



# Menopausal hormone therapy in healthy women: a new look at an old topic?

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# Index

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## Introduction

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### Main studies on MHT in postmenopausal women

- > Nurses' Health Study (1985)
  - > Framingham Heart Study (1985)
  - > Women's Health Initiative (2002)
  - > Women's Health Initiative (2004)
  - > Systematic Cochrane Review
- 

### Risk/benefit balance. Main clinical effects

- > MHT and cardiovascular risk
  - > MHT and hip fractures
  - > MHT and cognitive impairment
  - > THM and cancer
  - > MHT and mortality
  - > Other aspects of MHT
- 

### Are all oestrogens similar?

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### Use of MHT in Navarre

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## Annexes

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## Conclusions

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## References

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## > Abstract

Menopausal hormone therapy (MHT) is an effective treatment for controlling vasomotor symptoms in peri- and postmenopausal women. The *Women's Health Initiative* trials linked the use thereof to a potential increase in cardiovascular risk and breast cancer in MHT users, which led to restrictions on the use of this treatment in postmenopausal women.

The FDA (Food and Drug Administration) has recently lifted the restrictions concerning cardiovascular risk and breast cancer due to the use of MHT in women aged 50 to 59 years. However, this decision does not appear to be based on scientific evidence of a minimally acceptable quality. The EMA has maintained its warnings regarding these risks. This article reviews the evidence underlying these regulatory decisions.

A post-hoc reanalysis of the effects of MHT in women aged 50–59 years with vasomotor symptoms showed no increase in the incidence of atherosclerotic cardiovascular disease, a composite outcome of myocardial infarction, angina-related hospitalisation, coronary revascularisation, ischaemic stroke, peripheral arterial disease, carotid disease or cardiovascular-related death. In the case of women aged over 60 years, it appears that MHT may increase cardiovascular risk, especially the incidence of stroke and thromboembolic events.

The adjusted results from the WHI clinical trial did not show any significant differences in the incidence of colorectal or breast cancer with or without MHT. However, recent observational evidence suggests that the combination oestrogen plus progestogen may double the risk of invasive breast cancer in women aged 50 to 59 years.

Around half of MHT users in Navarre are in that age range. In both this age group and in all women using MHT, half receive treatment for at least 3 years. Given that the risk of breast cancer appears to increase with length of treatment, it is recommended to use the minimum effective dose and the shortest time possible when, after a personalised assessment, MHT is indicated for the control of vasomotor symptoms in women in this age range.

## > Keywords

Menopause, post menopause, oestrogen-replacement therapy, progestogens.



## Introduction

A decrease in oestrogen levels, which affects the heat-regulating centre of the brain, occurs in women during menopause and perimenopause. This often results in vasomotor symptoms, such as night sweats, hot flushes, palpitations, muscle or joint pain, chills and insomnia, amongst others, which may affect quality of life to a greater or lesser extent<sup>1</sup>.

Of the different options available to treat vasomotor symptoms, it is generally recommended to avoid hot food or drinks, caffeine, alcohol or tobacco, wear light clothing, avoid overweight or obesity and undertake regular physical activity. Other additional measures that may also be used include mind-body therapy, phytoestrogens, medicinal plants, menopausal hormone therapy (MHT), bazedoxifene and non-hormone drugs (antidepressants, gabapentin, clonidine, oxybutynin, vitamin E and, more recently fezolinetant). However, some of these drugs are not indicated for the treatment of menopause symptoms or are not funded by the National health System. Amongst these options, MHT has shown proven efficacy for the control of vasomotor symptoms<sup>2</sup>.

Indeed, the use of MHT during perimenopause or post-menopause has generated some controversy in the scientific community in the past few years and is currently being reconsidered. The findings of the *Women's Health Initiative* clinical trials caused regulatory agencies to restrict the use thereof due to a possible increase in cardiovascular risk and the onset of cancer associated with MHT use<sup>3,4</sup>. More recently, the US *Food and Drug Administration* (FDA) has lifted these restrictions ("*black box*") in women aged less than 60 years<sup>5</sup>. To a large extent, this was justified on the basis of a reanalysis of the Women's Health Initiative trial data concerning the use of conjugated oestrogens<sup>6</sup>. It has also become known that this decision was adopted by a panel of experts selected by the FDA who had conflicts of interest with pharmaceutical companies producing MHT drugs<sup>7</sup>. However, the European Medicines Agency (EMA) currently maintains the restrictions originally put in place<sup>8</sup>. As such, the postures of the FDA and EMA currently differ markedly.

The objective of this article is to analyse the evidence on which the FDA's decision to lift restrictions on the use of MHT to treat vasomotor symptoms in women aged less than 60 years was based and to make a series of recommendations based on said analysis. To that end, evidence from the individual studies



providing data concerning our topic of interest has been taken into consideration. The main clinical practice guidelines and other consensus documents have also been reviewed to identify original studies on which our conclusions can be based.

## Main studies on MHT in postmenopausal women

### Nurses' Health Study (1985)<sup>9</sup>

A study performed with the so-called "*Nurses' Health Study*" cohort, the objective of which was to shed light on the effects of MHT on coronary heart disease in postmenopausal women, was published in 1985. As part of that study 121,964 nurses aged between 30 and 55 years were surveyed. The first questionnaires were sent in 1976, with subsequent questionnaires being sent in 1978 and 1980, with a follow-up of 92.7%. The outcomes of interest in participants were documented using the information recorded in their medical history.

In comparison with the risk in women who had never used MHT, the relative risk (RR) of coronary heart disease adjusted for the age at which they had received MHT at some point was 0.5 (95% CI: 0.3–0.8), and the risk in those women currently taking MHT was 0.3 (95% CI: 0.2–0.6). The RRs were similar for fatal and non-fatal disease and did not change after adjusting for smoking habit, hypertension, diabetes, high cholesterol, family history of myocardial infarction, prior use of oral contraceptives and obesity.

### Framingham Heart Study (1985)<sup>10</sup>

The results of a cohort study, known as the "*Framingham Heart Study*", which recruited 1234 postmenopausal women aged between 50 and 83 years, were published at around the same time as those of the "*Nurses' Health Study*". This study evaluated the effects of MHT on cardiovascular disease-related death. In comparison with women who did not receive MHT, those who received this treatment presented a higher RR for coronary (RR 1.90;  $p < 0.01$ ) and cerebrovascular events (RR 2.27;  $p < 0.01$ ). An increase in heart attack risk was also observed in MHT users, especially smokers (RR 3.21;  $p < 0.05$ ). Amongst non-smokers, the use of MHT was only associated with a higher incidence of stroke (RR 2.35;  $p < 0.05$ ). No differences in mortality were observed between the two groups. The original article did not provide the confidence intervals (CIs) for the RR values.

The findings of these two studies differed markedly, although the age of the participants was also different.



Curiously, both studies were published on the same day (24/10/1985) and in the same journal, although the media impact of the *Nurses’ Health Study*<sup>9</sup> meant that the *Framingham Heart Study* was somewhat overshadowed<sup>10</sup>.

Women’s Health Initiative (2002)<sup>3</sup>

Some years later, two clinical trials that contradicted the findings of the *Nurses’ Health Study* were published. These studies are known jointly as the “*Women’s Health Initiative*”. The first, which was published in 2002, evaluated the risks and benefits of using conjugated equine oestrogens (0.625 mg/d) together with medroxyprogesterone (2.5 mg/d) (n= 8506) versus placebo (n=8102) in non-hysterectomised postmenopausal women. Around 33% (5522 women) of participants were aged between 50 and 59 years, 45% (7510 women) between 60 and 69 years, and 21% (3576 women) between 70 and 79 years. The primary efficacy outcome was the incidence of coronary disease (non-fatal heart attack and coronary-related mortality) and the primary safety outcome was the incidence of invasive cancer. The results of a global index comprising heart disease, invasive cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture and death due to other causes were also evaluated.

After a mean follow-up of 5.2 years, the following *hazard ratio* (HR) values were observed for the MHT group (Table 1):

Table 1. Risk of presenting various events associated with MHT use in comparison with placebo (*Women’s Health Initiative* trial, 2002)<sup>3</sup>.

| Event type        | Event                        | HR (95% CI)         | HRa* (95% CI)       |
|-------------------|------------------------------|---------------------|---------------------|
| Cardiovascular    | Ischaemic heart disease      | 1.29 (1.02 to 1.63) | 1.29 (0.85 to 1.97) |
|                   | Stroke                       | 1.41 (1.07 to 1.85) | 1.41 (0.86 to 2.31) |
|                   | Pulmonary embolism           | 2.13 (1.39 to 3.25) | 2.13 (0.99 to 4.56) |
|                   | Total cardiovascular disease | 1.22 (1.09 to 1.36) | 1.22 (1.00 to 1.49) |
| Fractures         | Hip fracture                 | 0.66 (0.45 to 0.98) | 0.66 (0.33 to 1.33) |
|                   | Total fractures              | 0.76 (0.69 to 0.85) | 0.76 (0.63 to 0.92) |
| Cancer            | Breast cancer                | 1.26 (1.00 to 1.59) | 1.26 (0.83 to 1.92) |
|                   | Colorectal cancer            | 0.63 (0.43 to 0.92) | 0.63 (0.32 to 1.24) |
|                   | Endometrial cancer           | 0.83 (0.47 to 1.47) | 0.83 (0.29 to 2.32) |
|                   | Total cancer                 | 1.03 (0.90 to 1.17) | 1.03 (0.86 to 1.22) |
| Mortality         | Total mortality              | 0.98 (0.82 to 1.18) | 0.98 (0.70 to 1.37) |
| Composite outcome | Global index                 | 1.15 (1.03 to 1.28) | 1.15 (0.95 to 1.39) |

(\*) HR adjusted for multiplicity.

The adjusted data are similar to their non-adjusted counterparts but with wider confidence intervals, thus meaning that statistical significance is lost for most outcomes. As risks are the key factor in this case, it is worth evaluating the raw HRs as these provide indications concerning possible risks.



The authors conclude that the risk/benefit profile found in this trial does not meet the requirements of a viable intervention for the primary prevention of chronic diseases and that the results indicate that this regimen should not be initiated or continued for the primary prevention of coronary heart disease.

Women’s Health Initiative (2004)<sup>4</sup>

The second of these trials, which was published in 2004, evaluated the results of conjugated equine oestrogens in hysterectomised postmenopausal women. Women were randomised to receive conjugated equine oestrogens (0.625 mg/d) or placebo. The variables evaluated were the same as in the previous trial. Women younger than 60 years represented approximately one third of the sample.

Table 2 provides the HRs for the different outcomes when comparing the MHT group with placebo after a mean follow-up of 6.8 years.

Table 2. Risk of presenting various events associated with MHT use in comparison with placebo in women with hysterectomy (*Women’s Health Initiative* trial, 2004)<sup>4</sup>.

| Event type        | Event                        | HR (95% CI)         | HRa* (95% CI)       |
|-------------------|------------------------------|---------------------|---------------------|
| Cardiovascular    | Ischaemic heart disease      | 0.91 (0.75 to 1.12) | 0.91 (0.72 to 1.15) |
|                   | Stroke                       | 1.39 (1.10 to 1.77) | 1.39 (0.97 to 1.99) |
|                   | Pulmonary embolism           | 1.34 (0.87 to 2.06) | 1.34 (0.70 to 2.55) |
|                   | Total cardiovascular disease | 1.12 (1.01 to 1.24) | 1.12 (0.97 to 1.30) |
| Fractures         | Hip fracture                 | 0.61 (0.41 to 0.91) | 0.61 (0.33 to 1.11) |
|                   | Total fractures              | 0.70 (0.63 to 0.79) | 0.70 (0.59 to 0.83) |
| Cancer            | Breast cancer                | 0.77 (0.59 to 1.01) | 0.77 (0.57 to 1.06) |
|                   | Colorectal cancer            | 1.08 (0.75 to 1.55) | 1.08 (0.63 to 1.86) |
|                   | Total cancer                 | 0.93 (0.81 to 1.07) | 0.93 (0.75 to 1.15) |
| Mortality         | Total mortality              | 1.04 (0.88 to 1.22) | 1.04 (0.81 to 1.32) |
| Composite outcome | Global index                 | 1.01 (0.91 to 1.12) | 1.01 (0.89 to 1.14) |

(\*) HR adjusted for multiplicity.

For each 10,000 women treated with oestrogens for one year, 12 additional strokes and six fewer hip fractures were observed. No significant differences were found in the global events index. As explained above, the authors based their calculations on the non-adjusted HR values.

They concluded that the use of conjugated equine oestrogens increases the risk of stroke, decreases the risk of hip fracture and does not affect the incidence of ischaemic heart disease in postmenopausal women with prior hysterectomy during a mean follow-up period of 6.8 years. Given that the number of events was similar in both groups, the authors suggested that oestrogens should not be used for the prevention of chronic diseases in postmenopausal women.



## Systematic Cochrane Review<sup>11</sup>

An update to a Cochrane review on the effects of long-term MHT treatment (at least one year) in peri- and postmenopausal women was published in 2025.

The authors concluded that oestrogens as monotherapy probably do not significantly increase the risk of coronary events, although they appear to increase the risk of stroke and gall bladder disease. In addition, they probably do not substantially modify the risk of breast cancer and appear to have a beneficial effect in terms of reducing total fractures. After a mean follow-up of 5.6 years, combined MHT increased the risk of thromboembolism [RR 2.03 (1.55 to 2.64)] and breast cancer [RR 1.27 (1.03 to 1.56)].

**The use of oestrogens to prevent chronic diseases in postmenopausal women is not recommended.**

The authors indicate that these findings should be interpreted with care as they are based on a single study with oral hormone therapy (*Women's Health Initiative*), which may not represent the risks of the hormone therapy currently used in clinical practice. In addition, this systematic review does not provide findings for different age ranges.

## Risk/benefit balance. Main clinical effects

The findings of the *Women's Health Initiative* regarding a potential increase in cardiovascular risk and breast cancer in MHT users led to a restriction on the use of this treatment in postmenopausal women<sup>8</sup>. However, the FDA has recently reconsidered these restrictions<sup>5</sup>. We will now analyse the current scientific evidence regarding this decision.

The FDA has recently modified its restrictions on the use of MHT, allowing a more widespread use of these drugs in postmenopausal women aged between 50 and 59 years<sup>12</sup>. This decision was based on a re-analysis of the *Women's Health Initiative* trials<sup>6</sup>. As noted by the authors themselves, one limitation of this study is that it is a *post-hoc* (not pre-specified) analysis of the *Women's Health Initiative* trials in which a series of variables were considered jointly in order to achieve statistical power. Another limitation identified by the authors is the lack of information concerning the incidence of other conditions that may be of interest for decision-making, except for some types of cancer and hip fractures, which were included.



MHT and cardiovascular risk<sup>6</sup>

In this re-analysis of the Women’s Health Initiative trials<sup>6</sup>, the main measurement endpoint was the incidence of atherosclerotic cardiovascular disease (ACVD), a composite outcome of myocardial infarction, angina-related hospitalisation, coronary revascularisation, ischaemic stroke, peripheral arterial disease, carotid disease or cardiovascular-related death. In the 50–59 years age range, no differences in ACVD were found between the group receiving conjugated equine oestrogens and that receiving placebo. However, after 9 years of follow-up, a statistically significant increase was found for the 60–69 years age group, and a similar increase was found for the estimated score in the 70–79 years age group. In the trial concerning oestrogens in combination with progestogens, no significant differences were found between the MHT and placebo groups for any age range (Table 3).

Table 3. Total cardiovascular effects by age range in the *Women’s Health Initiative* trials after 9 years of follow-up<sup>6</sup>.

| Conjugated equine oestrogens vs. placebo                                   |             |                |                     |               |
|----------------------------------------------------------------------------|-------------|----------------|---------------------|---------------|
| Age (years)                                                                | MHT. n (%)  | Placebo. n (%) | HR (95% CI)*        | p interaction |
| 50-59                                                                      | 98 (0.82%)  | 119 (0.98%)    | 0.84 (0.64 to 1.11) | 0.09          |
| 60-69                                                                      | 348 (2.23%) | 307 (1.88%)    | 1.18 (1.01 to 1.38) |               |
| 70-79                                                                      | 258 (3.22%) | 232 (2.82%)    | 1.18 (0.99 to 1.41) |               |
| Total                                                                      | 704 (1.98%) | 658 (1.79%)    | 1.12 (1.01 to 1.25) |               |
| Conjugated equine oestrogens combined with medroxyprogesterone vs. placebo |             |                |                     |               |
| Age (years)                                                                | MHT. n (%)  | Placebo. n (%) | HR (95% CI)*        | p interaction |
| 50-59                                                                      | 86 (0.52%)  | 83 (0.53%)     | 1.02 (0.75 to 1.38) | 0.92          |
| 60-69                                                                      | 266 (1.28%) | 251 (1.29%)    | 1.04 (0.87 to 1.24) |               |
| 70-79                                                                      | 221 (2.39%) | 200 (2.23%)    | 1.04 (0.86 to 1.26) |               |
| Total                                                                      | 573 (1.22%) | 534 (1.21%)    | 1.04 (0.92 to 1.17) |               |

(\*) The HR values are adjusted for age, diet, prior history of atherosclerosis, cardiovascular disease, race and prior history of MHT.

As additional support for their decision to remove the restrictions on MHT use in postmenopausal women aged 50 to 59 years, the FDA notes that MHT has also been associated with a 25–50% reduction in fatal cardiovascular events<sup>13</sup>. This study, which was published in 1991, was very poorly designed. It is a narrative review of observational studies performed between 1953 and 1989, with small sample sizes and different designs, and which include series of autopsies or the reading of death certificates. Indeed, the study that provides the most patients is a reading of death certificates.



## MHT and hip fractures

Another argument put forward by the FDA is that the use of MHT is associated with a 50–60% reduction in bone fractures. This statement is based on a case control study published in 1980<sup>14</sup>. However, said study does not collect information from the patients' medical history and only obtains some information via questionnaires sent to women in 1976, 1977 and 1979 to request retrospective information. The authors state that the hip-fracture rates in women aged between 50 and 59 years who used oestrogens for more than 6 years was 0.2 cases /1000 compared with 0.5 cases/1000 in non-users. Neither the confidence interval nor any statistical treatment are provided.

Moreover, no statistically significant differences between the use of MHT or not and the incidence of hip fractures were found in either of the *Women's Health Initiative* trials: HRa = 0.61 (95% CI, 0.33 to 1.11) (oestrogens)<sup>3</sup> and HRa = 0.66 (95% CI, 0.33 to 1.33) (oestrogens with medroxyprogesterone). In contrast, statistically significant differences in favour of MHT were observed in terms of the reduction of total fractures (hip and vertebral), HRa = 0.70 (95% CI, 0.59 to 0.83)<sup>4</sup>. A re-analysis of the *Women's Health Initiative* trials provided data regarding the incidence of hip fracture in women aged between 50 and 59 years<sup>15</sup>. In the study with oestrogens + progestogens, a total of 45 fractures were recorded (HR 0.57; 95% CI, 0.31 to 1.04). In the study oestrogens as monotherapy, 19 fractures were recorded (HR 0.88, 95% CI 0.36 to 2.17). However, these findings must be considered with caution given the low incidence of fractures in this age group.

## MHT and cognitive impairment

The FDA notes that "MHT use is associated with a 64% reduction in cognitive impairment". This statement is based on a study published in 2005, which collates data from four studies performed between 1983 and 1996 and whose main goal was to investigate the role of MHT in bone mass loss<sup>16</sup>. The women included had a mean age of  $54.1 \pm 4.7$  years. The secondary outcomes included the *Blessed* test<sup>17</sup> to measure cognitive function. This tool is not considered to be appropriate. Indeed, other scales with a better sensitivity and specificity, such as the *Mini-Mental State Examination*, are currently available<sup>18</sup>.

Moreover, the value of the *Blessed* test for study participants was not determined at the start of said study, therefore it is not possible to know whether the groups were well balanced at the start or the evolution of the cognitive status of each group. The investigators only measured the scores at the end of the study. Statistically significant differences were observed in favour of women treated with MHT in the short term (2–3 years) but not for long-term use (more than 3



years). However, care should be taken when interpreting these findings given the methodological limitations mentioned above.

Finally, the FDA also mentions a possible association between MHT use and a 35% reduction in the incidence of Alzheimer's disease<sup>19</sup>. This is based on a case-control study, published in 1996, the participants of which were extracted from a cohort of 3760 women who died between 1981 and 1995. Of these, and according to the death certificate, 240 women died due to Alzheimer's disease or another type of dementia. Information about these women was obtained from the data provided by them in a health questionnaire that was sent to them by mail in 1981. Information regarding the type of MHT used and the length of treatment was recorded, but no clinical data were available to adjust the results. The non-adjusted OR was 0.65 (95% CI 0.49 to 0.88).

In addition to this study, at least 10 other studies, of very poor quality and with widely differing results as regards the role of MHT in the onset of Alzheimer's disease, ranging from a 67% decrease in risk to a 2.30-fold increase in the risk of developing this disease, were published between 1984 and 1995<sup>19</sup>.

## THM and cancer

### Breast cancer

One of the objections to the use of MHT in postmenopausal women is related to a possible association between the use thereof and an increase in breast cancer. The *Women's Health Initiative* found one additional case of breast cancer per 1000 women/year, although this finding is not statistically significant when allowing for multiplicity fitting (Table 1). The FDA attributes this increased risk to medroxyprogesterone<sup>12</sup>, as this was the progestogen used in the *Women's Health Initiative* trial (2002)<sup>3</sup>, a formulation that is not currently widely used for MHT. In addition, as mentioned above, the authors reached their conclusions based on HR values that were not subjected to multiplicity fitting.

In 2019, Cancer Research UK, in collaboration with the UK Medical Research Council, published a meta-analysis of prospective and retrospective studies with individual data for participants, which evaluated the incidence of breast cancer by type and duration of MHT<sup>20</sup>. A total of 58 observational studies (24 prospective and 34 retrospective), which provided a total of 143,887 cases of invasive breast cancer and 424,972 controls, were included. The combination of prospective and retrospective studies may lead to different methodological biases. To limit these biases, the main analyses were restricted to prospective studies and the results adjusted for potential confounding factors: family history (first-degree family member with breast cancer), alcohol consumption and reproductive history (nullipara and, amongst women with children, parity and age at first childbirth).



An increase in breast cancer was observed in women receiving oestrogen treatment aged 50–54 years [OR 1.33 (95% CI, 1.25 to 1.42), mean treatment duration of 8.8 years] as well as those aged 55–59 years [OR 1.26 (95% CI, 1.12 to 1.41), mean treatment duration of 8.3 years].

Women receiving treatment with oestrogens and progestogens presented a somewhat higher risk in both the 50–54 years [OR 2.10 (95% CI, 2.01 to 2.21), mean follow-up of 8.8 years] and 55–59 years age groups [OR 1.97 (95% CI, 1.81 to 2.15), mean follow-up of 8.3 years].

A statistically significant increase in the onset of breast cancer from year 2 of treatment was observed in women in active treatment. This risk increased with greater exposure to the drug and was observed for both oestrogen monotherapy and when combined with progestogens. In the latter case, the increase in risk was greater than for oestrogen monotherapy (Table 4).

**The link between MHT and breast cancer from observational studies was not confirmed in the WHI trial.**

**Table 4. Association between duration of MHT and increase in breast cancer risk in women in active treatment (taken from reference<sup>20</sup>).**

| Duration of MHT | No. cases (O/O+P) | Mean duration MHT | Oestrogens RR (95% CI) | Oestrogens + progestogens RR (95% CI) |
|-----------------|-------------------|-------------------|------------------------|---------------------------------------|
| <1 year         | 109/189           | <1.0              | 1.08 (0.86 to 1.35)    | 1.20 (1.01 to 1.43)                   |
| 1-4 years       | 1150/2230         | 2.8               | 1.17 (1.10 to 1.26)    | 1.60 (1.52 to 1.69)                   |
| 5-9 years       | 2391/4968         | 7.0               | 1.22 (1.17 to 1.28)    | 1.97 (1.90 to 2.04)                   |
| 10-14 years     | 2478/3350         | 11.7              | 1.43 (1.37 to 1.50)    | 2.26 (2.16 to 2.36)                   |
| ≥15 years       | 2183/1424         | 20.1              | 1.58 (1.51 to 1.66)    | 2.51 (2.35 to 2.68)                   |

**MHT** Menopausal hormone therapy. **O** Oestrogens. **P** Progestogens.

Similarly, a cohort that included one million women from the UK evaluated, amongst others, the possible association between breast cancer incidence and MHT use. The mean age at the start of follow-up was 56±5 years<sup>21</sup>. In comparison with women who did not receive MHT, an increase in breast cancer-related mortality was observed in women who received MHT for more than 5 years: HR = 1.35 (95% CI, 1.24 to 1.47) [oestrogen monotherapy] and HR = 1.64 (95% CI, 1.52 to 1.76) [oestrogens + progestogens]<sup>22</sup>.



## Ovarian and endometrial cancer<sup>23</sup>

The findings of the *Women's Health Initiative* clinical trials regarding the effects of MHT on the incidence of ovarian and endometrial cancer in a total of 27,347 women followed up for 20 years were published in 2024. It was found that the administration of oestrogen monotherapy increased both the incidence of ovarian cancer (HR 2.04; 95% CI, 1.14 to 3.65) and ovarian cancer-related mortality (HR 2.79; 95% CI, 1.30 to 5.99). In contrast, the combined use of oestrogens and progestogens did not result in a significant increase in ovarian cancer, and a decrease in endometrial cancer was observed (HR 0.72; 95% CI, 0.56 to 0.92). These HR values are not adjusted.

Women younger than 60 years represented approximately one third of the sample. The trial with oestrogens as monotherapy did not record any cases of ovarian cancer, whereas the trial combining oestrogens and progestogens recorded only 8 cases, with no statistically significant differences between groups.

## Colorectal cancer

The *Women's Health Initiative* clinical trial with oestrogen monotherapy<sup>4</sup> did not find any differences in the incidence of colorectal cancer between groups [HRa 1.08 (95% CI, 0.63 to 1.86)]. However, the trial combining oestrogens with medroxyprogesterone<sup>3</sup> found a protective effect in the group of women with MHT [HR 0.63 (95% CI, 0.43 to 0.92)]. This led to a secondary analysis of the results of the latter trial to obtain more detailed information<sup>24</sup>. The authors of said re-analysis found a lower incidence of colorectal cancer in the MHT group, although the tumours detected in MHT users were at a more advanced stage. As such, they published an additional article assessing the clinical relevance of MHT in colorectal cancer prevention<sup>25</sup>.

This new re-analysis evaluated the incidence of cases observed at around 5 years post-intervention after a mean total follow-up of around 11 years. Fewer colorectal cancers were diagnosed in the MHT group than in the placebo group [annual incidence of 0.12% vs. 0.16%; HR 0.72 (95% CI, 0.56 to 0.94)]. A higher proportion of positive lymph nodes was found in the MHT group (50.5% vs. 28.6%;  $p < 0.001$ ) and these were found at a more advanced stage (regional or metastatic, 68.8% vs. 51.4%;  $p = 0.003$ ). In addition, there was a higher number of colorectal cancer-related deaths in the MHT group, although the difference was not statistically significant [37 (0.04%) vs. 27 (0.03%) deaths; HR 1.29 (95% CI, 0.78 to 2.11)]. The authors concluded that these findings are suggestive of a delay in diagnosis and do not support the existence of a significant clinical benefit of MHT in colorectal cancer.



## MHT and mortality

The FDA based its argument that MHT reduces mortality in women aged less than 60 years on a meta-analysis published by Salpeter SR et al. in 2004<sup>26</sup>. This study includes trials performed between 1976 and 2022 that vary markedly in terms of quality, design and the profile of the women included. The authors observed a statistically significant reduction in mortality: OR 0.61 (95% CI, 0.39 to 0.95). The OR was used to estimate the effect, whereas relative risk (RR) is more typically used in meta-analyses of clinical trials. If the latter is used, no statistically significant differences in mortality between MHT and placebo are found (Annex. Figure S1).

**MHT is not a  
"one size fits all  
solution".**

Moreover, a single clinical trial has a marked effect on the final results by representing 76.7% of the total weight of the meta-analysis. This is the study by Guidozzi F, et al.<sup>27</sup>, which was performed in women with ovarian cancer and, therefore, in a very specific population group. Moreover, the aim of our article is based on the effects of MHT in healthy postmenopausal women.

The prognosis of breast cancer depends on various factors<sup>28</sup>. This trial presents an imbalance between women treated with MHT and those without at the start of the study. Thus, the women who did not receive MHT were older, were in more advanced stages of the disease, had more aggressive tumours (based on the histology) and received a worse surgical approach.

As such, we should be very careful when interpreting the findings of this trial. It is highly likely that the imbalances in the prognostic factors for ovarian cancer at the start of treatment had a marked impact on the mortality findings.

Moreover, the *Women's Health Initiative* trials showed that MHT increases both the incidence of ovarian cancer (HR 2.04; 95% CI, 1.14 to 3.65) and the mortality of this type of tumour (HR 2.79; 95% CI, 1.30 to 5.99) in a total of 27,347 women followed-up over 20 years<sup>23</sup>. This clearly contradicts the findings of Guidozzi F et al.<sup>27</sup>.

In the meta-analysis by Salpeter SR<sup>26</sup>, if we consider only those clinical trials carried out in healthy women (no prior cancer or cardiovascular events), no statistically significant differences are observed between the study groups (Annex Figure S2).



## Other aspects of MHT

### The so-called “window of opportunity”

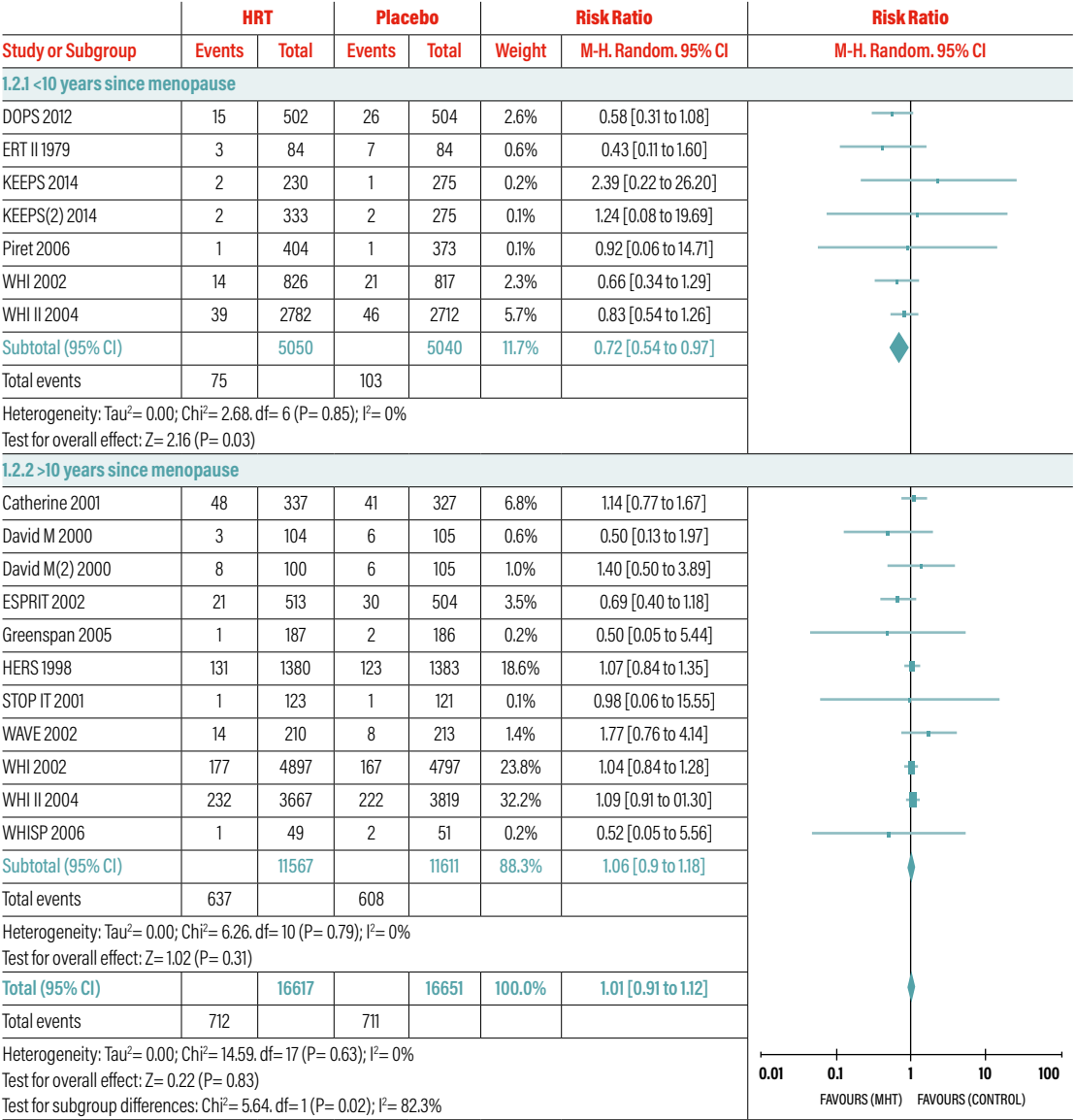
Various clinical practice guidelines and consensus documents from different scientific societies mention the concept of “window of opportunity”. These include guidelines from the British Menopause Society & Women’s Health Concern<sup>29</sup>, International Menopause Society<sup>30</sup> American Academy of Physician Associates<sup>31</sup> or the North American Menopause Society<sup>32</sup>. As such, it can be said that starting MHT within the first 10 years post-menopause or prior to 60 years of age appears to have a favourable risk/benefit balance over and above symptom treatment<sup>29-33</sup>. This finding is mainly based on the findings of the meta-analysis reported by Boardman HMP et al.<sup>34</sup>, which was subsequently updated by Gu Y. et al.<sup>33</sup>. This study performed a subgroup analysis, highlighting the results of MHT vs. placebo on the incidence of coronary events and total mortality in women who had started MHT before or after 10 years post-menopause.

**The best available evidence does not support the idea of a “window of opportunity”.**

A reduction in total mortality (Figure 1) and in the incidence of cardiovascular events (Figure 2) was observed in the subgroup that started MHT prior to 10 years post-menopause [reference 33, Figure S5].



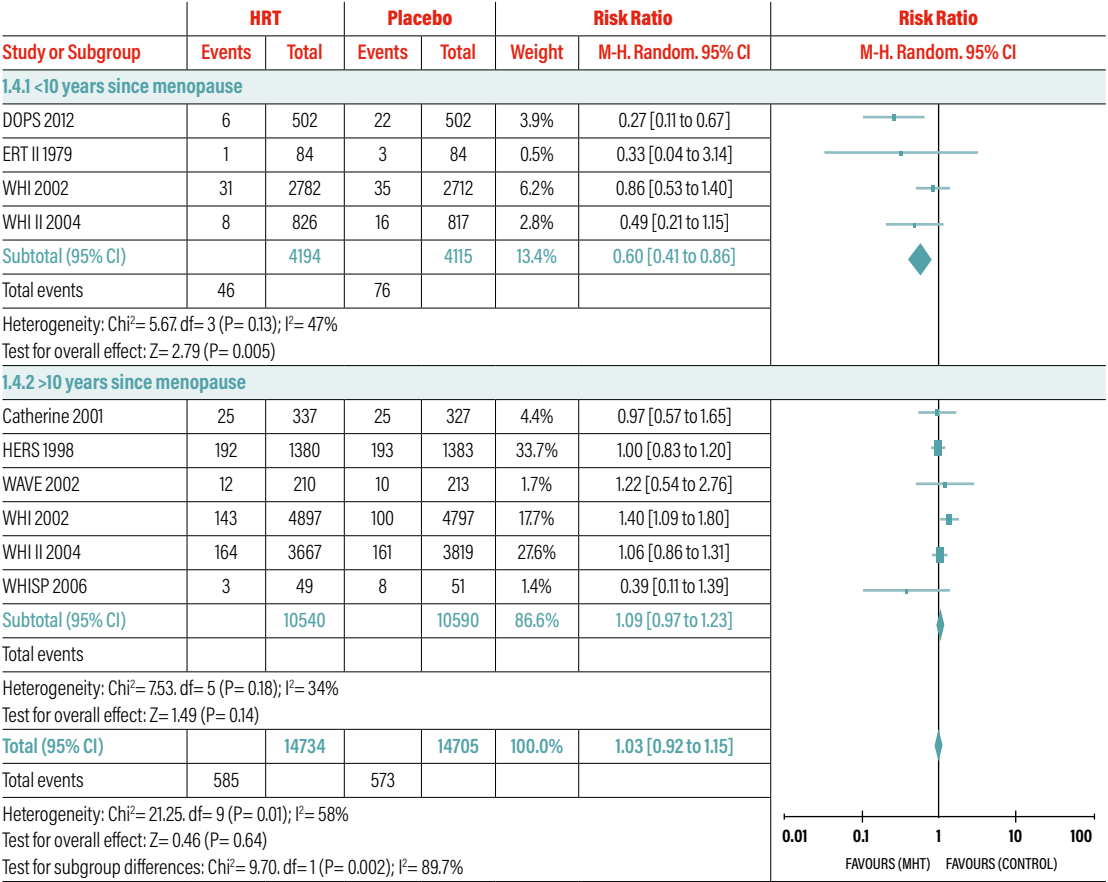
Figure 1. Total mortality in the review by Gu Y et al.<sup>33</sup>.



The well-known NAMS (North American Menopause Society) guideline<sup>32</sup> states that, in comparison with placebo, the administration of oestrogens reduces the incidence of heart disease, stroke, breast cancer, colorectal cancer, total cancer and total mortality. This is based on a publication by Manson JE et al.<sup>15</sup>. However, when the original data from the study by Manson JE et al. are checked, the results for these variables are not statistically significantly different between the group receiving oestrogens and that receiving placebo.



Figure 2. Incidence of cardiovascular events in the review by Gu Y et al.<sup>33</sup>.

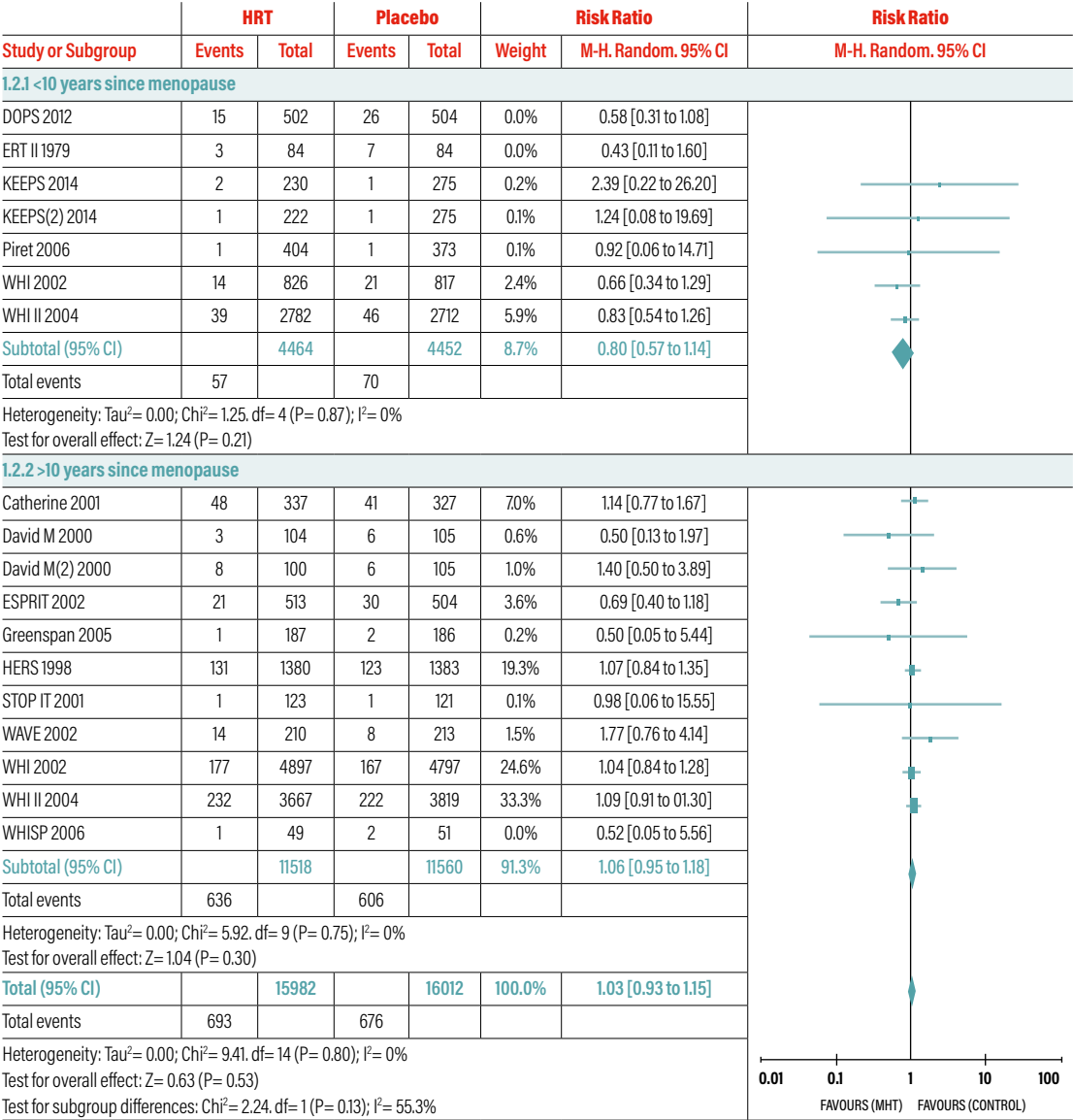


However, Gu Y. et al.<sup>33</sup> clearly recognise the presence of three problematic trials in their review: DOPS 2012, ERT II 1979 and WHISP 2006. Thus, the first had problems with blinding and the in the blind evaluation of results. The second presented randomisation problems and in hiding of the randomisation sequence, and the third presented incomplete data. All were categorised as trials with a high risk of bias. Moreover, the DOPS 2012 trial was the same trial as Mosekilde<sup>35</sup>, which was suspended 11 years after starting and the authors performed a follow-up (out of trial) 16 years after the start.

A sensitivity analysis excluding these trials with a high risk of bias shows no benefits in terms of a reduction in cardiovascular events in women treated with MHT. This is applicable to those women who started MHT 10 years prior to, or after menopause (Figures 3 and 4).



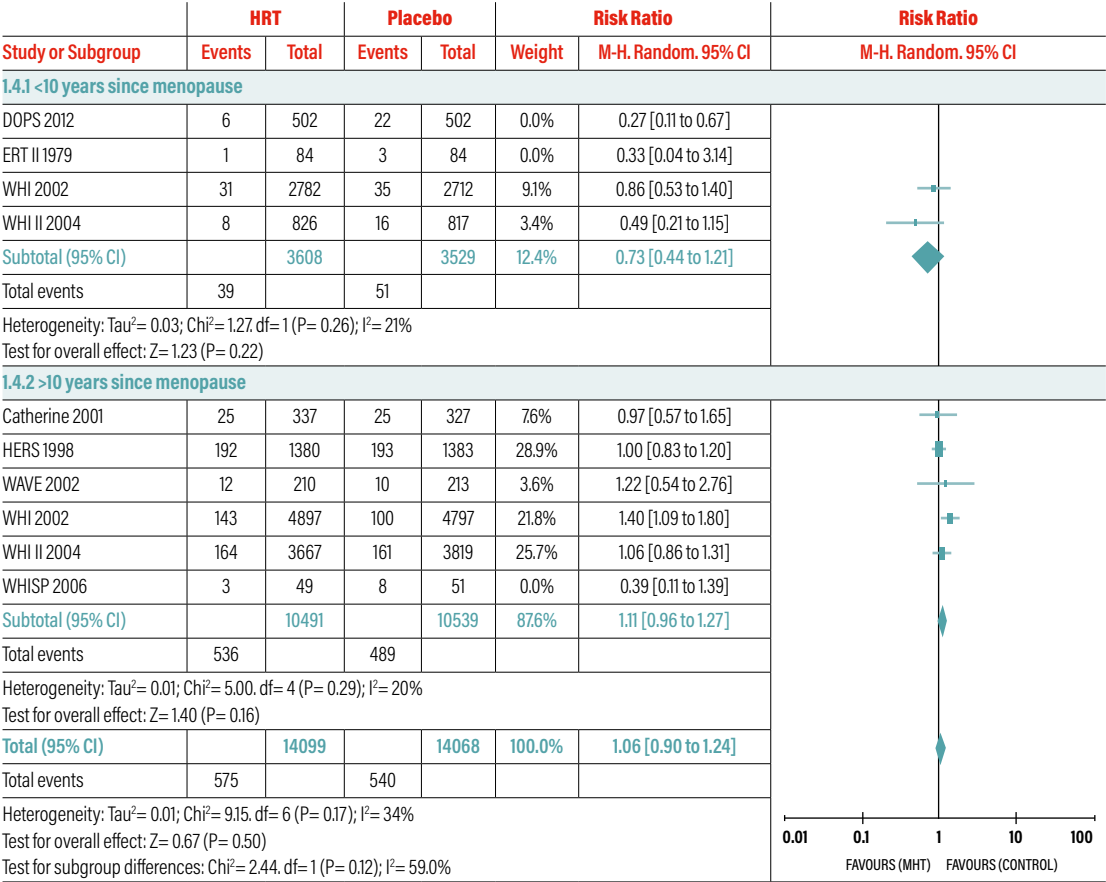
Figure 3. Total mortality in the review by Gu Y et al.<sup>33</sup>. Sensitivity analysis excluding the DOPS 2012, ERT II 1979 and WHISP trials (own calculations).



The subgroups tests is not significant, therefore there appears to be no differences in the incidence of cardiovascular events between the two subgroups in this study.



Figure 4. Incidence of cardiovascular events in the review by Gu Y et al.<sup>33</sup>. Sensitivity analysis excluding the DOPS 2012, ERT II 1979 and WHISP trials (own calculations).



Similarly to total mortality, there were also no differences in the incidence of cardiovascular events between the two subgroups in this study.

Consequently, although several scientific societies promote the widespread use of MHT in healthy women within the first 10 years post-menopause, indicating that this is a “window of opportunity” given the various benefits in addition to an improvement in vasomotor symptoms, a rigorous analysis of the evidence in this regard does not support this recommendation. Moreover, we know that MHT has other positive and negative effects, such as a reduction of the risk of bone fractures or a possible increase in breast cancer, thus complicating decision-making. As such, the concept of a “window of opportunity” should perhaps not be generalised and MHT should be indicated on an individual basis considering the risk/benefit balance in each woman.



## Are all oestrogens similar?

MHT has changed over time in terms of the type of hormones and the routes of administration used. Thus, the *Women's Health Initiative* trials used conjugated equine oestrogens and medroxyprogesterone acetate, which were widely used in the 1990s. 17-Beta estradiol, which is the natural human oestrogen used nowadays, has a slightly different receptor affinity than conjugated equine oestrogens. Similarly, micronised progesterone, which is equivalent to the natural human substance, has a different receptor affinity than medroxyprogesterone<sup>36</sup>.

From a theoretical viewpoint, it is reasonable to consider that the effects observed in the older trials may differ to some extent to those that may be expected with the hormones used currently. For example, those hormones with greater affinity for the receptor may exhibit a greater size effect. The meta-analysis of case-control studies mentioned above highlights the differences between the effects of oestrogens as monotherapy or when combined with progestogens. However, the results obtained with different types of oestrogens or progestogens are very similar<sup>20</sup>. As such, there is currently no solid evidence suggesting a different effect depending on the type or pharmaceutical formulation of the drug.

**There is no solid evidence for different effects depending on the type of oestrogen or its pharmaceutical formulation.**

**We must allow each woman to reach a well-informed decision.**

## Use of MHT in Navarre

Figure 5 shows that the number of women aged less than 60 years receiving MHT increased between 2016 and 2019 (from 867 to 1171). This value subsequently decreased and then increased again from 2022 to reach a value of 1235 women receiving MHT in 2025. The number of women aged more than 60 years receiving MHT remained essentially constant between 2015 and 2025 (100).

Between 01/01/2015 and 30/03/2026, 1441 women started MHT in the Navarre Health Service. The mean duration of MHT was 3.2 years (Table 5).



Of these, 813 had completed treatment and, of these, 400 (49%) received MHT for less than 1 year, 147 (18%) for between 1 and 2 years, 87 (11%) for between 2 and 3 years and 179 (22%) for more than 3 years.

Figure 5. Evolution of number of women receiving MHT in the SNS-O.

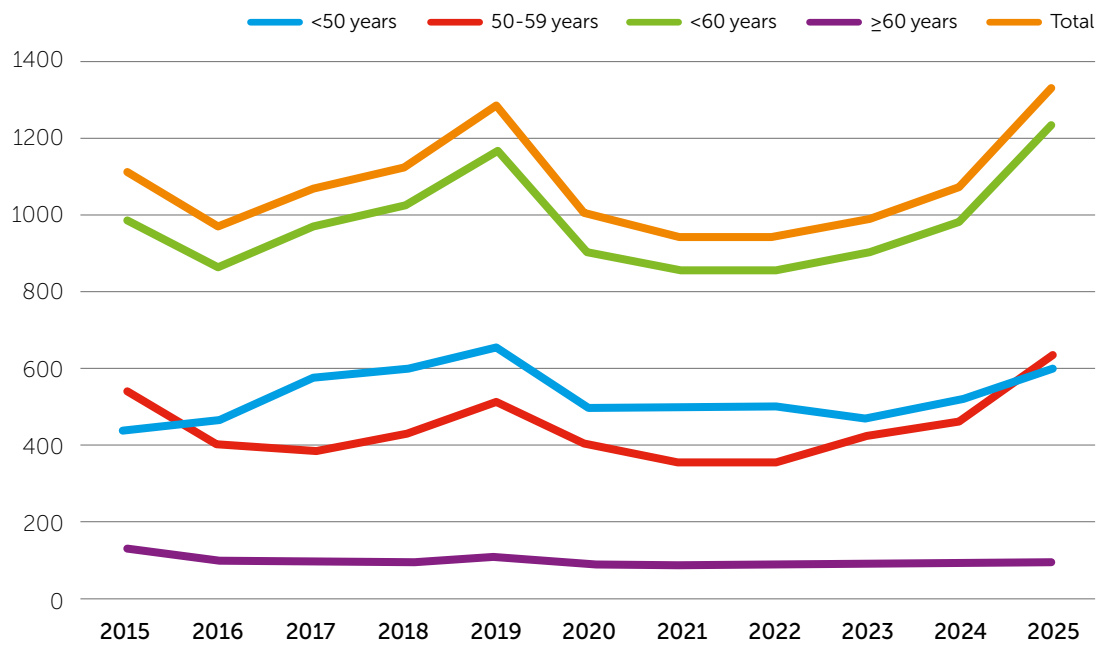


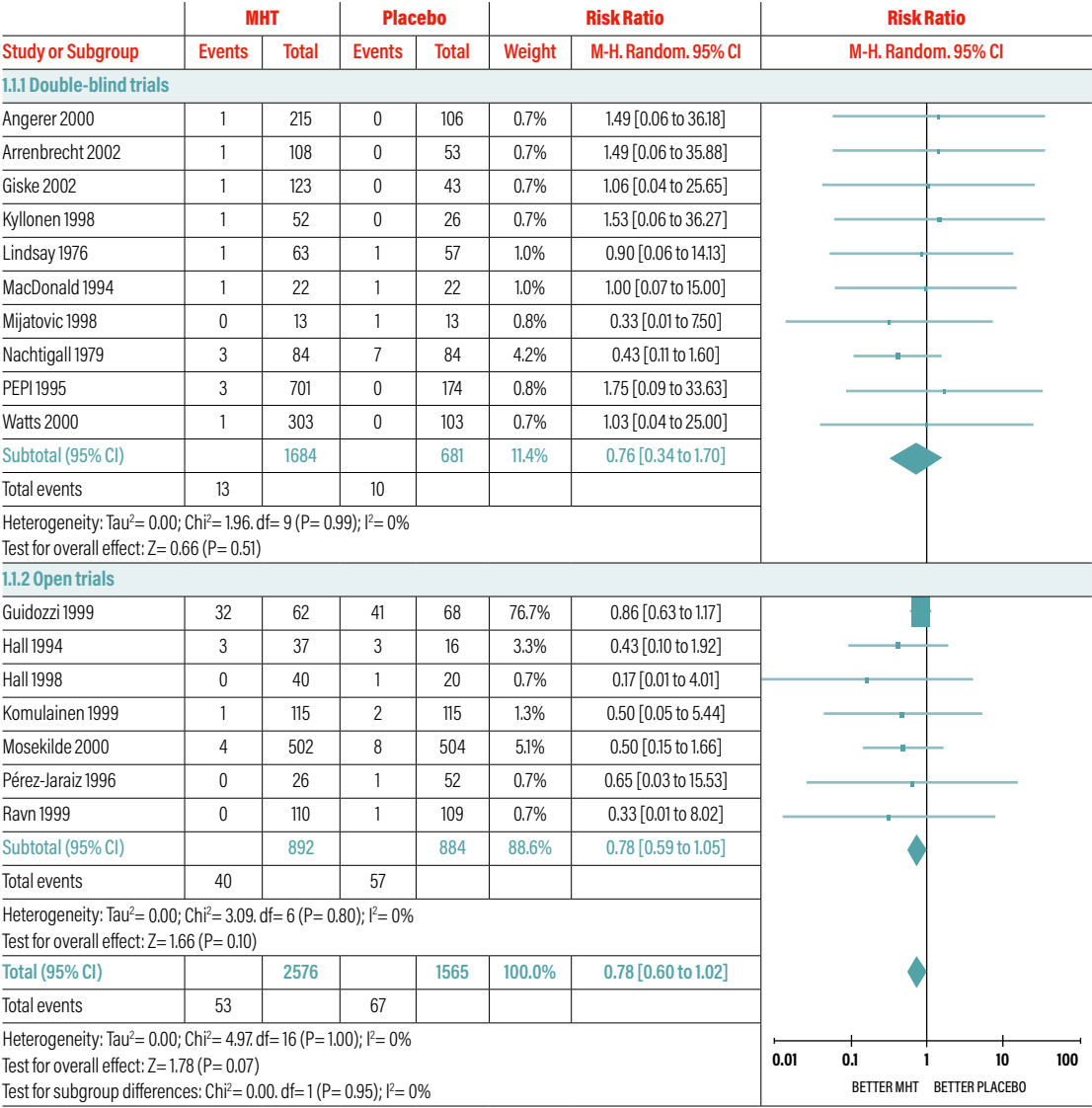
Table 5. Duration of MHT in the Navarre Health Service by age range.

| Starting age (years) | N    | Mean duration in years (95% CI) |
|----------------------|------|---------------------------------|
| 40-44                | 376  | 2.9 (2.1 to 3.7)                |
| 45-49                | 403  | 3.3 (2.7 to 4.0)                |
| 50-54                | 462  | 2.9 (2.2 to 3.7)                |
| 55-59                | 163  | 3.4 (2.7 to 4.1)                |
| 60-64                | 30   | 2.9 (1.5 to 4.2)                |
| 65-69                | 3    | -                               |
| 70-74                | 3    | 0.5                             |
| 75-79                | 1    | 5.2                             |
| Global               | 1441 | 3.2 (2.8 to 3.5)                |



Annexes

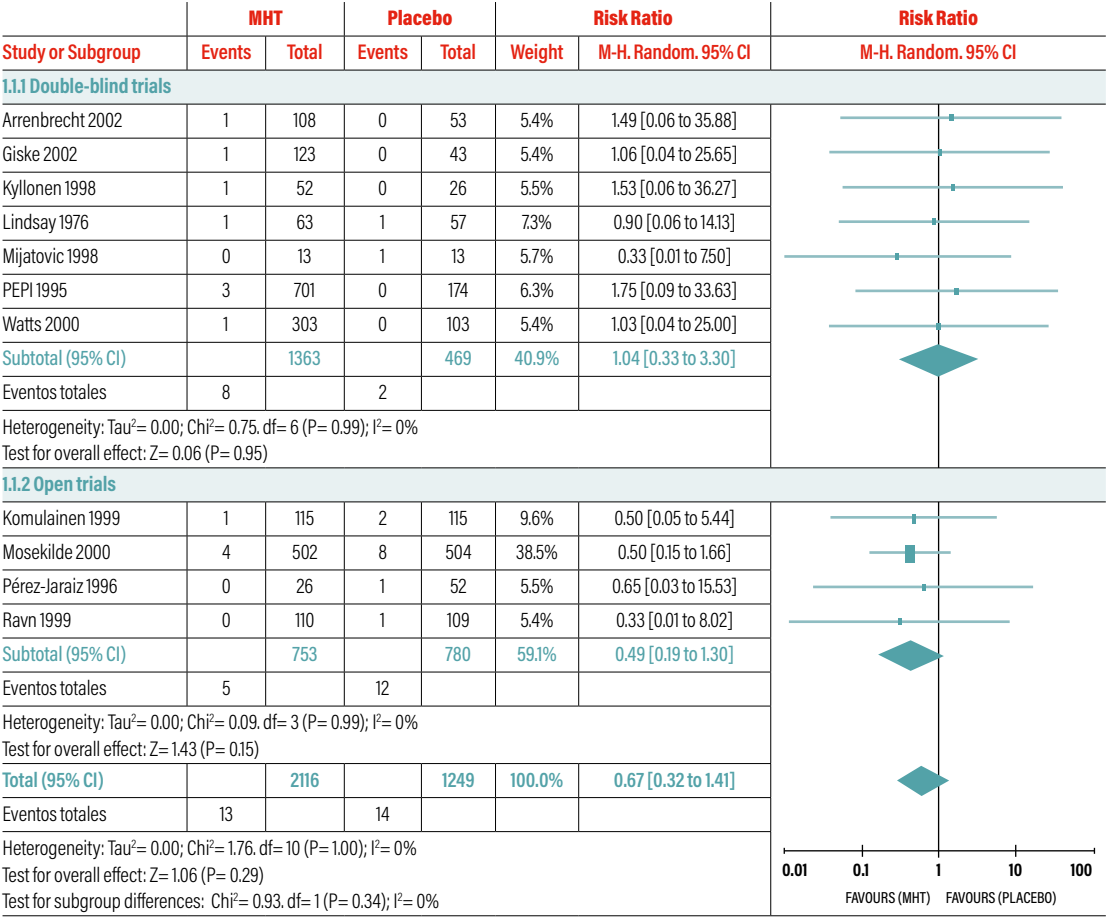
Figure S1. Mortality in women receiving MHT versus placebo (or no MHT) in clinical trials involving healthy or unhealthy women. Meta-analysis by Salpeter et al. modified\* (own calculations).



(\*) The meta-analysis by Salpeter et al. used the Odds Ratio (OR) to estimate the effect. We have used the relative risk (RR), which is more commonly used in clinical trial meta-analyses. In addition, according to the original data from the trial by Mosekilde et al<sup>35</sup>, a total of 8 subjects who did not receive MHT died. The original meta-analysis by Salpeter et al.<sup>26</sup> used a total of 9 deaths (one more than the actual value) due to a transcription error. This error has been corrected in Figure S1 herein.



Figure S2. Mortality in the meta-analysis by Salpeter et al. in healthy women aged < 60 years (own calculation).



## CONCLUSIONS

- MHT is an effective treatment for controlling vasomotor symptoms in peri- and postmenopausal women.
- The *Women's Health Initiative* trials, which were performed with different oestrogens to those used currently, related this use to a potential increase in cardiovascular risk and breast cancer in MHT users, thus leading to restrictions on the use of this treatment in postmenopausal women. The clinical effects of the oestrogens used currently have received little attention, although the limited evidence available does not suggest any substantial clinical differences with regard to those used in the *Women's Health Initiative* trials.
- A post-hoc reanalysis of the effects of MHT in women aged 50–59 years with vasomotor symptoms showed no increase in the incidence of atherosclerotic cardiovascular disease, a composite outcome of myocardial infarction, angina-related hospitalisation, coronary revascularisation, ischaemic stroke, peripheral arterial disease, carotid disease or cardiovascular-related death. In the case of women aged over 60 years, it appears that MHT may increase cardiovascular risk, especially the incidence of stroke and thromboembolic events.
- The FDA has recently reassessed the evidence and has lifted the restrictions concerning cardiovascular risk and breast cancer due to the use of MHT in women aged 50 to 59 years. However, this decision does not appear to be based on scientific evidence of a minimally acceptable quality. Indeed, the European Medicines Agency maintains its warnings concerning these risks.



- The adjusted results from the WHI clinical trial did not show any significant differences in the incidence of breast or cancer colorectal with or without MHT. However, recent observational evidence suggests that the combination oestrogen plus progestogen may double the risk of invasive breast cancer in women aged 50 to 59 years. The use of oestrogens as monotherapy in this age group increased the risk by 30%.
- Around half of MHT users in Navarre are aged between 50 and 59 years. In both this age group and in all women using MHT, half receive treatment for at least 3 years.
- When, after a personalised assessment, MHT is indicated for the the control of vasomotor symptoms in women in this age range, it is recommended to use the minimum effective dose for the shortest time possible given that the risk of breast cancer appears to increase with duration of treatment.



## REFERENCES

1. Nappi RE, Kroll R, Siddiqui E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. *Menopause*. 2021;28(8):875-882. <https://doi.org/10.1097/GME.0000000000001793>
2. Villiers T De. The management of vasomotor symptoms of menopause (VMS) with menopausal hormone therapy (MHT). *Curr Opin Endocr Metab Res*. 2022;27:100420. <https://doi.org/10.1016/j.coemr.2022.100420>
3. Rossouw J, Anderson G, Prentice R, LaCroix A, Kooperberg C. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. *JAMA*. 2002;288(3):321-333.
4. Anderson GL, Limacher M, Assaf AR, et al. Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy. *JAMA*. 2004;291(14):1701-1712.
5. U.S. Food and Drug Administration (FDA). FDA Requests Labeling Changes Related to Safety Information to Clarify the Benefit/Risk Considerations for Menopausal Hormone Therapies. 2025.
6. Rossouw JE, Aragaki AK, Manson JE, et al. Menopausal Hormone Therapy and Cardiovascular Diseases in Women With Vasomotor Symptoms A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. *JAMA Intern Med*. 2025;185(11):1330-1339. <https://doi.org/10.1001/jamainternmed.2025.4510>
7. Block J. How a menopause campaign with industry ties became official US policy. *BMJ*. 2025;391:r2491. <https://doi.org/10.1136/bmj.r2491>
8. European Medicines Agency. Meeting highlights of the Pharmacovigilance Risk Assessment Committee (PRAC) 11-14 May 2020 [Internet]. Amsterdam: European Medicines Agency. 2020.
9. Stampfer M, Willett W, Colditz G, Rosner B, Speizer F, Hennekens C. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med*. 1985;313(17):1044-1049.
10. Wilson PWF, Garrison RJ, Castelli WP. Postmenopausal Estrogen Use, Cigarette Smoking, and Cardiovascular Morbidity in Women over 50 — The Framingham Study. *N Engl J Med*. 1985;313(17):1038-1043.
11. Bofill Rodriguez M, Yong LN, Mirkov S, Bekos C, Lethaby A, Farquhar C. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane database Syst Rev*. 2025;11(11):CD004143. <https://doi.org/10.1002/14651858.CD004143.pub6>
12. Makary MA, Nguyen CP, Høeg TB, Tidmarsh GF. Updated Labeling for Menopausal Hormone Therapy. *JAMA*. Published online 2025:10-11. <https://doi.org/10.1001/jama.2020.9482>



13. Barret-Connor E, Bush T. Estrogen and coronary heart disease in women. *JAMA*. 1991;265:1861-1867.
14. Weiss N, Ure C, Ballard J, Williams A, Daling J. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen.pdf. *N Engl J Med*. 1980;303:1195-1198.
15. Manson JE, Chlebowski RT, Stefanick ML, 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(13):1353-1368. <https://doi.org/10.1001/jama.2013.278040>
16. Bagger YZ, Alexandersen P, Qin G, Christiansen C. Early postmenopausal hormone therapy may prevent cognitive impairment later in life. *Menopause*. 2005;12(1):12-17. <https://doi.org/10.1097/00042192-200512010-00005>
17. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. *Am J Psychiatry*. 1983;140:734-739.
18. Davous P, Lamour Y, Debrand E, Rondot P. A comparative evaluation of the short orientation memory concentration test of cognitive impairment. *J Neurol Neurosurg Psychiatry*. 1987;50:1312-1317.
19. Paganini-Hill A, Henderson V. Estrogen replacement therapy and risk of Alzheimer disease. *Arch Intern Med*. 1996;156:2213-2217.
20. Beral V, Peto R, Pirie K, Reeves G. Type and timing of menopausal hormone therapy and breast cancer risk : individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet*. 2019;394(10204):1159-1168. [https://doi.org/10.1016/S0140-6736\(19\)31709-X](https://doi.org/10.1016/S0140-6736(19)31709-X)
21. Green J, Reeves GK, Floud S, et al. Cohort Profile: the Million Women Study. *Int J Epidemiol*. 2019;(June 2018):28-29. <https://doi.org/10.1093/ije/dyy065>
22. Beral V, Peto R, Pirie K, Reeves G. Menopausal hormone therapy and 20-year breast cancer mortality. *Lancet (London, England)*. 2019;394(10204):1139. [https://doi.org/10.1016/S0140-6736\(19\)32033-1](https://doi.org/10.1016/S0140-6736(19)32033-1)
23. Chlebowski RT, Aragaki AK, Pan K, et al. Menopausal Hormone Therapy and Ovarian and Endometrial Cancers: Long-Term Follow-Up of the Women's Health Initiative Randomized Trials. *J Clin Oncol Off J Am Soc Clin Oncol*. 2024;42(30):3537-3549. <https://doi.org/10.1200/JCO.23.01918>
24. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus Progestin and Colorectal Cancer in Postmenopausal Women. *N Engl J Med*. 2004;350:991-1004.
25. Simon MS, Chlebowski RT, Wactawski-wende J, et al. Estrogen Plus Progestin and Colorectal Cancer Incidence and Mortality. *J Clin Oncol*. 2012;30:3983-3990. <https://doi.org/10.1200/JCO.2012.42.7732>



26. Salpeter SR, Walsh JME, Greyber E, Ormiston TM, Salpeter EE. Mortality Associated with Hormone Replacement Therapy in Younger and Older Women. A Meta-analysis. *J Ger Intern Med*. 2004;19:791-804.
- 
27. Guidozzi F, Daponte A. Estrogen Replacement Therapy for Ovarian Carcinoma. *Cancer*. 1999;86(6):1013-1018.
- 
28. Borella F, Mitidieri M, Cosma S, et al. Update on Prognostic and Predictive Markers in Mucinous Ovarian Cancer. *Cancers (Basel)*. 2023;15(February):1-14.
- 
29. Hamoda H, Panay N, Pedder H, Arya R, Savvas M. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. *Post Reprod Heal*. 2020;26(4):181-209. <https://doi.org/10.1177/2053369120957514>
- 
30. Baber RJ, Panay N, Fenton A. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric*. 2016;19(2):109-150. <https://doi.org/10.3109/13697137.2015.1129166>
- 
31. Church A, Biagi M. Menopausal hormone therapy: Making sense of current guidelines. *JAAPA*. 2025;38(7):19-25. <https://doi.org/10.1097/01.JAA.0000000000000226>
- 
32. The 2022 Hormone Therapy Position Statement of The North American Menopause Society Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. <https://doi.org/10.1097/GME.0000000000002028>
- 
33. Gu Y, Han F, Xue M, Wang M, Huang Y. The benefits and risks of menopause hormone therapy for the cardiovascular system in postmenopausal women: a systematic review and meta-analysis. *BMC Womens Health*. 2024;24(1):60. <https://doi.org/10.1186/s12905-023-02788-0>
- 
34. Boardman H, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane review. *Cochrane Database Syst Rev*. 2015;(3):Art. No.: CD002229.
- 
35. Mosekilde L, Beck-Nielsen H, Sørensen OH, et al. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women - results of the Danish Osteoporosis Prevention Study. *Maturitas*. 2000;36(3):181-193. [https://doi.org/10.1016/s0378-5122\(00\)00158-4](https://doi.org/10.1016/s0378-5122(00)00158-4)
- 
36. Foschi M, Groccia G, Rusce ML, et al. Estradiol and Micronized Progesterone: A Narrative Review About Their Use as Hormone Replacement Therapy. *J Clin Med*. 2025;14(20). <https://doi.org/10.3390/jcm14207328>
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