual function in postmenopausal women. Am J Obste t Gynecol 2008; 1978:265e1-265.e7

evaluation of sexual function of post-menopausal women with a mean age of 66.7 years (60-80 years). The primary study endpoint, bone density, was the subject of a previous publication.
The final evaluation focused on the sexually active patients which was 44% of the included population.
The only endpoint for which a significant difference between groups was noted (4.3 points, p<0.04) was dyspareunia and vaginal dryness, evaluated using a visual analogue scale from 0 to 100 points.

Combined HRT
Placebo controlled study - quality of life - 2008[139] (level 2 evidence).
The WISDOM study aimed to evaluate the risks and benefits of long-term MHT (conjugated equine oestrogen combined with medroxyprogesterone) versus placebo. The study was ended prematurely in 2002 after a median follow-up duration of 1 year due to interruption of the WHI study. One of its aims was to evaluate the effect of treatment on the quality of life of post-menopausal women.
The included women did not necessarily have menopausal disorders: only 30% of the women in the treated group and 29% in the placebo group had hot flushes at inclusion; their mean age was 63.8 years. The data from 1191 women/1856 in the treated group and 1193/1857 in the placebo group were analysed (after exclusion of deaths, six in the treated group and two in the placebo group and women with less than 40 weeks of follow-up); the most common reasons for treatment discontinuation were bleeding (32%) and mastalgia (13%).
After 1 year of treatment, there was a significant difference between the groups for vasomotor symptoms (9% versus 25%, p<0.001), night sweats (14% versus 23%, p<0.001), muscle or joint pains (57% versus 63%, p=0.001), insomnia (35% versus 41%, p<0.001) and vaginal dryness (14% versus 19%, p<0.001).
Mastalgia (16% versus 7%, p<0.001) and leucorrhoea (14% versus 5%, p<0.001) were more common in the treated group.
The quality of life assessment was performed using a visual analogue scale scored from 0 to 100 assessing the overall state of health of patients. The results were significantly worse in the treated group at 4 and 14 weeks. There was then no longer any difference between groups until the end of the study (three evaluations).

Tibolone
- Cochrane systematic review (level 1 evidence)[90] - 2012

This systematic review compared the efficacy and safety of combined HRT and tibolone in the treatment of menopausal symptoms.
- The combined HRT was more effective than tibolone at a dose of 2.5 mg/day in reducing vasomotor symptoms (two studies): OR = 4.16 [1.50; 11.58].
- Metrorrhagia was less severe on tibolone at a dose of 2.5 mg/day than on combined HRT (15 studies, however, with significant heterogeneity): OR = 0.35 [0.26; 0.46].

08.10 Endometrial hyperplasia/cancer

Oestrogen-only and combined HRT
- Cohort study (Italy)[42] - 2008 (level 2 evidence)

This study revealed that there was a significant trend for the risk to reduce with increasing treatment duration.

- Cohort study (Nurses' Health Study - USA)[91] - 2010 (level 2 evidence)

Only the cases of type 1 invasive endometrioid adenocarcinoma confirmed in the medical records (88% of the total number of cases) were included in this analysis. For a mean follow-up of 19.3

90 Formoso G *et al.* Short and long term effects of tibolone in postmenopausal women (review). *Cochrane database of systematic reviews 2012, Issue 2*
91 Karageorgi S. et al. Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976 – 2004. Int J. Cancer. 2010; 126: 208-16

years, 778 cases were identified, 658 of which were in post-menopausal women. The analysis was adjusted for age, parity, age at first and last childbirth, duration of taking oral contraceptives, BMI, tobacco use, diabetes, family history of endometrial cancer, and age at menopause and first menstrual period.
Compared with women never having used MHT, the risk was significantly increased in women using or having used oestrogen-only HRT: RR = 2.78 [2.17; 3.57] or combined HRT: RR = 1.33 [1.01; 1.75].
Amongst the types of combined HRT, the risk was significantly increased with sequential combined HRT including 1 to 8 days of progestogen: RR = 3.00 [1.43; 6.28]. The risk was not significantly increased with sequential combined HRT containing 9 to 18 days of progestogen: RR=1.25 [0.76; 2.04] nor with continuous combined HRT: RR = 1.34 [0.88; 2.04].

- Cohort study (CTS - USA) - 2010[92] (level 2 evidence).

In total, 28,418 post-menopausal women (no menstruation for at least 6 months, oophorectomy or aged 56 years or over) participating in this cohort were included in an analysis studying the risk of endometrial cancer with obesity and combined or oestrogen-only HRT; 395 of them had type 1 invasive endometrial cancer. Data collection stopped on 31 December 2006; the follow-up duration was calculated from the date of the initial questionnaire until the diagnosis of endometrial cancer, death, permanent departure from California or the date of the database lock. The relative risk calculation was stratified by age at inclusion and adjusted for age at first menstrual period, parity, age at first pregnancy, use of oral contraceptives and its duration, physical activity, height, existence of hypertension and its interaction with age during follow-up; for the groups receiving MHT, the relative risks were adjusted for its duration and its interaction with age.
Women treated or having been treated with oestrogen-only HRT had a higher risk than those who had never been treated: RR= 2.2 [1.7-2.9]; the women treated with combined HRT also had a slightly higher risk: RR = 1.4 [1.1-1.8].
Obesity (BMI ≥30 versus <25) was associated with a significantly increased risk of endometrial cancer: RR= 1.9 [1.5-2.5] for all the included women. This increased risk was more pronounced in the women who had never taken MHT: RR = 3.5 [2.2 -5.5]. For oestrogen-only HRT, the relative risk was increased for the overweight or obese women (BMI ≥25 versus <25): RR = 1.6 [1.1-2.3]. For combined HRT, the relative risk was not increased for the overweight or obese women.
The authors concluded that obesity was strongly associated with a risk of endometrial cancer in women who had never used MHT: on the contrary, obesity was not associated with an increase in this risk for women treated with combined HRT.

- Cohort study (EPIC - Europe) - 2010[93] (level 3 evidence).

This analysis aimed to study the risk of endometrial cancer on different types of MHT.
The cases of endometrial cancer were identified according to the country using links to cancer registries or using a combination of methods including links with health insurance systems, cancer registries, or disease registries and active follow-up of participants.
The participants were recruited between 1992 and 2000 and the data collection stopped between December 2003 and November 2006 depending on the centre. The diagnosis of endometrial cancer was based accordingly on a histology report, physical examination, declaration by the patients or an autopsy report.
The analysis was stratified by centre and age, and adjusted for BMI, parity, age at menopause and use of oral contraceptives.
Amongst the 115,474 women included, 601 had endometrial cancer during the follow-up which lasted 9 years on average.
Women being treated with oestrogen-only HRT had a higher risk than those who had never used MHT: RR= 2.52 [1.77-3.57]; this risk increased significantly (p for trend = 0.02) with duration of use: RR= 1.84 [0.88-3.83] for treatment < 2 years, RR= 2.59 [1.32-5.07] for treatment ≥ 2 years.

92 Canchola A.J. *et al*. Body size and the risk of endometrial cancer by hormone therapy use in postmenopausal women in the California teachers study cohort. Cancer causes control/ 2010 ;21: 1407-16
93 Allen N. *et al*. menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the european prospective investigation into cancer and nutrition. Am. J. Epidemiol. 2010; 172: 1394-1403

The ongoing use of combined HRT was associated with a higher risk than the absence of treatment: RR= 1.41 [1.08-1.83]; the use of sequential combined HRT was associated with an increased risk: RR= 1.52 [1.00-2.29]; the use of continuous combined HRT was associated with an reduced risk: RR= 0.24 [0.08-0.77], with a significant difference between the two groups; however, this result is only based on three cases. Treatments containing micronised progesterone were associated with a significantly increased risk: RR= 2.42 [1.53-3.83] while treatments containing a progesterone derivative: RR= 1.23 [0.84-1.79] or testosterone derivative RR= 1.09 [0.74-1.61] were not associated with a significantly increased risk, with a significant difference between the groups.

- Cochrane review - 2009[94] (level 1 evidence).

The objective of this review of published data was to assess the effect of different types of menopausal hormone therapy on the risk of hyperplasia and/or cancer, diagnosed by endometrial biopsy. The included studies were randomised versus placebo or compared different treatments with each other, with a minimum duration of 1 year.
The authors concluded that treatment with oestrogen-only HRT increased the risk of endometrial hyperplasia regardless of the dose and treatment duration between 1 and 3 years. For women who had an intact uterus, the risk of endometrial hyperplasia with continuous combined HRT including a low-dose oestrogen and a minimum dose of 1 mg of norethisterone acetate or 1.5 mg of medroxyprogesterone acetate was not significantly different from the risk on the placebo.

- Meta-analysis - 2010[95] (level 3 evidence).

This meta-analysis of published data aimed to evaluate the risk of endometrial cancer depending on BMI and to investigate an influence of MHT on this relationship.
The study of the relationship between endometrial cancer and BMI included a nested case-control study and 24 cohort studies. This analysis, stratified by the main geographical regions (North America, Europe and Australia, Asia-Pacific and multi-ethnic populations), however, with heterogeneity for all the studies and between the groups, concluded that there was an overall relative risk of 1.60 [1.52; 1.68] per increase in BMI of 5 kg/m^2.
The stratified analysis based on the use (present or past) of MHT or the absence of use included four cohort studies. The relative risk was 1.90 [1.57; 2.31] per increase in BMI of 5 kg/m^2 for women never having been treated; it was 1.18 [1.06; 1.31] for the women using or having used any form of MHT, with significant interaction between BMI and MHT administration.

Combined HRT

- Cohort study (Finland) - 2009[96] (level 3 evidence).

This study identified all the Finnish women aged over 50 years having used combined HRT for more than 6 months between 1994 and 2006. They were identified from the national registry of reimbursements. The only oestrogen used in Finland is oral or transdermal oestradiol. The treatment could be sequential (progestogen administered 10 to 14 days per month), long-cycle (progestogen administered 10 to 14 days every 3 months) or continuous combined (progestogen and oestradiol administered together). Women using tibolone or a levonorgestrel coil were excluded from the study. In total, 224,015 women were included in the analysis for a total follow-up of 1.6 million women-years and 1364 cases of type 1 invasive endometrial cancer (endometrioid adenocarcinoma) were identified from the Finnish cancer registry.
The expected number of endometrial cancers in the study population was calculated from the observed incidence of endometrial cancers in the general population, in increments of 5 years of age, during the same period of observation. The standardised incidence ratio (SIR) was calculated by dividing the number of observed cases by the expected number.

94 Furness S *et al*. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane database of Systematic reviews 2009, Issue 2.
95 Crosbie E. J. *et al*. Body mass index, hormone replacement therapy, and endometrial cancer risk : a meta-analysis. Cancer epidemiol biomarkers prev 2010; 19: 3119-30
96 Jaakkola S et al. Endometrial cancer in postmenopausal women using estradiol-progestin therapy. Obstet gynecol. 2009; 114: 1197-203

For sequential HRT, the risk was significantly increased from 5 years of use: SIR=1.69 [1.43; 1.96] for 5 years or more, SIR=2.56 [1.28; 4.58] for 10 years or more. It was the same for long-cycle HRT: SIR=3.76 [2.90; 4.79] for 5 years or more, SIR=6.64 [1.81; 16.99] for 10 years or more. For sequential HRT, there was no significant difference in the risk based on the type of progestogen used (norethisterone, medroxyprogesterone, dydrogesterone).
For continuous HRT, the risk was significantly reduced from 3 years of treatment: SIR=0.24 [0.06; 0.60] for 3 to 5 years, SIR=0.36 [0.19; 0.62] for 5 years or more. For treatment durations of 10 years or more, the risk reduction was not significant.

- Case-control study (Finland) - 2011[97] (level 3 evidence).

From the Finnish cancer registry, this study identified women aged 50 to 80 years with endometrial cancer diagnosed between 1995 and 2007 (n = 7261). For each case, three controls of the same age (± 1 month) (19,490 in total), not having endometrial cancer at the time of diagnosis of the case and having an intact uterus according to the registry of hospitalised patients, were selected randomly from the registry of the Finnish population which also provided information on the dates of their childbirths from October 1953. The use of MHT was established from the national registry of medical reimbursements which registered them from 1994. The only oestrogen used in Finland is oestradiol.
Combined HRT was classified as sequential (progestogen sequence for 10 to 14 days every month), long-cycle (progestogen sequence of 10 to 14 days every 3 months) or continuous (progestogen administered every day or levonorgestrel coil). The oral and transdermal treatments were grouped. The type of treatment used for >50% of the total duration of exposure determined the treatment group in which the patient was recorded. The use of MHT for less than 6 months was considered as a non-use. The statistical analysis was adjusted for age at first and last childbirth and parity, but not for the menopausal status or the BMI.
The use for < 5 years of a combined HRT was associated with a significantly reduced risk of endometrial cancer for sequential HRT (OR=0.67 [0.52; 0.86]), continuous HRT (OR=0.45 [0.27; 0.73]) and HRT including a levonorgestrel coil (OR=0.39 [0.17; 0.88]).
For the treatment durations between 5 and 10 years, the risk was significantly reduced with continuous HRT (OR=0.57 [0.37; 0.88]) and HRT including a levonorgestrel coil (OR=0.16 [0.37; 0.68]); it was significantly increased for long-cycle HRT (OR=1.63 [1.12; 2.38]).
For treatment durations over 10 years, the risk was significantly increased for sequential HRT (OR = 1.38 [1.15; 1.66]) and long-cycle HRT (OR=2.95 [2.40; 3.62]).
The risk analysis based on the type of progestogen was performed in women where the type of the entire treatment was known (born between 1944 and 1957). It revealed similar results regardless of the progestogen used (norethisterone acetate, medroxyprogesterone acetate, dydrogesterone or another progestogen).

Tibolone

- Randomised versus placebo study (level 2 evidence)[98].

The aim of this study was to monitor the endometrial safety of tibolone administered for 3 years. The primary efficacy endpoint was endometrial thickness. In total, 3519 women aged between 60 and 85 years were included.
Four cancers were diagnosed in the tibolone group; none in the placebo group. Two cases of hyperplasia, one of which was atypical, were diagnosed in the tibolone group; one case of complex atypical hyperplasia in the placebo group.

- Cohort study - (EPIC - Europe) - 2010[93] (level 3 evidence).

The users of tibolone had a significantly increased risk of endometrial cancer: RR = 2.96 [1.67-5.26]. The number of cases did not enable a possible influence of treatment duration to be studied.

- Case-control study (Finland) - 2011[97] (level 3 evidence).

The users of tibolone did not have a significantly increased risk.

97 Jaakkola S. et al. Endometrial cancer associated with various forms of postmenopausal hormone therapy: a case control study. Int J Cancer. 2011; 128: 1644-51
98 Ettinger B, Kennemans P, Johnson SR et al. Endometrial effects of tibolone in elderly osteoporotic women. Obstet & gynecology; 112: 653-659

08.11 Ovarian cancer

Oestrogen-only and combined HRT

- Cohort study (Denmark) - 2009[99] (level 2 evidence)

A prospective cohort study started in 1995 (Danish Sex Hormone Register Study) including all Danish women aged from 15 to 79 years.
This study included the women from this cohort aged 50 to 79 between 1995 and 2005. The use of a menopausal hormone treatment and the occurrence of ovarian cancers were identified through links with other national registries. The adjustment factors did not include oral contraceptive use.
For a mean follow-up duration of 8 years (7.3 million women-years), 3068 incident ovarian cancers were detected, 2681 of which were epithelial cancers. Compared with women who had never used HRT in menopause, the risk in treated women was 1.38 [1.26; 1.51]. It reduced after treatment discontinuation depending on the duration of interruption: 1.22 [1.02; 1.46] from 1 to 2 years, 0.98 [0.75; 1.18] from > 2 to 4 years, 0.72 [0.5; 1.05] from > 4 to 6 years and 0.63 [0.41; 0.96] for > 6 years.
The study did not reveal a significant difference between the oestrogen-only and combined HRT, between the cyclical and continuous combined HRT, between the different progestogens (norethisterone acetate, medroxyprogesterone acetate, levonorgestrel and cyproterone acetate), or between the oral and transdermal routes of administration, or any influence of treatment duration.

- Cohort study (Cancer Prevention Study II Nutrition cohort - USA) - 2010[100] (level 2 evidence).

The CPS II Nutrition cohort was initiated in 1992 and formed by inviting the members of the CPS II mortality prospective cohort, initiated in 1982 by the American Cancer Society, who were aged 50 to 74 years on this date to participate. The subjects who consented completed a self-administration questionnaire; the subsequent questionnaires were sent every 2 years until 1997 with a response rate of ≥ 89% each time. The incident cancers were identified from the questionnaires, or on death certificates and verified on medical records or through links with cancer registries.
The analysis was adjusted for level of education, origin (Caucasian/non-Caucasian), age at first menstrual period, parity, use of oral contraceptives, existence of tubal ligation or difficulties conceiving, BMI, physical inactivity, and family history of ovarian or breast cancer.
In total, 297 ovarian cancers were identified in 54,436 post-menopausal women at the start of the study; the histological diagnosis was not known for 35 of them.
The incidence of ovarian cancers was significantly increased in ongoing users of oestrogen-only HRT: RR = 2.07 [1.50; 2.85]; the relative risk increased by 25% for each period of 5 years of use: RR = 1.25 [1.15; 1.36]; it was 2.89 [1.71; 4.87] for ongoing use ≥ 20 years; it was not significantly increased in former users of oestrogen-only HRT.
No significant increase of incidence was observed in women using or having used combined HRT, regardless of the treatment duration.
The sensitivity analyses excluding the 35 cases of unknown histology gave similar results to those of the primary analyses; it was the same when the cases were limited to serous tumours.

Cohort study (Italy)[42] - 2008 (level 2 evidence).
This study did not reveal any change in risk on MHT.

- Cohort study (CTS - USA) - 2010[101] (level 2 evidence).

The analysis of the CTS cohort aimed to investigate the influence of obesity and MHT on the risk of invasive epithelial ovarian cancer.

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99 Morch L.S *et al.* Hormone therapy and ovarian cancer. JAMA. 2009; 302, 298-305
100 Hildebrand J.S. *et al.*: Postmenopausal hormone use and incident ovarian cancer: associations differ by regimen. Int J Cancer; 2010; 127: 2928-35
101 Canchola A. *et al.* Body size and the risk of ovarian cancer by hormone therapy use in the California Teachers Study cohort. Cancer causes control. 2010 ; 21: 2241-48.

In total, 277 cases of invasive epithelial ovarian cancer were diagnosed from 1995 to 2007, for a median follow-up of 12.1 years in 56,091 women aged 45 to 84 years who had not had an oophorectomy and who had no history of ovarian cancer. The Cox model was stratified by age at inclusion and adjusted for ethnicity, use of oral contraceptives and their duration, parity, consumption of wine prior to inclusion, physical activity and intensity during the 3 years prior to inclusion, height and tobacco use at inclusion, and existence of tubal ligation. The analyses looking for a link between cancer and obesity tested several criteria: BMI, waist circumference/hip circumference ratio, weight gain since the age of 18 years and waist circumference/height ratio.
Compared with women who had never used hormone therapy, the risk of ovarian cancer was significantly increased in women having used hormone therapy > 5 years: RR = 1.6 [1.2; 2.2] while it was not in women having used it ≤ 5 years: RR = 1.0 [0.75; 1.4].
The analysis including all the selected women did not reveal a relationship between obesity (BMI ≥ 30 versus < 25 kg/m^2) and the risk of ovarian cancer. Compared with women with a BMI <25 who had never been treated, the risk was increased for non-obese women with long-term treatment: RR= 1.8 [1.2; 2.6] with BMI <25 and RR= 1.7 [1.1; 2.8] with BMI between 25 and 29; the risk was not significantly increased in obese women.

- Cohort study (EPIC - Europe) - 2001[102] (level 3 evidence).

This analysis of the EPIC cohort included 126,920 women, 424 of whom had been diagnosed with invasive epithelial ovarian cancer for a follow-up of 1,142,898 women-years. Information on MHT was collected on the questionnaires at inclusion in the cohort. The analysis was stratified by recruitment centre and age group at inclusion and adjusted for BMI, tobacco use, history of a unilateral oophorectomy orhysterectomy, age at first menstrual period, number of full-term pregnancies, and duration of oral contraceptive use.
The risk of ovarian cancer in treated women (all treatments included) at inclusion was significant increased: HR=1.29 [1.01; 1.65] compared with untreated women, and women treated with oestrogen-only HRT: HR=1.63 [1.08; 2.47]. The risk was not significantly increased for women treated with combined HRT and for those having discontinued treatment. However, there was no significant heterogeneity between these different risks; there was also no heterogeneity of the risks for different types of oestrogens, their route of administration or the different progestogens, however, there were few cases for the majority of these treatments. For the previous or ongoing treatments, the risk compared with untreated women was significantly higher for the women treated for 5 years or more HR = 1.45 [1.08; 1.94] than for those treated for less than 5 years ($p<0.04$).

- Cohort study (NIH-AARP Diet and Health study - USA) - 2011 (level 3 evidence).[103]

This prospective cohort initiated in 1995-1996 involved members of the American Association of Retired Persons living in six states with cancer registries. The participants had answered an initial questionnaire concerning the use of MHT.
This analysis which included 169,119 women for a total follow-up of 1,657,966 women-years, studied the risk factors for ovarian cancer based on histological type. The cases of incident cancer were identified from the cancer registries. In total, 849 cases were identified and classified according to the histological type as serous, endometrioid, mucinous, clear-cell and other epithelial cancers.
For the women using or having used MHT at inclusion compared with women who had never used MHT, the risk of cancer regardless of the histological type was significantly increased RR = 1.33 [1.16; 1.53]. Based on the histological type, it was significantly increased for the serous cancers: RR=1.50 [1.24; 1.81] and significantly reduced for mucinous cancers: RR = 0.37 [0.18; 0.80].

102 Tsilidis K.K. *et al.* Menopausal hormone therapy and risk of ovarian cancer in the european prospective investigation into cancer and nutrition. Cancer Causes Control 2011; 22: 1075-84
103 Yang H.P. et al. Ovarian cancer risk factors by histologic subtypes in the NIH-AARP Diet and Health Study. Int.J.Cancer: 2011; 131 :938-948

- Case-cohort study (Prospective Netherlands Cohort Study on Diet and Cancer - Netherlands) - 2010[104] (level 3 evidence).

This cohort was started in 1986 and included a total of 62,573 women aged 55 to 69 years, all presumed to be post-menopausal.
The data analysis was based on a case-cohort study: the cases of ovarian cancer were from the entire cohort and the number of person-years at risk for the entire cohort was estimated from a subcohort of women randomly identified from the total cohort at inclusion.
After the exclusion of women with cancer at inclusion, an oophorectomy and/or incomplete data concerning the adjustment variables, 375 cases of histologically confirmed cancers and 2331 members of the subcohort were included in the analysis for a follow-up period of 16.3 years.
The use of MHT, and the start and end dates of treatment were recorded on a questionnaire.
The analysis was adjusted for age, parity and use of oral contraceptives.
The mean age at the time of diagnosis was 70.4 years.
There was no increase of the ovarian cancer risk in women having used MHT compared with those never having used it: RR = 0.97 [0.69 -1.37]. The age at the start and end of treatment (before or after 50 years) did not change the risk.

- Meta-analysis - 2008[105] (level 3 evidence).

This meta-analysis of published data included 27 studies, 19 of which were case-control studies and 8 cohort studies analysed separately. With ongoing or previous use of MHT, the relative risk was 1.24 [1.15; 1.34] for the cohort studies and the odds ratio was 1.19 [1.02; 1.40] for the case-control studies; however, there was significant heterogeneity between the studies. Four cohort studies and six case-control studies made a distinction between oestrogen-only and combined HRT. The risk was higher with oestrogen-only HRT: OR=1.51 [1.21; 1.88] for the cohort studies and OR= 1.19 [1.01; 1.40] for the case-control studies than with combined HRT: OR=1.24 [1.00; 1.54] for the cohort studies and OR= 1.01 [0.83; 1.22] for the case-control studies. It was not specified if the difference in risk between the treatments was significant. The analysis of six case-control studies did not reveal any relationship between the risk and the duration of treatment.

- Meta-analysis - 2009[106] (level 3 evidence).

This meta-analysis of published data included 14 studies providing information on the duration of treatment and their type (oestrogen-only or combined HRT), 8 of which were case-control studies, 5 cohort studies (including the MWS and NIH-AARP Diet and health study) and the WHI controlled study including an arm treated with combined HRT. It was carried out without stratification by study type. These studies concerned the risk of invasive epithelial ovarian cancer, some also included borderline cases of epithelial cancers. Eleven of these studies: 6 case-control studies and 5 cohort studies were included in the previous meta-analysis [32].
For 13 studies concerning the administration of oestrogen-only HRT, the odds ratio for 5 years of treatment was 1.22 [1.18; 1.27] for previous or ongoing use.
For 11 studies concerning combined HRT, the odds ratio for 5 years of treatment was 1.10 [1.04; 1.16] for previous or ongoing use.
The difference between the two odds ratios was significant ($p > 0.04$).
The results were similar when restricting the analysis to invasive cancers.
This study did not enable the effect of sequential and continuous combined HRT, previous or ongoing, or a possible dose effect to be differentiated.

Combined HRT

- Cohort study (Finland) - 2013[107] (level 3 evidence)

104 Braem M. G. M. *et al.* Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. Am. J. Epidemiol. 2010; 172: 1181-89
105 Zhou B. *et al.* Hormone replacement therapy and ovarian cancer risk: a meta-analysis. Gynecologic Oncology 2008; 108: 641-51.
106 Pearce C.L. *et al*. Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. Cancer. 2009; 115: 531-9
107 Koskela-Niska V *et al.*Ovarian cancer risk in postmenopausal women using estradiol-progestin therapy – a nationwide study. Climacteric. 2013; 16: 48-53

All Finnish women aged 50 years or over having bought combined HRT for at least 6 months between 1994 and 2006 were identified from the Finnish registry of medical reimbursements. The women having used an intrauterine device or tibolone were excluded.
The only oestrogen used in Finland is oral or transdermal oestradiol; the most commonly used progestogens were norethisterone acetate, medroxyprogesterone acetate and dydrogesterone. The combined HRT was given continuously or sequentially (administration of progestogen for 10 to 14 days every 1 to 3 months of oestrogen therapy).
A total of 224,015 women were included in the analysis. Amongst them, 602 ovarian cancers were diagnosed. The risks were assessed by calculating the standardised incidence ratio (SIR).
There was a significantly increased risk for treatment durations of more than 5 years: SIR = 1.21 [1.06; 1.37] the increased risk was no longer significant for treatment durations of 10 years or more.
The risk was significantly increased with treatment of more than 5 years including norethisterone acetate SIR = 1.42 [1.11; 1.77], but not with medroxyprogesterone acetate SIR = 1.26 [0.94; 1.64] or dydrogesterone; however, there were few patients in this group.

Tibolone

- Cohort study (EPIC - Europe) - 2001[102] (level 3 evidence).

The use of tibolone was associated with a more than doubled risk, based however on only eight exposed cases: RR = 2.19 [1.06; 4.50].

08.12 Colorectal cancer

Oestrogen-only and combined HRT

- WHI observational study and reminder of the results from the interventional studies - 2009[108] (level 2 evidence).

In the interventional combined HRT versus placebo WHI study, the relative risk for invasive colorectal cancer was 0.56 [0.38-0.81], however, the cancers in the arms receiving combined HRT were diagnosed at a more advanced stage than in the placebo group; these results were actually linked to a lower risk for the localised tumours and tumours without lymph node involvement in the treated group. No difference in mortality risk from colorectal cancer was revealed between the groups for a total follow-up duration of 8 years (treatment phase + post-treatment follow-up). In the interventional oestrogen-only WHI study, the relative risk of invasive colorectal cancer was 1.12 [0.77-1.63] with no suggestion of treatment effect on the diagnosis.
The WHI study investigators therefore wanted to compare the incidences and characteristics of colorectal cancer between the interventional and observational WHI studies.
The women included in the observational WHI study were treated with the same doses (0.625 mg CEO or 0.625 mg CEO + 2.5 mg MPA) as those included in the interventional studies or not taking any MHT.
In total, 10,582 women treated at inclusion and 10,970 non-users who had had a hysterectomy were included in the oestrogen-only HRT study; 6756 women treated at inclusion and 25,328 non-users were included in the combined HRT analysis.
The relative risks were 0.80 [0.53-1.20] for the oestrogen-only HRT analysis and 1.15 [0.74-1.79] for the combined HRT analysis. No difference in the risk of localised tumours and tumours without lymph node involvement was revealed in the group treated with combined HRT.
In total, this analysis of the observational WHI study did not reveal any change in the risk of colon cancer on oestrogen-only or combined HRT during the follow-up of 7 to 8 years and did not enable the results of the interventional study to be confirmed.

- Cohort study (BCDDP- USA) - 2009[109] (level 2 evidence).

108 Prentice R.L. et al. Colorectal cancer in relation to postmenopausal estrogen and estrogen plus progestin in the Womens's health Initiative Clinical Trial and Observational Study. Cancer Epidemiol. Biomarkers Prev. 2009; 18: 1531-37
109 Johnson J. et al. Menopausal hormone therapy and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2009 ; 18: 196-203

Out of the cohort of 56,733 women, 960 cases of colorectal cancer were identified, 461 of which were confirmed from medical records, for a mean follow-up duration of 15.02 years (extremes 1 month-19.8 years) and a mean age at inclusion of 55.7 years.
All the women using or having used an oestrogen-only HRT had a significantly lower risk than those who had never been treated: RR= 0.83 [0.70; 0.99]; amongst which the women being treated had a relative risk of 0.75 [0.54; 1.05]; the women with a treatment duration ≥10 years had a significantly lower risk than those who had never been treated: RR = 0.74 [0.56; 0.96].
All the women using or having used a combined HRT had a risk which was not significantly different to those who had never been treated: RR = 0.78 [0.60; 1.02]. The women on sequential combined HRT (use of a progestogen<15 days/month) had a significantly lower risk than those who had never been treated: RR= 0.64 [0.43; 0.95], contrary to those on continuous combined HRT: RR = 0.75 [0.46; 1.21].

- Cohort study (CPS II - USA) - 2009[110] (level 2 evidence).

This cohort CPS II analysis included 67,412 post-menopausal women, 776 of which had colorectal cancer for a follow-up of 13.2 years from 1992 to June 2005. The cancers were identified on questionnaires and verified on medical records, links with the cancer registries or death certificates.
Information on the use of hormones was collected at inclusion and on the follow-up questionnaires. The analysis was adjusted for age in 1992, BMI, tobacco use, level of education, ethnicity, physical activity, use of non-steroidal anti-inflammatories, use of multivitamins, family history of colorectal cancer, type of menopause, consumption of meat, and history of a colorectal endoscopy.
The women being treated with oestrogen-only HRT had a lower risk of colon cancer than women who had never been treated: RR = 0.76 [0.59; 0.97]. The duration of treatment was inversely and significantly linked (p=0.001) to the risk: this was not reduced for a duration < 5 years; it was 0.55 [0.36; 0.86] for a duration of use of ≥ 20 years. The risk was not modified for women having interrupted oestrogen-only HRT.
The women with ongoing or interrupted combined HRT, did not have a significantly different risk to the women who had never been treated.

- Cohort study (CTS - USA) - 2010 [111]

This CTS cohort analysis included 56,864 women, 442 of which had invasive colon cancer (identified from the California cancer registry) during follow-up. The analysis was adjusted for ethnicity, BMI, physical activity and stratified by age at inclusion. The women using MHT at inclusion had a significantly reduced risk compared with those who had never used MHT: RR=0.64 [0.51; 0.80] the risk did not differ based on the type of HRT (oestrogen-only or combined). The risk was even lower with a longer treatment duration: RR=0.76 [0.54; 1.08] for treatments < 5 years and RR=0.49 [0.35; 68] for treatments having lasted 5 to 15 years. This risk reduction trend did not continue beyond 15 years.

- Cohort study (EPIC - Europe) - 2001[112] (level 3 evidence).

This EPIC cohort analysis concerning the risk of colon cancer included 136,275 women, 1186 of which had colorectal cancer (839 colon cancers and 347 rectal cancers) for a mean follow-up duration of 9 years. The analysis was stratified by centre and age and adjusted for BMI, tobacco use, existence of diabetes, physical exercise and alcohol consumption. The risk of colorectal cancer was not statistically different with oestrogen-only MHT: RR=1.02 [0.79; 1.31] or combined HRT: RR = 0.94 [0.77; 1.14] nor according to the type of treatment (oestradiol, conjugated equine oestrogen, oral or transdermal, progestogen derived from progesterone or testosterone, micronised progesterone, duration, previous or recent use). However, even though the difference in risk between the progestogen groups was not significant (p=0.08), the oestrogen and

110 Hildebrandt J. et al. Colorectal cancer incidence and postmenopausal hormone use by type, recency and duration in Cancer Prevention Study II; Cancer Epidemiol Biomarkers Prev. 2009. 18: 2835-41
111 Delellis Henderson K *et al.* Menopausal hormone therapy use and risk of invasive colon cancer. The California Teachers Study. Am J Epidemiol. 2012; 171: 415-25
112 Tsilidis C.K. *et al.* Menopausal hormone therapy and risk of colorectal cancer in the european prospective investigation into cancer and nutrition. Int.J.Cancer. 2011; 128: 1881-9

testosterone derivative combinationwas associated with a reduced risk of colorectal cancer HR = 0.47 (0.27-0.81).

- Cohort study (Canada) - 2008[113] (level 3 evidence).

This study was performed from data collected during a randomised study concerning breast cancer screening (Canadian National Breast Screening Study) which included 89,835 women aged 40 to 59 years between 1980 and 1985 until 1998-2000. Information particularly concerning MHT use was collected at inclusion using a self-administered questionnaire.
The incident cases of colorectal cancer were checked in relation to the Canadian database of cancers and the national database of deaths. For a mean follow-up of 16.4 years, which is 786,588 person-years, 1142 incident cases of colorectal cancer were identified. The analyses were adjusted for age, BMI, menopausal status (pre-, peri-, post-menopausal), duration of tobacco use and level of education, and in a second analysis, for the supplementary nutritional data including total calorie and alcohol intake, and physical activity.
No change in the risk of colorectal, colon, proximal colon, distal colon or rectal cancer was revealed based on the use of MHT or its duration.

- Cohort study (Italy)[42] - 2008 (level 2 evidence).

The risk of colorectal cancer was significantly reduced in women who had been treated for less than 25 months: RR= 0.78 [0.68; 0.92]. There was a significant trend for the risk to decrease with lengthening of the treatment duration, with no difference in the risk between the treatments including oral or transdermal oestrogen.

- Case-control study (Israel)-2009[114] (level 3 evidence).

This study included women aged over 45 years with colorectal cancer between 1998 and 2006 and controls affiliated to the same health insurance system, matched on age and place of residence. The use of MHT was determined retrospectively from questionnaires; less than 10% of women were using or had used MHT. The studied treatments were oral or transdermal oestrogen with or without progestogens. The women were considered to be post-menopausal if they had declared this on the questionnaire or if they were over 55 years of age.
In an analysis including 1014 post-menopausal patients and 1142 post-menopausal controls, the risk of colorectal cancer was significantly lower in women who declared that they used MHT than in the non-users: OR= 0.67 [0.51; 0.89], after adjustment for the use of aspirin, non-steroidal anti-inflammatories, and statins, the consumption of vegetables, and physical activity, it was: OR = 0.37 [0.22; 0.62]. The risk was significantly reduced with combined HRT: OR= 0.71 [0.50; 0.99] and oral treatment OR= 0.68 [0.52; 0.90] but not with oestrogen-only HRT or transdermal treatment (however, with few cases in this group).

- Meta-analysis - 2012[115] (level 3 evidence).

This meta-analysis of published data aimed to assess the risk of colorectal cancer on oestrogen-only and combined HRT in peri- or post-menopausal women. Twenty-eight studies were included: 4 randomised studies, 8 cohort studies (including [109] and [110]) and 8 case-control studies. Fourteen studies involved oestrogen-only HRT, 17 involved combined HRT.
The ongoing or previous use of oestrogen-only HRT was associated with a significantly reduced risk: RR = 0.79 [0.69; 0.91]. However, only the ongoing use was associated with a significantly reduced risk: RR= 0.70 [0.57; 0.85], contrary to previous use: RR = 0.86 [0.67; 1.11]; these risks were significantly different (p<0.0001). In addition, there was significant heterogeneity between the different study types, only the analysis of the case-control studies concluding that there was a significantly reduced risk (p<0.001).

113 Kabat G.C. *et al.* Oral contraceptive use, hormone replacement therapy, reproductive history and risk of colorectal cancer in women. Int J Cancer. 2008;122: 643-46
114 Rennert G. *et al.* Use of hormone replacement therapy and the risk of colorectal cancer. J.Clin.Oncol. 2009; 27, 4542-47
115 Lin K.J. The effect of estrogen versus combined estrogen-progestogen therapy on the risk of colorectal cancer. Int J Cancer. 2012; 130: 419-30

The ongoing or previous use of combined HRT was associated with a significantly reduced risk in the overall analysis: RR= 0.74 [0.68; 0.81] and in the analysis by study type. The risk was not significantly different with ongoing or previous use of such a treatment.
The risk was not significantly different between the two types of treatment with ongoing use; the previous use of combined HRT was associated with a significantly lower risk of colorectal cancer than the previous use of an oestrogen-only HRT.

Tibolone
- Placebo-controlled study[53]- 2008 (level 2 evidence).

The objective of this study was to demonstrate the effect of tibolone treatment on bone density and fracture risk. In total, 4,538 women aged between 60 and 85 years were included.
There was a reduced risk of colon cancer in the treated group: HR=0.31 [0.10; 0.96].
The study was stopped after 34 months of treatment (median duration) due to an increased risk of strokes in the treated group.

08.13 Other cancers

8.13.1 Lung cancer

Oestrogen-only HRT
- Post-hoc analysis of the WHI study (oestrogen-only) - 2010[116] (level 2 evidence).

After a mean duration of 7.1 ± 1.6 years of treatment with oestrogen-only HRT and 7.9 ± 1.8 years of follow-up, no significant increase in the incidence of lung cancer on treatment compared with the placebo was revealed: RR = 1.17 [0.81; 1.63].
The number of non-small cell cancers was comparable in the two groups. The incidence of deaths was also not different in the two groups: RR = 1.07 [0.66; 1.72].

Oestrogen-only and combined HRT
- Cohort study (CPS II - USA) - 2008[117] (level 2 evidence).

Lung cancers were reported by the patients on questionnaires and verified on medical records or identified through cancer registries or the national index of deaths.
The analysis was stratified by age at inclusion and adjusted for level of education, cigarette use, passive smoking, BMI, age at menopause, use of oral contraceptives, physical activity, and consumption of fruits and β-carotene.
In total, 72,772 women were included in this analysis and 659 cases of primary lung cancer were diagnosed between 1992 and June 2003.
Compared with women who had never been treated, the women being treated had a reduced risk of lung cancer: RR = 0.76 [0.62; 0.92]. It was 0.76 [0.60; 0.94] for the women treated with oestrogen-only HRT and 0.76 [0.57; 1.01] for women treated with combined HRT. There was no variation with the duration of MHT use. The risk reduced identically regardless of the smoking status. The risk was not different for the women having discontinued MHT and those who had never been treated.

- Cohort study (Italy)[42] - 2008 (level 2 evidence).

This study did not reveal any change in risk on MHT.

- Cohort study (Rancho Bernardo - USA) - 2009[118] (level 4 evidence).

This cohort was formed between 1972 and 1974 from the population of Ranch Bernardo, California; the participants had annual follow-up examinations. This analysis was based on 2861

116 Chlebowski RT, *et al.* Lung cancer among post menopausal women treated with estrogen alone in the Women's Health Initiative randomized trial. J. Natl. Cancer Instit. 2010; 102:1413-21
117 Rodriguez C. *et al.* Postmenopausal hormone therapy and lung cancer risk in the cancer prevention study II nutrition cohort. Cancer Epidemiol. Biomarkers Prev. 2008; 17: 655-660
118 Smith J. *et al.* Hormone use and lung cancer incidence: the Rancho Bernardo cohort study. Menopause. 2009; 16: 1044-48

women aged 31 to 79 years at inclusion, for whom follow-up data were available. The diagnosis of lung cancer was declared by the patients themselves or on death certificates and confirmed by the California Cancer Registry after 1988; the women with a history of lung or breast cancer were excluded to prevent metastases being recorded. The information about hormone use was only collected at the inclusion visit, without making a distinction between contraceptive hormones and MHT. The inclusion data did not specify if the participants were post-menopausal or not. By approximation of the age at menopause, they were stratified by age (< or > 55 years), assuming that the hormones used were MHT after menopause and an oral contraceptive pill before.
The analysis was adjusted for age, BMI, level of education and cigarette use.
The mean follow-up duration was 22.4 years during which 87 cases of incident lung cancer were identified.
No association between the use of hormones at inclusion and the risk of future lung cancer was revealed: RR = 1.13 [0.73; 1.73].

- Cohort study (USA) - 2010[119] (level 3 evidence).

Between the end of 2000 and the end of 2002, questionnaires were sent to 168,953 women aged between 50 and 76 years, living in the region covered by the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) registry. Their names were obtained from a direct mail company.
The diagnosed lung cancers were obtained from SEER between inclusion and 31 December 2007.
The data on MHT were obtained through a questionnaire; the information concerning the long-term use of MHT was retrospective. The reference group was made up of women who had never used MHT. The women with confirmed lung cancer who were not peri-menopausal or post-menopausal or for whom no information about MHT was available were excluded.
The relative risks were adjusted for age, duration of tobacco use and the number of packet years, personal history of cancer, family history of lung cancer, chronic obstructive pulmonary disease, BMI, age at menopause, existence of a hysterectomy, and ethnicity.
In total, 24.4% of women answered the questionnaire, 36,588 women were included in the cohort, mean follow-up duration was 5.9 ± 1.2 years.
Overall, the use of MHT was not associated with an increased risk of lung cancer, whether for ongoing use (HR = 1.23 (95% CI 0.92-1.66) or previous use (HR= 1.18 (95% CI 0.86-1.63).
The exclusive use of oestrogen-only HRT was not associated with an increased risk: RR = 1.04 [0.73; 1.48]. This did not vary significantly with duration of use (< or ≥ 10 years).
The exclusive use of combined HRT was associated with a significantly higher risk than that of non-users: RR = 1.47 [1.06; 2.04]. Combined HRT was associated with a significantly increased risk for durations of use ≥ 10 years: RR=1.48 [1.03; 2.12], with a significant trend for the risk to increase (p=0.03) and the stages to become more advanced (p=0.03) with duration.
It was not specified if there was a significant difference in the risk between the two types of treatment.

- Cohort study (Nurse s' Health Study - USA) - 2010[120] (level 2 evidence).

The analysis concerning the relationships between lung cancer and hormones used the data collected from 1984. Data collection stopped on 1 June 2006.
The post-menopausal women included in this study had not reported a cancer diagnosis at inclusion (apart from skin cancers other than melanomas). They were included after natural menopause, bilateral oophorectomy, at 54 years of age for smokers or at 56 years of age for non-smokers in cases hysterectomy or lack of menstrual periods after a unilateral oophorectomy (age when 90% of participants with an intact uterus were post-menopausal). The lung cancers were reported by the participants or identified on their death certificates and then confirmed on medical records. They were only taken into account if a histological report indicated that this was a primary lung cancer and then classified based on its histological type.

119 Slatore C.G. *et al.* Lung cancer and hormone replacement therapy: Association in the Vitamins and Lifestyle Study. J. Clin.Oncol. 2010; 28: 1540-6
120 Baik C.S *et al*. Reproductive factors, hormone use, and risk for lung cancer in postmenopausal women, the nurse's health study. Cancer Epidemiol Biomarkers Prev. 2010 ;19 : 2525-33

The analysis was stratified by existence of tobacco use and histological type (adenocarcinoma, squamous cell cancer or small cell cancer).
During the 22 years of follow-up, 107,171 post-menopausal women were included, totalling 1,590,432 women-years; 1729 incident cases of lung cancer were identified corresponding to an incidence of 109/100,000 women-years.
No significantly increased risk of lung cancer was observed in relation to the use of hormone replacement therapy in menopause.

Combined HRT

- Post-hoc analysis of the WHI study (combined HRT) - 2009.[121] (level 2 evidence).

After a mean duration of combined HRT of 5.6 years and 2.4 years of follow-up after treatment discontinuation, the annual incidence of lung cancer was 0.16% in the treated group and 0.13% in the placebo group; the risk of lung cancer was not significantly different between the groups: RR = 1.23 [0.92-1.63]. The incidence of non-small cell cancers was not significantly different in the treated group and in the placebo group: 0.14 versus 0.11, RR= 1.28 [0.94; 1.73]. Mortality from lung cancer was higher in the treated group: 0.11% versus 0.06, RR = 1.71 [1.16-2.52] mainly related to a higher number of deaths due to non-small cell cancers HR = 1.87 (1.22-2.88).

8.13.2 Central nervous system tumours

Oestrogen-only and combined HRT

- Cohort study (Million Women Study - United Kingdom) - 2010[122] (level 2 evidence).

The information concerning incident invasive and non-invasive cancers of the central nervous system and deaths was provided by the National Health Service registries.
For a mean follow-up of 5.3 years, 1266 tumours of the central nervous system were diagnosed in 1,147,894 post-menopausal women.
Analysis was stratified by the place of residence.
Compared with women who had never used MHT, the relative risk for all the tumours was 1.20 [1.05; 1.36] in the treated women and 1.07 [0.93; 1.24] in women who had discontinued treatment. These risks were not significantly different (heterogeneity p=0.2). In all treated women, the relative risk was 1.34 [1.03; 1.75], for meningiomas, 1.58 [1.02; 2.45] for acoustic neuromas and 1.09 [0.89; 1.32] for gliomas. These risks were not significantly different (heterogeneity p=0.2).
In women receiving oestrogen-only HRT, the risk was significantly increased for all the tumours: RR=1.42 [1.21; 1.67], for gliomas RR=1.34 [1.05; 1.72], for meningiomas: RR=1.44 [1.03; 2.02] and acoustic neuromas RR=1.94 [1.15; 3.29].
There was a significant difference in the risk between the oestrogen-only and combined HRT (heterogeneity p=0.001).
With the combined HRT, the risk was not increased either for all the tumours: RR=0.97 [0.82; 1.16] or for any type of tumour.

- Cohort study (EPIC - Europe) - 2001[123] (level 3 evidence).

A study of the relationship between meningiomas, gliomas and hormone therapies (oral contraceptives and MHT) was performed within this prospective cohort initiated at the start of the 1990s and including 23 centres in 10 European countries. The cases of gliomas and meningiomas were identified from the cancer registries or from a combination of means including links with insurance systems, and cancer registries, and active monitoring of the cohort participants. The incident cases were recorded until the end of follow-up, from January 2003 to November 2006 depending on the centre. The data concerning the use of hormone therapies was collected at inclusion from the patients in the study; the data concerning the use of these treatments during

121 Chlebowski R.T.*et al.* Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial) : a post-hoc analysis of a randomised controlled trial. Lancet. 2009; 374: 1243-51
122 Benson V.S. *et al.* Hormone replacement therapy and incidence of central nervous system tumours in the Million Women Study. Int J Cancer; 2010; 127: 1692-98
123 Michaud D.S. *et al.* Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large european cohort study. Cancer Epidemiol Biomarkers Prev. 2010 ;19 : 2562-69

follow-up are not available. In total, 276,451 women underwent follow-up for a mean duration of 8.4 years; 193 cases of gliomas and 194 cases of meningiomas were diagnosed. No relationship was revealed between the hormone therapies and the risk of glioma. The ongoing use of MHT was associated with a significantly increased risk of meningioma: RR = 1.79 [1.19; 2.71].

- Cohort study (NIH-AARP Diet and Health study - USA) - 2011[124] (level 3 evidence).

The participants answered an initial questionnaire (n=225,355) and another 6 months later (n=134,514) concerning the use of MHT.

Since the benign tumours were not uniformly identified by the cancer registries, the mostly benign tumours, including meningiomas, were not included in the analysis which was limited to gliomas, mostly malignant. The histologically confirmed cases of glioma were identified from cancer registries until 31 December 2003. Amongst the 225,355 participants, 174 gliomas were identified for a mean follow-up of 7.5 years. The analysis concerning MHT focused on 134,514 participants in whom 106 gliomas were identified. The variables included in the Cox model were: age at inclusion, age at first menstrual period, age at menopause, ethnicity, age, parity, history of a hysterectomy, and tobacco use. No association was revealed between the risk of glioma and the use of MHT, regardless of it duration (retrospective data at inclusion).

- Cohort study (Finland) - 2012[125] (level 3 evidence).

The data concerning women having received MHT between 1994 and 2009 were collected from the national registry of reimbursements. Meningioma cases were identified from the Finnish cancer registry. Women having bought a treatment for at least 6 months and aged 50 years or over were included in the cohort. The only oestrogen used in Finland is oral or transdermal oestradiol; the most commonly used progestogens were norethisterone acetate, medroxyprogesterone acetate and dydrogesterone. In total, 289 meningiomas were diagnosed in 131,480 women treated with oestradiol-only and 196 meningiomas were diagnosed in 131,248 women treated with oestradiol + progestogen. The analyses were indirectly adjusted for age and period of the study, and on the observed number of cases divided by the expected number for the standardised incidence ratios calculation.

In women using or having used an oestrogen-only HRT, all durations included, the standardised incidence ratio was increased compared with the general population of Finnish women: 1.29 [1.15; 1.44]; it was 1.40 [1.18; 1.64] for the women treated for at least 3 years. In women using or having used a combined HRT, the standardised incidence ratio was not increased: 0.93 [0.80; 1.06].

- Case-control study (USA) - 2009[126] (level 3 evidence).

The cases of histologically confirmed gliomas, occurring in women aged 20 years or over, residing in the San Francisco Bay region between August 1991 and April 1994 were included. The controls resided in the same region and were selected at random from a telephone list. They were matched on age and ethnicity. In total, 619 cases and 650 controls were included, 52% of which were definitely post-menopausal.

Information concerning the gynaecological history and the hormone therapies were collected during direct or telephone interviews with the participants or their family. The analyses were adjusted for age, ethnicity and level of education.

In post-menopausal women, the previous or ongoing use of MHT was inversely associated with the risk of glioma, by taking into account the cases having directly answered the questionnaire (n=155): OR=0.56 [0.37; 0.85] and all the post-menopausal women with a glioma (n=310): OR = 0.57 [0.41; 0.79]. The previous use of an oral contraceptive (also associated with a reduced risk) did not change the inverse association between the use of MHT and the glioma risk.

- Retrospective case-control study (THIN - UK) - 2011[127] (level 4 evidence).

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124 Kabat G. *et al.:* Reproductive factors and exogenous hormone use and risk of adult glioma in women in the NIH-AARP Diet and health study. Int. J. Cancer. 2011; 128: 944-950

125 Korhonen K. *et al:* A nationwide cohort study on the incidence of meningioma in women using postmenopausal hormone therapy in Finland. Am J Epidemiol. 2012; 4: 309-314

126 Felini M.J. *et al.* Reproductive factors and hormone use and risk of adult gliomas. Cancer Causes Control.2009;20:87-96

This study was performed from the English general practitioner database, The Health Improvement Network.
This analysis included all the patients in the database aged 12 to 89 years between January 1996 and June 2008, monitored for at least 2 years by a general practitioner and having at least 1 year of prescriptions listed in the database.
An index date chosen at random was generated for each participant of the cohort. If this was included in their follow-up period, the participant was included as a control.
The controls were matched on age, sex and index year (year of diagnosis for the cases and index date for the controls).
The incident cases of meningioma were identified from the database, then confirmed with a questionnaire sent to the general practitioner, and hospitalisation and additional examination reports or from manual review of the data recorded in the database.
Treatment exposure was considered as ongoing if the most recent prescription duration contained the index date or finished in the year preceding the index date.
In total, 549 incident cases of meningioma were diagnosed in the women, for which 7347 controls were selected. Amongst the women with a meningioma, 58 were being treated with MHT (oestrogen-only, tibolone or combined); they did not have an increased risk of meningioma: RR=0.99 [0.73; 1.35]; no type of treatment was associated with an increased risk.

- Systematic review of epidemiological literature - 2011[128] (level 4 evidence).

This review aimed to research epidemiological studies published until September 2010 and concerning the relationships between hormone factors and the occurrence of gliomas and meningiomas. The selected studies were published between 1990 and 2010. Seven of them focused on the glioma risk in relation with MHT (references for which are[122,126]), two studies concluded that there was a significantly reduced risk of glioma in treated women (reference of which is [126]) and one concluded that there was a significantly increased risk in women on oestrogen-only HRT [122]. Seven studies focused on the meningioma risk in relation to MHT (reference of which is [122]); four of these studies concluded that there was a significantly increased risk of meningioma in treated women (the reference of which is [122]).

8.13.3 Oesophageal cancer

Oestrogen-only and combined HRT

- Post-hoc analysis of the interventional and observational WHI studies - 2011[129] (level 2 evidence).

This analysis included women having participated in the WHI studies, i.e. the two studies concerning MHT (oestrogen-only and combined HRT), two other interventional studies; one concerning treatment with calcium + vitamin D, the other using a low fat diet, and the observational study.
All the analyses were adjusted for age at inclusion, existence of a hysterectomy, type of study (MHT, observational or non-MHT). The analyses concerning the risk of adenocarcinoma were adjusted for BMI, existence of "heartburn" and ethnicity (Caucasian/non-Caucasian). The analyses concerning the risk of squamous cell carcinoma were adjusted for tobacco use and alcohol consumption.
In total, 161,080 women were included in the analysis for a median follow-up duration of 11.82 years, which is 1,730,836.8 person-years; 63 cases of oesophageal cancer were diagnosed, 34 of which were squamous cell cancers, 23 adenocarcinomas and 6 cancers of unspecified histology which were excluded from the analysis.
There was no significant change in the adenocarcinoma risk on MHT.

127 Cea-Soriano L. *et al:* Hormonal therapies and meningioma : is there a link ?. Cancer epidemiology (2011), doi:10.1016/j.canep.2011.08.003
128 Cowppli-Bony A *et al.* Brain tumors and hormonal factors : review of the epidemiological literature. Cancer Causes Control. 2011; 22: 697-714
129 Bodelon C. Hormonal factors and risk of esophageal squamous cell carcinoma and adenocarcinoma in postmenopausal women. Cancer Prev Res. 2011; 6: 840-850

Compared with women who had never been treated, the risk of squamous cell cancer was significantly lower in women being treated with any type of MHT: RR=0.41 [0.18; 0.94] (nine cases) and in those receiving combined HRT: RR=0.25 [0.07; 0.86] (three cases); the risk was not significantly different in women treated with oestrogen-only HRT.

8.13.4 Gastric cancer

Oestrogen-only and combined HRT

- Meta-analysis - 2012[130] (level 3 evidence).

This meta-analysis of published data included seven studies: three case-control and four cohorts. The relative risk of gastric cancer was significantly reduced in treated women or women who had been treated compared with women who had never been treated: RR = 0.77 [0.64; 0.92].

8.13.5 Skin cancer

Oestrogen-only and combined HRT

- Post-hoc analysis of the randomised oestrogen-only and combined HRT WHI studies - 2011[131] (level 2 evidence).

Information on the major risk factors for skin cancer was not collected, the analysis was adjusted for level of UV per region, and the data concerning the occurrence of skin cancers apart from melanomas were only based on self-declaration. No significant difference in the risks of melanoma and cancers other than melanomas was revealed between the treated groups and the placebo groups in a combined analysis or in a separate analysis of the two studies.

- Cohort study (Italy)[42] - 2008 (level 2 evidence).

This study did not reveal any change in risk (melanoma and other cancers) on MHT.

- Cohort study (Diet, Cancer and Health – Denmark) - 2012 (level 3 evidence)[132].

This cohort concerned women living in the Copenhagen region, born in Denmark, and aged 50 to 64 years, with no history of cancer. Inclusion took place between 1993 and 1997. Information concerning MHT was collected at inclusion. The analysis concerning the skin cancers other than melanomas included 27,176 women. The incident cancer cases were identified from a database listing the cases of skin cancer apart from melanomas diagnosed between 1978 and 2007. The analysis was adjusted for age, sensitivity to sun exposure, number of freckles, nevi on the arms, BMI and alcohol consumption. It was not possible to adjust the analysis for exposure to UV. In total, 1175 cases of basal cell epithelioma and 76 cases of squamous cell cancers were identified for a median follow-up of 11.5 years. The incidence ratio of basal cell cancers in women using or having used MHT at inclusion compared with women who have never used MHT was 1.15 [1.07; 1.37]. The present or previous use of MHT at inclusion was not associated with an increased risk of squamous cell cancer; however, there was a significant trend for the risk to increase with the treatment duration at inclusion.

- Systematic review and meta-analysis of published data - 2011[133] (level 3 evidence).

This systematic review aimed to look for a link between the hormone factors and the risk of histologically confirmed melanoma.

The analysis concerning MHT included 10 studies: three cohort studies and seven case-control studies.

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130 Camargo M. *et al*. Sex hormones, hormonal interventions, and gastric cancer risk : a meta-analysis. Cancer epidemiol biomarkers prev. 2012; 21: 20-38

131 Tang J.Y. *et al*. Menopausal hormone therapy and risk of melanoma and nonmelanoma skin cancers : women's health initiative randomized trials. JNCI 2011; 19: 1469-75.

132 Birch-Johansen F. Does hormone rplacement therapy and uts of oral contraceptives increase the risk of non-melanom skin cancer ? Cancer Causes Contrlo .2012; 23: 379-88

133 Gandini S. *et al*. Hormonal and reproductive factors in relation to melanoma in women: current review and meta-analysis. European J cancer.2011; 47: 2607-17.

The relative risk adjusted for sun exposure and/or the phenotype was not significantly increased for the women using or having used MHT compared with those having never used MHT: RR = 1.16 [0.93; 1.44].

8.13.6 Thyroid cancer

Oestrogen-only and combined HRT

- Cohort study (NIH-AARP - USA) - 2011[134] (level 3 evidence).

This cohort study looked for an association between the hormone factors and the risk of thyroid cancer.
The use of MHT was recorded at the start of follow-up from two questionnaires completed by the participants 1 year apart. The incident cases of thyroid cancer were identified from the cancer registries. In total, 187,867 women aged between 50 and 71 years were included.
The analyses were adjusted for cigarette use, alcohol consumption, ethnicity, level of education and BMI.
For a mean follow-up of 9.3 years, 312 incident cancers were identified.
Compared with women who had never been treated, the women being treated had a significantly increased risk: RR= 1.38 [1.07; 1.79], contrary to those having discontinued the treatment. There was no trend for the risk to increase with treatment duration (more or less than 5 years of use).
The risk was not significantly increased for the separate analyses focusing on the ongoing or previous use of oestrogen-only and combined HRT.

08.14 Various

8.14.1 Diabetes

Oestrogen-only and combined HRT

- Cohort study (Finland) - 2009[135] (level 2 evidence).

This analysis of the Kuopio prospective cohort on the risk factors and prevention of osteoporosis aimed to assess the effect of MHT on the incidence of diabetes in post-menopausal women. This cohort includes women residing in the province of Kuopio, born in 1932-1941 and having answered a postal questionnaire in 1989; questionnaires were then sent in 1994 and 1999.
Follow-up started on 1 June 1994 and finished on the date an antidiabetic medicinal product was prescribed (validated by the national health insurance system) or on 31 May 1999. The MHT was defined as the use of a systemic oestrogen therapy, regardless of route of administration, whether or not combined with a progestogen. The analysis was adjusted for age, parity, BMI, existence of hypertension, hypercholesterolaemia, or a hysterectomy, and tobacco use.
In total, 162 new cases of diabetes were recorded during follow-up in the population of 8483 post-menopausal women selected for analysis.
The use of MHT was associated with a reduced risk of diabetes compared with women who had never used MHT: RR=0.53 [0.24; 1.15] for women having used MHT < 2.5 years during the follow-up and RR=0.31 [0.16; 0.60] for women having used MHT for 2.5 to 5 years.

Combined HRT

- Cohort study (E3N - France) - 2009[136] (level 2 evidence).

This analysis of the E3N cohort aimed to assess the influence of MHT according to the route of administration of oestrogen and the type of progestogen used on the risk of onset of diabetes. The post-menopausal women included in the analysis must have answered a questionnaire sent in

134 Schonfeld S.J. et al. Hormonal and reproductive factors and risk of postmenopausal thyiroid cancer in the NIH-AARP Diet and health study. Cancer epidemiology 2011; 35:e85-e90.
135 Pentti K *et al*. Hormone therapy protects from diabetes :the kuoppio osteoporosis risk factor and prevention study ; European J. Endocrinol. 2009; 160: 979-983.
136 Lauzon-Guillain B. Menopausal hormone therapy and new-onset diabetes in the French etude epidemiologique de femmes de la mutuelle générale de l'éducation nationale (E3N) cohort. Diabetologia. 2009 ; 52 : 2092-2100.

1993 concerning their diet and their response must have been validated. The incident cases of diabetes reported by the participants had to have been validated by identification of the reimbursement of an antidiabetic treatment between January 2004 and June 2007 (data collection stopped) or by a glucose assay result in accordance with the WHO guidelines. Given the age of the population, the incident cases were considered to be type 2 diabetes.
The participants were included in the analysis until the date of diagnosis of diabetes, of the last completed questionnaire or 30 June 2007.
The analysis was stratified by age and adjusted for level of education, physical activity at the first questionnaire, age at first menstrual cycle, parity, breastfeeding, type and age at menopause, family history of diabetes, cholesterol level, existence of hypertension, alcohol consumption, calorie intake, tobacco use and BMI.
In total, 1220 new cases of diabetes were validated in 63,624 post-menopausal women for a follow-up of 663,087 women-years (mean duration: 10.4 ± 3.6 years).
The incidence of diabetes during the follow-up was lower in women using or having used MHT than in those who had never used it: RR = 0.82 [0.72; 0.93]. The administration of oral oestrogen was associated with a greater risk reduction: RR=0.68 [0.55; 0.85] than the transdermal administration: RR= 0.87 [0.75; 1] (significant difference between the two risks at 0.028).
No difference in risk was found based on the progestogen used.

8.14.2 Gallstones

Oestrogen-only and combined HRT

- Cohort study (Million Women Study - United Kingdom) - 2008[137] (level 2 evidence).

This analysis of the MWS concerned the post-menopausal women, hospitalised for the first time for gallstones, cholecystitis or cholecystectomy after their inclusion in the cohort.
The participants were recruited between 1996 and 2001. The data collection stopped in December 2003 for Scotland and March 2005 for England.
The analysis was adjusted for place of recruitment, BMI, parity and stratified by age and history of a hysterectomy.
The use of MHT and its type were determined from the responses to the questionnaire at inclusion.
In total, 1,001,391 women were included which is 6,102,811 person-years, for a mean follow-up of 6.1 years during which 19,889 women had an initial hospitalisation for gallbladder conditions.
No difference in risk between the users of oestrogen-only HRT and the users of combined HRT was found.
Compared with women who had never been treated, the women being treated had a significantly increased risk of a gallbladder condition: RR= 1.64 [1.58; 1.69], as did the women having discontinued the treatment: RR= 1.27 [1.22; 1.32] in these latter women, the risk reduced with time.
The risk on transdermal treatment: RR= 1.17 [1.10; 1.24] was significantly lower than on oral treatment: RR = 1.74 [1.68; 1.80], ($p<0.001$).
Amongst the oral treatments, women treated with conjugated equine oestrogen had a significantly increased risk RR = 1.79 [1.72; 1.87] than those using oestradiol: RR 1.62 [1.54; 1.70], ($p< 0.001$).
The risk increased significantly with the oestrogen dose for conjugated oestrogen (>0.625 mg/day or ≤ 0.625 mg/day) and oestradiol (> 1 mg/day or ≤ 1 mg/day).

Tibolone

- Cohort study (Million Women Study - United Kingdom) - 2008[137] (level 2 evidence).

Women on tibolone treatment had a significantly increased risk, not different to the risk on oral oestrogens or combined HRT: RR = 1.84 [1.69; 2.00].

8.14.3 Asthma

137 Liu B. Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. BMJ. 2008; 337: a386. doi:10.1136/bmj.a386

Oestrogen-only and combined HRT

- Cohort study (E3N - France) - 2009[138] (level 2 evidence).

Asthma attacks were considered as incident when the participants had declared on the initial questionnaire that they had never had an asthma attack and on the subsequent questionnaire that they had had an asthma attack, confirmed by a doctor.

The analysis was based on 57,664 post-menopausal patients not having had an asthma attack before their inclusion, which is 495,448 person-years. The participants contributed to the follow-up until their first asthma attack or until July 2002; 569 incident cases of asthma were reported. The analysis was adjusted for existence of tobacco use, BMI, use of oral contraceptives, parity, total calorie intake, and type of menopause, and stratified by year of birth.

Compared with women who had never been treated, there was a significant increase in the risk of incident asthma in women using or having used MHT: RR = 1.21 [1.00; 1.46]. The increased risk was limited to women having used oestrogen-only HRT: RR = 1.54 [1.13; 2.09]. No increased risk was found in women having used combined HRT, regardless of the type of progestogen; the difference between the two risks was significant (p=0.04).

8.14.4 Depression

Oestrogen-only and combined HRT

- Controlled study - quality of life - 2008[139] (level 1 evidence).

The WISDOM study aimed to evaluate the risks and benefits of long-term MHT (conjugated equine oestrogen combined with medroxyprogesterone) versus placebo. The study was ended prematurely in 2002 after a median follow-up duration of 1 year due to interruption of the WHI study. One of its aims was to evaluate the effect of treatment on the quality of life of post-menopausal women.

The mean age was 63.8 years The data from 1191 women / 1856 in the treated group and 1193 / 1857 in the placebo group were analysed. There was no significant difference between the groups for the assessment of depression using the Center for Epidemiologic Studies Depression scale (CES-D).

- Cohort study (Three Cities - France) - 2010[140] (level 2 evidence).

The participants in this study were selected randomly from the electoral rolls of three French towns between 1999 and 2001, amongst people aged 65 years or over and not living in institutions. They had an interview at inclusion and then every 2 years.

This analysis aimed to examine if MHT administration at inclusion changed the risk of occurrence of depression during the 4-year follow-up. It was adjusted for age, level of education, centre, widowhood, age at menopause, existence of insomnia, a disability, cognitive deterioration, or a chronic disease, and history of depression, and focused on 4069 women with 4 years of follow-up.

The symptoms of depression were assessed using the CES-D scale; the women with a score ≥ 23 or taking antidepressants were considered depressed for this analysis.

The risk of occurrence of depression with any form of ongoing MHT at inclusion was: OR=1.35 [1.00; 1.03] p=0.06; it was not significantly increased with oestrogen-only HRT. The risk was significantly increased with combined HRT including transdermal oestrogen: OR=1.48 [1.03; 2.12] and with the use of a progestogen other than progesterone associated with a transdermal oestrogen: OR=1.59 [1.01; 2.50]; it was not significantly increased with treatment combining a transdermal oestrogen and a progesterone, or with combined HRT including an oral oestrogen. Women who interrupted the MHT during the study had a significantly increased risk of occurrence of depression during follow-up: OR = 2.63 [1.52; 4.55]. The authors did not specify if the risks were significantly different between the oestrogen-only HRT and the combined HRT, between the

138 Romieu I. *et al.* Postmenopausal hormone therapy and asthma onset in the E3N cohort. Thorax. 2009 ; 65: 292-297

139 Welton A. *et al.* Health related quality of life after combined hormone replacement therapy : randomised controlled trial. BMJ 2008;337:a1190.

140 Scali J. *et al*. A prospective study of hormone therapy and depression in community-dwelling elderly women : the Three City Study.J Clin Psychiatry. 2010;71:1673-6

progesterone and other progestogens, or between women having continued treatment and those having discontinued it during follow-up.

8.14.5 Kidney stones

Oestrogen-only HRT

- Post-hoc analysis of the oestrogen-only and combined HRT WHI study - 2010[141] (level 2 evidence).

The cases of kidney stones were only identified from questionnaires regularly completed by the patients. The incident cases were those occurring during the study in the patients with or without a history of kidney stones. The incidence was determined for a mean follow-up of 7.1 years for the oestrogen-only study and 5.6 years for the oestrogen + progestogen study.
The analysis was adjusted for allocation in the randomisation arm of the different WHI studies (MHT, calcium, vitamin D, dietary changes), age group at inclusion, ethnicity, BMI and history of kidney stones at inclusion. Women with information missing on the history of kidney stones at inclusion were excluded from the analysis.
In total, 335 incident cases of kidney stones were identified amongst the patients (24,620) receiving one of the active treatments and 284 amongst the patients receiving the placebo, corresponding to 39 cases/10,000 person-years for the treated patients and 34 cases/ 10,000 person-years for the patients receiving the placebo: HR=1.21 [1.03; 1.44].
When the data was censored at treatment discontinuation, the hazard ratio was 1.39 [1.08; 1.78].

8.14.6 Urinary incontinence

Oestrogen-only and combined HRT

- Systematic review of controlled studies on the non-surgical treatments of urinary incontinence in women - 2008[142] (level 4 evidence).

The authors concluded that the administration of oral oestrogen alone or combined with a progestogen was associated with an increased risk of urinary incontinence compared with the placebo in the majority of studies. It should be noted that urinary incontinence was a secondary endpoint in these studies or that these studies had a low level of evidence.
The administration of transdermal oestrogen (two studies) was associated with an improvement in urinary incontinence.

8.14.7 Cataracts

Combined HRT

- Cohort study - Australia - 2010[143] (level 2 evidence).
  - This cohort (Blue Mountains Eyes Study) included a population over 49 years of age, urban, from the Blue Mountains region. 2,072 women (83% of the eligible population) consented to participate in the cohort. History taking was performed at inclusion, in particular focusing on the use of MHT, along with an eye examination to check for cataracts. The history taking and the examination were repeated at 5 and 10 years of follow-up. In total, 1484 women were examined, at least once after the inclusion examination. The analysis was adjusted for age, cigarette use, use of steroids, socioeconomic status, myopia, hypertension and diabetes.

141 Maalouf N. postmenopausal hormone use and the risk of nephrolithiasis. Arch intern med. 2010; 18: 1678-84
142 Shamliyan T.A. *et al.* Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. Annals of internal medicine. 2008; 6:459-74.
143 Kanthan G.L. *et al.* exogenous oestrogen exposure, female reproductive factors and the long-term incidence of cataract: the Blue Mountains Eye Study. Acta Ophtalmologica 2010; 88: 773-78

- The current or previous use of MHT was not significantly associated with the incidence of any type of cataract or cataract surgery, the same as with the oestrogen-only and combined HRT studied separately.

09 SUMMARY & DISCUSSION

09.1 New elements since the last AFSSAPS review in 2008

Currently, no level 1 evidence information enables us to know whether or not the risks associated with MHT are influenced by the type of oestrogen, its route of administration, the type of progestogen or by the time between menopause and MHT initiation. The level 2 evidence information suggests that these risks vary depending on the different types of treatments.

No randomised study studied the benefit/risk ratio of MHT in post-menopausal women under the age of 45.

In the WHI studies, the follow-up of the women after the double-blind phase, as specified at the start in the study protocols, revealed that the increased risk of strokes (Conjugated Equine Oestrogen - CEO -, combined or not with Medroxyprogesterone Acetate -MPA), thromboembolic events (CEO, CEO + MPA), and breast cancer (CEO + MPA) and the benefits in terms of reducing the risk of hip fracture (CEO, CEO + MPA) and colorectal cancer (CEO + MPA) were no longer different to those for women on placebo after treatment discontinuation.

Analysis by age group or the time between menopause and treatment initiation:

- In women under 60 years of age taking conjugated equine oestrogen only, the analyses of the WHI study since 2008 did not reveal an increased risk, regardless of the condition considered, or a reduction in the risk of coronary heart disease and myocardial infarction in treated women compared with the placebo group.
- Concerning the combined CEO + MPA treatment, there was no new data on the risks per age group since the WHI analysis in 2007 (Rossouw: increased risk of coronary heart disease with time between menopause and treatment initiation becoming significant with a period of 20 years or more).
- Several level 2 evidence studies including the observational WHI study and the E3N study suggest that the risk of breast cancer would be higher for the treatments started shortly after menopause, regardless of whether it is oestrogen-only or combined HRT. This could be involved in the reduced risk of breast cancer observed in the WHI study on oestrogen-only HRT, the treatments having been mainly started a while after menopause.
- It should be noted that the conclusions of the analyses by age group focusing on the treatment phase of the randomised WHI studies are level 2 evidence because the initial protocol did not plan an analysis by per age group or by time since menopause.

Route of administration of the oestrogen and type of progestogen

- No randomised trial was conducted to confirm the absence of increased venous thromboembolic risk associated with transdermal oestrogen administration and the absence or reduction of the risk associated with the use of progestogens containing natural progesterone or norpregnane derivatives in the epidemiological studies.
- In the E3N study (level 2 evidence), the risk of breast cancer was lower for combined HRT including micronised progesterone and restricted to treatments started less than 3 years after menopause and having lasted more than 5 years, but these data have not been confirmed by other studies.
- The increased risk of endometrial cancer associated with the administration of oestrogen combined with micronised progesterone which was revealed in the EPIC cohort (level 2 evidence) requires confirmation by other studies.

Benefits of MHT

- The data do not change the conclusions from 2008: MHT is the most effective treatment for menopausal disorders, in particular the vasomotor symptoms.
- A level 2 evidence study also concluded on its efficacy in the treatment of certain muscular and joint pains.

MHT is the only treatment having demonstrated its efficacy in the primary prevention of osteoporotic fractures in the general population, regardless of the initial fracture risk.

Tibolone

- Tibolone at a daily dose of 2.5 mg is less effective than the oestrogen-only or combined HRT in the treatment of hot flushes but with lower risk of metrorrhagia.
- The associated risks, in particular breast cancer and CVA, remain poorly defined. There is no proven difference in the long-term effects of tibolone compared with oestrogen-only or combined HRT, but the benefit-risk balance of these is better known.

09.2 Summary by condition

9.2.1 Mortality from any cause

No publication concluded on increased mortality from any cause in treated women compared with untreated women or women on placebo.

Overall analyses

Seven level 1 to 4 evidence publications [27,28] [29,30,31,33,34] did not reveal any significant difference for mortality from any cause in treated women (oestrogen-only or combined HRT) compared with untreated women or women on placebo. Five of these publications focused on the WHI studies or included analyses in which these were preponderant.

Analysis based on age

Three level 2 evidence studies[27,34,35,36] concluded that mortality from any cause was lower in treated women (oestrogen-only or combined HRT) aged less than 60 years than in untreated women or women on placebo. One of these studies[34], with level 2 evidence, concluded that mortality from any cause was significantly lower in treated women aged 60 to 64 years compared with untreated women.

Another of these studies[32], with level 3 evidence, concluded that mortality was significantly lower in women aged 50 to 55 years and in those aged over 55 yeas than in untreated women.

9.2.2 Mammary conditions

Benign proliferative breast diseases

Three level 2 evidence studies[37,38] [39] concluded that there was a significantly increased risk of benign breast disease on MHT (oestrogen-only or combined HRT).

Breast cancer

Data published since 2008 confirmed the results of the previous studies: increased risk on combined HRT while it appears that there is little or no increase in the risk on oestrogen-only HRT.

Several level 2 evidence studies suggest that the risk of breast cancer is higher for the treatments started shortly after menopause, regardless of whether they are oestrogen-only HRT or combined HRT.

The observational studies did not reveal any difference in risk according to the route of administration.

Oestrogen-only HRT:

In three level 2 evidence publications of the WHI study[27,28,] [40], the risk of breast cancer was significantly reduced in treated women compared with untreated women apart from women with risk factors[40]. The risk was not significantly changed in the four studies with level 2 or 3 evidence[41,] [45, 47, 48]. Two studies of level 3 and 2 evidence[43,] [44] concluded that there is a lower increased risk than with combined HRT.

Two level 2 evidence publications studied the influence of the time between menopause and treatment initiation: one publication of the WHI study did not find any difference in risk depending on whether the treatment was started more or less than 5 years after menopause[40]; the other study[44] concluded that there was a significantly increased risk when treatment was started less than 5 years after menopause.
Two level 2 evidence studies[43, 61] and one level 3 evidence study[51] did not reveal any difference in the risk between the oral and transcutaneous administration of oestradiol, nor between oral conjugated equine oestrogen and oestradiol[43]. A level 2 evidence study[42] and a level 3 evidence study[45] concluded that there was a lower risk on treatment including transdermal oestrogen than on treatment including oral oestrogen.

Combined HRT:
Ten level 2 evidence publications[28,30,42,31,49,50] or level 3 evidence publications[32,45,43,47,51] four of which are based exclusively on the WHI study[28,30,31,49] and one on the observational WHI study[50] concluded that there was a significantly increased risk.
Five level 2 and 3 evidence studies concluded that risk increased with treatment duration[42,43,46,48,51]. This increase became significant after 1[42], 3[47,51] or 4[30,46] years of treatment. An analysis of the WHI study[49] and an analysis of the observational WHI study[50] of level 2 evidence concluded that there was increased mortality from breast cancer or after breast cancer in women treated with CEO and MPA.
Three level 2 evidence studies[44,54,55] found a significantly increased risk of breast cancer for the treatments started during the 5 years following menopause compared with treatments started later. In a level 2 evidence study[55], the risk was not increased with combined HRT (all progestogens included) which lasted less than 2 years and started more than 3 years after menopause.

Influence of the type of progestogen
No level 1 evidence study enabled a conclusion to be drawn on a difference in risk depending on the progestogen used.
The results of the level 2 or 3 evidence studies published since 2008 are contradictory:
- one study concluded that there was a lower risk with progesterone or dydrogesterone than with other progestogens[55]; another did not reveal an increased risk on progesterone, unlike synthetic progestogens in general;[46] and a third concluded that the risk was lower on medroxyprogesterone and dydrogesterone than on norethisterone[51].
- one level 2 evidence study did not reveal any difference between the testosterone derivatives and the progesterone derivatives,[43] one level 3 evidence study concluded that the risk was higher with progesterone derivatives than with testosterone derivatives[45], and another study concluded the inverse[46]. One study concluded that the risk was significantly increased with continuous HRT including norethisterone or levonorgestrel compared with those containing progesterone derivatives[48], and a third concluded that the risk was significantly increased with treatments including norethisterone acetate, levonorgestrel or medroxyprogesterone acetate but not with dydrogesterone[47].

Tibolone
One randomised versus placebo study in women having had surgery for breast cancer (situation contraindicated in the MA) (level 1 evidence)[52] revealed an increased risk of recurrence in the treated group.
A cohort study (level 2 evidence)[44] concluded that the risk on tibolone was similar to that observed on MHT. Another level 2 evidence study[53] concluded that there was a reduced risk on tibolone.
Two level 3 evidence studies did not reveal any change in risk[46,48].

9.2.3 Venous thromboembolic risk

No randomised trial was conducted to confirm the absence of increased venous thromboembolic risk associated with the administration of transdermal oestrogens and combined HRT containing progesterone or pregnane derivatives observed in the epidemiological studies.

Twelve publications compared the venous thromboembolic accident risk on MHT and on placebo or in the absence of treatment, one of which[67] was updating a previous one[66].On oral oestrogen combined or not with a progestogen, four level 1 evidence studies[27,31,66,67] five level 2 evidence studies,<4493/><4494[28,62,63,65,68] and one level 3 evidence study[64] revealed an increased risk of venous thrombosis; the risk was higher at the start of treatment [62, 64, 66] and returned to normal after treatment discontinuation[27, 31, 62, 64, 66]. The risk was higher on combined HRT (medroxyprogesterone acetate being the most commonly used progestogen in these studies) than on oestrogen-only HRT[62, 65].
The risk was not changed by the time between the date of menopause and the start date of treatment in a level 2 evidence study[29]. It was increased at the start of treatment in a level 2 evidence study[62] and two level 3 evidence studies[64, 66].
A meta-analysis of randomised studies (level 1 evidence) did not reveal any difference in the risk between the oral and transdermal administration (but with a low number of transdermal treatments)[65]. Conversely, for two level 2 evidence studies[62, 68] and three level 3 evidence studies,[64, 66, 67] the risk was not increased on transdermal treatment, unlike the oral administration.
The risk varied depending on the combined progestogen for two level 2 studies. On transdermal treatment, it was increased when associated with norpregnane derivative progestogens, intermediate but not significant for pregnane derivatives and testosterone derivatives, and not increased with micronised progesterone[66]. In combination with oral oestrogen, the risk was significantly increased with medroxyprogesterone than with other progestogens (norethisterone or norgestrel) [62].

9.2.4 Ischaemic cardiomyopathy

The follow-up data from the WHI study confirmed the previous data by supplementing them:
- the increased cardiovascular risk was limited to women over the age of 60 taking conjugated equine oestrogen and MPA treatment and disappeared after treatment discontinuation.
- the follow-up data revealed a reduced risk of myocardial infarction associated with oestrogen-only HRT administration in women aged 50 to 59 years.

Death
The risk of death from coronary heart disease was not increased on conjugated equine oestrogen combined or not with MPA in a level 1 evidence study [27] and two level 2 evidence studies[28,70]. One level 2 evidence study[34] concluded that there was a reduced risk of death from coronary heart disease in treated women aged 36 to 64 years compared with non-treated women; there was a significant trend for the risk to increase with increasing age group at inclusion.

A level 2 evidence study[69] concluded that there was a significant reduction at 10 years in the risk of a composite endpoint (death, hospitalisation for myocardial infarction or heart failure) on treatment with oral oestradiol, combined or not with norethisterone, started shortly after menopause compared with the absence of treatment.

Coronary heart disease
Eight publications (seven of which were post-hoc analyses of the WHI studies or meta-analyses in which the weight of these studies was preponderant) compared the risk of coronary heart disease on MHT and on placebo or in the absence of treatment:
- on oestrogen-only HRT, the risk of coronary heart disease was not increased in two level 1 evidence studies[27, 65] and one level 2 evidence study[28]. The risk of coronary heart disease and myocardial infarction was reduced in women aged 50 to 59 years on conjugated equine oestrogens only compared with a placebo in a level 1 evidence study[27].
  A level 2 evidence study[71] concluded that the risk of myocardial infarction was lower with transdermal treatment compared with oral treatment.
- On combined HRT, two level 2 evidence studies concluded that there was an increased risk[30, 72], and three level 1 and 2 evidence studies did not reveal any increase[28, 65, 31, 32]. A level 2

evidence study[71] concluded that there was an increased risk on continuous combined HRT, but not on cyclical treatment.

- For oestrogen-only or combined HRT, two level 2 evidence studies[29, 65] did not reveal an increased risk of coronary heart disease regardless of the time of treatment initiation after menopause (< or > 5 years)[29].

- On tibolone, according to a level 2 evidence study[71], the risk of infarction was not significantly changed.

9.2.5 Strokes

The randomised studies did not reveal any difference in risk between oestrogen-only HRT or oestrogen HRT combined with MPA.
The follow-up data from the WHI study confirmed the previous data by supplementing them:
- the increased stroke risk associated with combined HRT and oestrogen-only HRT disappeared at treatment discontinuation.
Treatment with tibolone is also associated with an increased risk of CVA.

Nine publications (six of which are post-hoc analyses of the WHI studies i.e. meta-analyses including these studies) compared the risk of strokes on MHT and on placebo or in the absence of treatment.
The risk of death from a stroke was not increased in one level 2 evidence study in women taking conjugated equine oestrogens combined or not with MPA,[30] compared with those on a placebo.
The stroke risk was increased in women taking MHT; the increase was of similar magnitude on oral oestrogen-only HRT and on oestrogen combined with MPA[27, 30, 31](level 1 and 2 evidence studies).
The increased risk disappears after treatment discontinuation[27,28,31](level 1 and 2 evidence).
The time between the start of menopause and treatment initiation does not appear to change the risk in the level 2 evidence studies[29, 73], unlike the dose administered[73].
The stroke risk was lower on transdermal treatment than on oral treatment in a level 3 evidence study[74], however, a meta-analysis of randomised trials[65] (level 1 evidence) did not reveal any difference in risk between the two routes of administration (but with a low number of transdermal treatments).

A controlled study comparing tibolone with a placebo[53] was prematurely stopped due to an increased stroke risk in the treated group.

9.2.6 Cognitive function

The new data have not changed the conclusions from 2008: no reduction of the risk of dementia associated with MHT administration, and maybe increased in elderly women.

Fourteen publications studied the effect of MHT on cognitive function.

- Oestrogen-only HRT: three level 1 evidence publications [77, 85, 86] and four level 2 evidence publications[30, 75, 76, 81] did not reveal any change in cognitive function associated with treatment administration, including with long-term treatment[81]. One level 1 evidence publication[84,] concluded that there was no positive effect on cognitive function and there was a possible negative effect after 1 year of treatment. One level 1 evidence study[79] concluded that there was a slight reduction in cognitive function, not clinically significant on an individual level, and another level 2 evidence study[83] concluded that there was a reduction in the risk of overall cognitive decline and an increased risk of general memory decline if the treatment was started during the 3 years following menopause.
- Combined HRT: one level 2 evidence publication[30] concluded that there was a significantly increased risk of probable dementia in women over 65 years of age (this result is only based on the results of the WHI study). Two level 1 evidence publications[84, 86] and one level 2 evidence publication[81] concluded that there is no effect on cognitive function but there is a possible negative effect for long-term treatments, especially for those including

medroxyprogesterone acetate[86]. One level 1 evidence study[79] concluded that there was a slight reduction in cognitive function, not clinically significant on an individual level, and another level 2 evidence study[83] concluded that there was an increased risk of general memory decline if the treatment was started during the 3 years following menopause.

- On MHT with no distinction regarding the type of treatment, one level 2 evidence study[82] concluded that there was a reduced risk of dementia when MHT was used around fifty years of age while the risk was increased in late use.

9.2.7 Osteoporotic fractures

Oestrogen-only or combined HRT is the only treatment having demonstrated its efficacy in the primary prevention of osteoporotic fractures in the general population, regardless of the initial fracture risk. The follow-up data from the WHI study reveal a disappearance of this efficacy after treatment discontinuation.

Oestrogen-only or combined HRT is associated with a significantly reduced fracture risk including hip fractures[27, 31](level 1 evidence)[32, 88](level 2 evidence) which does not persist after treatment discontinuation[28, 31, 27]. One level 2 evidence study[88] concluded that the reduced risk persisted for 5 years following treatment discontinuation, with an inverse relationship between fracture risk and treatment duration. The risk reduction was more evident during oral treatment than with transdermal treatment, without being able to exclude a dose difference between the two types of treatment.

On tibolone, a level 1 evidence study[53] revealed a significant reduction in the risk of vertebral and non-vertebral fractures.

9.2.8 Quality of life - Menopausal symptoms

The new data do not change the conclusions from 2008: they confirm that MHT is the most effective treatment for menopausal disorders, in particular the vasomotor symptoms.
A level 2 evidence study also concluded on its efficacy in the treatment of certain muscular or joint pains.

- Oestrogen therapy at a very low dose reduced dyspareunia and vaginal dryness in a level 2 evidence study[89].
- The number of women with vasomotor symptoms, night sweats, muscle or joint pains, insomnia and vaginal dryness reduced on combined HRT in a level 1 evidence study[139].

- A meta-analysis[90] compared tibolone at a dose of 2.5 mg with combined HRT. It concluded that combined HRT is more effective in reducing vasomotor symptoms and that tibolone is safer regarding metrorrhagia.

9.2.9 Endometrial hyperplasia/cancer

The observational studies confirmed the reduced risk associated with continuous HRT administration.
The increased risk of endometrial cancer associated with the administration of oestrogen combined with progesterone which was revealed in the EPIC study requires confirmation by other studies.

Thirteen publications studied the risk of endometrial hyperplasia/cancer on MHT.

- The use of oestrogen-only HRT is associated with an increased risk of endometrial hyperplasia[94] (level 1 evidence) and endometrial cancer[91, 93, 101] (level 2 evidence).
- On combined HRT, three level 2 and 3 evidence studies concluded that there was a reduced risk of cancer on continuous combined HRT[93, 96, 97] . Four studies did not reveal an increased risk of endometrial hyperplasia on continuous combined HRT[91,94] (level 1 and 2

evidence), nor endometrial cancer on sequential HRT including MPA (WHI level 1 and 2 evidence study)[31, 29]. A follow-up analysis of the WHI study concluded that there was a reduced risk of cancer.[28] Five level 2 and 3 evidence studies concluded that there was an increased risk of cancer[92, 93], particularly on sequential HRT[91,93] of more than 5[96] or 10 years[97] and long-cycle HRT of more than 5 years[96, 97]. One level 2 evidence study[93] concluded that there was an increased risk of cancer on treatment containing progesterone, unlike treatments containing a progesterone or testosterone derivative. A level 2 evidence study[42] concluded that there was a significant trend for the risk to reduce with increasing treatment duration.

- On tibolone, one level 2 evidence study[98] revealed a higher number of endometrial cancers in the treated group than in the placebo group at 3 years of treatment. A level 3 evidence cohort study[93] revealed that there was an increased risk of endometrial cancer on tibolone, unlike a level 3 evidence case-control study[97].

9.2.10 Ovarian cancer

The observational studies are in favour of an increased risk associated with the administration of oestrogen-only HRT and a less increased risk associated with the administration of combined HRT.

Eleven publications studied the risk of ovarian cancer on MHT.

- On oestrogen-only HRT, five level 2 evidence[99, 100] and level 3 evidence studies[102,105,106] found an increased risk of cancer
- On combined HRT, four level 2 evidence[99] and level 3 evidence studies[105, 106,107]revealed an increased risk of cancer, one of which only found a significantly increased risk for the treatments lasting between 5 and 10 years[107], and two level 2 evidence studies[28,100]and one level 3 evidence study <4708/[102] did not find an increased risk.
- On MHT without specifying the type of treatment, two level 2 and 3 evidence studies did not find an increased risk[42, 104], and another level 3 evidence study found an increased overall risk, an increased risk of serous cancers and a reduced risk of mucinous cancers[103]. One level 2 evidence publications[101] and one level 3 evidence publication[102] concluded that there was an increased risk, limited to treatments of 5 years or more. In a level 2 evidence study[99], the risk reduced after treatment discontinuation, depending on the duration of interruption.

- On tibolone, a level 3 evidence study[102] concluded that there was an increased risk, however, with few exposed cases.

9.2.11 Colorectal cancer

The studies concluded that there was no change in the risk or a reduced risk on oestrogen-only and combined HRT.

Thirteen publications studied the risk of colorectal cancer on MHT.

- On oestrogen-only HRT, a level 1 evidence study[27] and three level 2 evidence studies[28, 29, 112] did not reveal a change in the risk of colorectal cancer; five level 2[32, 109, 110]and 3 evidence studies[114,115] concluded that there is a reduced risk.
- On combined HRT, one level 1 evidence study[31] and four level 2[29] and 3 evidence studies[115, 114] concluded that there is a reduced risk. Five level 2 evidence studies[28,108, 109, 110, 112] did not reveal any change in risk.
- On MHT with no distinction as regards the type of treatment, one level 2 evidence study did not reveal any change in the risk[113], two others[42, 111] concluded that there was a reduced risk in treated women with a significant trend for the risk to reduce over time.

- One level 3 evidence study[114] found a significantly reduced risk with orally administered treatment. Another level 2 evidence study[42] did not find any change in the risk based on the route of administration.

- On tibolone, a level 2 evidence study[53] concluded that there was a reduced risk of colon cancer.

9.2.12 Other cancers

Level 2 and 3 evidence studies (including the WHI analyses studying a type of cancer as a variable of interest not specified in the variables of interest listed in the protocol) studied the risk of other cancers associated with the use of MHT.
Regarding these conditions, the data are currently insufficient or too limited in terms of level of evidence to be able to draw a conclusion.

9.2.13 Other diseases

The new data confirm the reduced risk of diabetes associated with the treatment.
Regarding the other conditions, the data are currently insufficient or too limited in terms of level of evidence to be able to draw a conclusion.

APPENDIX 1:

AFSSAPS - point d'étape - - July 2006

What is established in terms of risks:

Currently, no data from randomised trials show whether the risks associated with MHT are influenced or not by the type of oestrogen (conjugated equine oestrogen, oestradiol), by the type of progestogen (medroxyprogesterone acetate, levonorgestrel, norethisterone, progesterone, etc.), or by the route of administration of the oestrogen (oral, transdermal), or finally by the methods of progestogen use (sequential or continuous administration).

Breast cancer

Several hormonal factors modulate the risk of breast cancer. This risk is correlated to oestrogen exposure, which depends on the duration of time between puberty and menopause. MHT prolongs the natural oestrogen exposure and places a treated woman at a higher risk than that of an untreated woman of the same age.

According to the WHI[8] study, there is an increased risk of breast cancer in women using combined HRT. This increased risk of cancer increases with treatment duration. For the first time, the WHI reports that mammary tumours were diagnosed at a more invasive stage[10]. The hypothesis of a delayed diagnosis is suggested, linked to increased mammary density caused by the MHT administration. Based on the current data, oestrogen-only MHT does not appear to increase the risk of breast cancer.[15,17] The increased risk of breast cancer linked to combined MHT could depend on the type of MHT, according to the French observational E3N study. The study suggests that there would be no increased risk when MHT combines oestrogen (mainly transdermal) with micronised progesterone[22]. This result needs to be confirmed with other studies.

Endometrial cancer

The absence of increase risk of endometrial cancer when oestrogens, known to increased this risk, are combined with a continuous progestogen was revealed by the MWS study while the progestogens administered sequentially did not completely remove the risk[1,11, 20]. Moreover, in this same study, it was suggested that tibolone increases the risk of endometrial cancer occurrence for a mean follow-up duration of 3.4 years.

Ovarian cancer

Some data suggest that MHT could be associated with an increased risk of ovarian cancer[11], but this would need to be confirmed with other studies.

Venous thromboembolic risk

MHT increases the venous thromboembolic risk (venous thrombosis, pulmonary embolism), especially during the first year of treatment, which means the contraindications for prescription must be strictly followed. This risk increases with age. Venous thromboembolic family history represents a risk factor which must be taken into consideration.

The venous thromboembolic risk linked to MHT could depend on the route of administration of oestrogens and the type of progestogen according to the French ESTHER case-control study[24, 25]. The study suggests that there would be no increased risk with transdermal MHT, apart from when oestrogens are combined with norpregnane derivatives. This result must be confirmed by other studies. In any case, it does not enable a conclusion to be drawn that the transdermal route would reduce all of the other risks induced by MHT, nor that this treatment can be prescribed with an increased risk of venous thromboembolic disease.

Cardiovascular risk

The HERS I and II (Heart and Estrogen/progestin Replacement Study) [6, 7] revealed that MHT, administered orally, did not reduce cardiovascular risks in women with coronary heart disease.

The WHI data[8,13,14] confirmed that combined MHT does not protect against the risk of a coronary accident and could even cause an increased risk of myocardial infarction and stroke during the first year of treatment in women with no cardiovascular history. This increased risk of an ischaemic accident was observed in women over 60 years of age, treated with conjugated equine oestrogen and medroxyprogesterone acetate. Similarly, the results of the analyses from the other WHI study reveal that treatment with oestrogen-only HRT does not provide a protective effect on the occurrence of coronary heart disease, in particular in women over 60 years of age, and increases the risk of stroke occurrence[15, 16].
A meta-analysis including 28 complete, randomised, controlled studies, with 39,769 subjects, confirms the increased risk of stroke occurrence in MHT users[1]. The same level of risk is found regardless of the type of MHT (oestrogen-only HRT or combined HRT). This study specifies that the risk is only significantly increased for strokes of ischaemic origin. It should be noted that the results are extremely influenced by the weight of the WHI study.

Cognitive disorders:
Contrary to what was hoped, there are currently no data revealing a protective effect of MHT on cognitive disorders. MHT could even increase the risk of dementia (in women over the age of 65)[12].

This new analysis of risk data remains in agreement with the conclusions already made in May 2004 in the ANAES /AFSSAPS public hearing report[3].

What is established in terms of efficacy

Menopausal disorders
The efficacy of MHT in the treatment of menopausal disorders, in particular vasomotor symptoms, has been widely demonstrated.

Prevention of osteoporosis
Effect on bone density
Bone loss, which is associated with a fracture risk, is rapid during the first year of menopause. MHT enables this bone loss to be prevented and the effect is dose-dependent. Upon discontinuation of MHT, bone loss resumes at a physiological rhythm.

Effects on fractures
MHT is the only treatment having demonstrated its efficacy in the primary prevention of osteoporotic fractures in the general population (in the absence of bone mineral density measurement -BMD-). The anti-fracture benefit (in terms of relative risk) is identical regardless of the initial fracture risk.
In the WHI study[2], the percentage of fractures observed after 5 years of treatment is 8.6% in women having received MHT versus 11.1% in untreated women.
The duration during which the fracture risk is reduced after treatment discontinuation is not known but it appears that it is not longer than several years.
It is also not established whether MHT administered at the start of menopause prevents fractures a while after treatment discontinuation.
Finally, there are few or no efficacy data on the prevention of fractures with premature menopause, of low BMD, and in women with a history of vertebral fractures.

Colorectal cancer
The WHI study focusing on the CEO + MPA treatment[8] reports a reduced risk of colorectal cancer; this possible protective effect of MHT on the occurrence of colorectal cancer is not yet sufficiently documented, in particular regarding the duration of this protection.

What is the benefit/risk ratio of MHT based on

[1] Bath PM *et al.* Association between hormone replacement therapy and subsequent stroke: a meta-analysis. BMJ. 2005, 30; 365: 1543-51

its indications?

In the treatment of menopausal disorders

The benefit/risk ratio of HRT is favourable when the menopausal disorders perceived by the patient are sufficiently troublesome to impair her quality of life. Treatment may be initiated if the woman wishes, at the minimum effective dose for the shortest possible duration. In fact, in the WHI study, the follow-up of the group treated with combined HRT was discontinued early at the end of 5 years of treatment and that of the group treated with oestrogen-only HRT at the end of 6.8 years because the benefit/risk ratio was deemed unfavourable relative to the placebo group.

In the treatment of osteoporosis

In the prevention of fracture risk, the benefit/risk ratio of MHT, regardless of the product considered, is unfavourable based on the currently available data.

Administration of MHT could be considered in post-menopausal women with an increased risk of fractures:

- when the patient presents menopausal disorders which she perceives as impairing her quality of life (cf. above);
- when the patient presents intolerance to another treatment indicated in the prevention of osteoporosis and after a precise and careful individual assessment of the benefit/risk ratio.

In post-menopausal women in good health with no menopausal disorders and with no osteoporosis risk factors, the prescription of MHT is not recommended.

In practice, what is the course of action?

The guidelines are identical to those previously issued in December 2003

• At the start of treatment, patients must be given all relevant information enabling an appropriate and informed prescription. Thus, the patient must be informed about the risks inherent to the treatment and the results of recent studies which suggest that the risk could vary depending on the product.

• In addition, the treatment should be reassessed regularly, at least once a year, taking into account changes in the benefit/risk ratio. The treatment may be temporarily suspended during this reassessment in order to verify the persistence of the menopausal syndrome and its severity.

• Regardless of the indication, it must be remembered that:

- before initiating or reinstituting MHT, a complete clinical and gynaecological examination (including an analysis of the family history) should be performed. Regular breast examinations should be performed according to current guidelines (palpation, mammography, ultrasound, etc.) and adapted in accordance with the individual case. MHT is contraindicated in confirmed or suspected cases of breast cancer, or other confirmed or suspected oestrogen-dependent tumours (for example, endometrial cancer);
- the use of a MHT in patients with a history of a venous thromboembolic accident or a known thrombotic condition requires careful assessment of the benefit/risk ratio. MHT is contraindicated in the event of progressing venous thromboembolic accident, or a history of recurrent thromboembolic accidents;
- MHT is also contraindicated in the following situations:

genital haemorrhage without established diagnosis, recent or progressing arterial thromboembolic accident, acute or chronic liver disease, or a history of liver disease, until liver tests have returned to normal, hypersensitivity to the active ingredients or to one of the excipients.

APPENDIX 2

AFSSAPS - Point of information, February 2008

The last guidelines released by AFSSAPS on MHT were in June 2006. Since then, new study results have led AFSSAPS to reconvene the working group on studies relating to MHT, composed of expert epidemiologists and biostatisticians, who, in 2005, described the situation of MHT use in France[1].

The assessment work mainly focused on the new data from Anglo-Saxon studies, the WHI (Women's Health Initiative) and MWS (Million Women Study):

- the re-analysis of the WHI study[2] did not provide new information in terms of arterial cardiovascular risk. MHT did not provide protection against the myocardial infarction risk (and other coronary heart diseases), including in women treated shortly after menopause. In addition, it exposes treated women to an increased stroke risk.
- The new data from the cohorts of the MWS[3] (Million Women Study) and the NIH-AARP Diet and health study[4] (cohort of retired people from the National Institute of Health) confirms the increased risk of ovarian cancer in women treated with MHT, whether it is with oestrogen-only HRT or combined HRT, and this is from 5 years.

AFSSAPS recalls that there is an increased risk of breast cancer in women receiving combined MHT. This risk has especially been demonstrated with certain treatments and could vary depending on the type of MHT used. The French E3N[5] study suggests that the risk would depend on the type of progestogen associated with the oestrogen and would be particularly lower with micronised progesterone and dydrogesterone.
Recently, the Fédération Nationale des Collèges de Gynécologie Médicale (FNCGM [National Federation of Medical Gynaecology Colleges]) presented the results of the MISSION study[6] which concluded that there was no increased risk of breast cancer in women treated with MHT. The AFSSAPS working group on the studies relating to MHT considers that the methodology of this exposed cohort/non-exposed cohort study presents numerous insufficiencies and bias. In particular, the number of included patients is too low to enable detection of an increased risk of breast cancer, and there is a selection bias linked to the decision of the prescriber on whether or not to treat his/her patient, in particular based on risk factors linked to the medical history. The group concluded that the MISSION study did not under any circumstances enable the increased risk of breast cancer in women receiving combined MHT to be challenged.

1- Rapport Afssaps / Costagliola - traitement hormonal substitutif de la ménopause: Caractéristiques de l'utilisation en France - Effets sur la survenue de cancers du sein et d'événements cardiovasculaires en France - Propositions d'études complémentaires - September 2005. [Characteristics of use in France - Effects on the occurrence of breast cancer and cardiovascular events in France - Propositions from additional studies - September 2005]
2- Rossouw JE et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007; 297:1465-1477.
3- Beral V et al. Ovarian cancer and hormone re-placement therapy in the Million Women Study. Lancet. 2007; 369: 1703-1710
4- Lacey JV et al. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. J Nat Cancer Inst. 2006; 98: 1397-1405
5- Fournier A et al. Unequal risk for breast cancer associated with different hormone replacement therapies : results from the E3N cohort study. Breast Cancer Res Treat, 2008; 107 (1): 103-11
6- Espié M et al. Breast cancer incidence and hormone replacement therapy : Results from the MISSION study, prospective phase. Gynecological endocrinology, 2007; 23 (7): 391-397

APPENDIX 3

SUMMARY ASSESSMENT REPORT OF THE PhVWP JANUARY 2010:

Hormone Replacement Therapy containing oestrogen with and without progesterone – 3rd revision of Core Summary of Product Characteristics

Key message

Product information of HRT products updated on risks of breast cancer, ovarian cancer, endometrial cancer, coronary artery disease, stroke and venous thrombosis

Reason for current safety review

A Core Summary of Product Characteristics (Core SmPC) for Hormone Replacement Therapy (HRT) products containing oestrogen with and without progesterone has been regularly updated at the level of the EU by the CMD(h) (previously by the Mutual Recognition Facilitation Group) since 2001.

The third revision of the Core SmPC was initiated to provide accurate information on the latest evidence.

Safety concern and data assessed

Latest evidence was mainly available from the Women's Health Initiative (WHI) trial (additional results for heart disease, stroke, venous thromboembolism and breast cancer) and the Million Women Study (MWS) (new findings on ovarian cancer and updated findings on breast cancer). There were also important meta-analyses of coronary heart disease and breast cancer and new observational data on stroke as well as endometrial and ovarian cancer.

Outcome of the assessment

The third revision of the core SmPC includes a new contra-indication (known thrombophilic disorders), new or adapted warnings regarding premature menopause, endometrial cancer risk of oestrogen-only HRT, breast cancer risk, ovarian cancer risk, venous thromboembolism risk, coronary artery disease risk and adapted wordings on undesirable effects (breast cancer, endometrial cancer, venous thromboembolism and stroke).

More specifically, it provides advice that the risks of HRT are likely to outweigh the benefits for the majority of women above the age of 60 years and that the risk is lower in women taking HRT during premature menopause. Further it includes the clearer evidence that the risk profile in women without a uterus using oestrogen-only HRT is more favourable than that associated with combined HRT.

The following was concluded in relation to particular risks:

Breast cancer: There is uncertainty over the increase in incidence of breast cancer in oestrogen-only users, given that low or no risk was observed in many recent studies including WHI. There is new evidence from the WHI trial on risks associated with oestrogen-only HRT, including lack of increase in risk of breast cancer in users of oestrogen-only compared with combined HRT.

Endometrial cancer: In MWS, no risk was observed in users of combined sequential or continuous HRT.

Ovarian cancer: There is possibly a small increase in risk in users of combined HRT. Estimates on additional numbers of cases in users of any HRT are available from MWS.

Coronary artery disease: An increase in risk is likely to be found only in combined HRT users, not in oestrogen-only HRT users. The risk increases with age. There is new evidence from the WHI trial on risks associated with oestrogen-only HRT, including lack of increase in risk of coronary artery disease in users of oestrogen-only compared with combined HRT.

Stroke: Data from the WHI trial show the same increase in risk of stroke in users of oestrogen-only HRT as in users of combined HRT, which is independent of duration of use.

Venous thromboembolism: A contra-indication of known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency) has been warranted necessary. There is new evidence from the WHI trial on risks associated with oestrogen-only HRT, including a lower risk of VTE compared with combined HRT.

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APPENDIX 4

SCIENTIFIC LEVEL OF EVIDENCE PROVIDED BY THE LITERATURE[1]

Level 1 - established scientific proof
- Randomised controlled trials of high power
- Meta-analysis of randomised controlled trials
- Analysis of decision based on well-conducted studies

Level 2 - scientific presumption
- Randomised controlled trials of low power
- Well-conducted non-randomised controlled studies
- Cohort studies

Level 3 - low level of evidence
- Case-control studies

Level 4 - low level of evidence
- Comparative studies with significant bias
- Retrospective studies
- Case series
- Descriptive epidemiological studies (cross-sectional, longitudinal)

In this reassessment document, the cohort studies during which the menopausal status of participants was not known, or for which exposure to treatment was defined according to the information collected at inclusion but not supplemented during the follow-up, were considered by the working group to be level 3 evidence.
One cohort study for which there was no indication of exposure duration before or during follow-up, only for the time of inclusion, was considered as level 4 evidence.

1 ANAES - literature analysis guide - January 2000.