
Studies identified in searches are summarised from the information presented in their abstracts. We did not specify any age limits on HRT treatment because this information was not consistently reported clearly across the abstracts.

Because of a large volume of evidence, we excluded randomised controlled trials that included less than 100 people.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline.

See the evidence tables for all studies considered in surveillance.

Individualised care

Surveillance proposal

No new information on individualised care was identified at any surveillance review.

Diagnosis of perimenopause and menopause

Surveillance proposal

No new information on diagnosis of perimenopause and menopause was identified at any surveillance review.

Information and advice

Surveillance proposal

No new information on information and advice was identified at any surveillance review.
Managing short-term menopausal symptoms

Surveillance proposal

The section of the guideline on managing short-term menopausal symptoms should not be updated.

Editorial amendments

In recommendation 1.4.25, the cross-reference to section 1.13 of the NICE guideline on early and locally advanced breast cancer should be amended to refer to because the guideline has been updated and the relevant section is now 1.12. The hyperlink should also be updated from the previous guideline so that users go directly to the updated guideline.

Hormone replacement therapy (HRT)

2019 surveillance summary

We identified 16 RCTs and 3 Cochrane reviews that assessed a range of short-term outcomes of HRT.

Vasomotor symptoms

Vasomotor and general menopausal symptoms, including quality of life were assessed in 8 RCTs (1–8) and 2 Cochrane reviews (9,10) (table 1 in the data tables appendix). The included studies assessed a variety of different HRT strategies including oestrogen only and combined HRT in a range of formulations including oral, transdermal and intravaginal preparations.

- HRT compared with placebo consistently improved menopausal symptoms, vasomotor symptoms such as hot flushes and, night sweats, sleep outcomes and quality of life.
- Vasomotor symptoms were worse with tibolone compared with combined HRT.
- There was no difference in hot flushes with bioidentical oestrogen compared with conjugated equine oestrogen.
**Vaginal symptoms**

Vaginal symptoms and sexual function were assessed in 7 RCTs (11–17) and 1 Cochrane review (18) (table 2 in the data tables appendix). Most studies assessed intravaginal preparations of HRT compared with placebo or another active treatment, usually HRT. HRT improved vaginal symptoms in 7 of the 9 comparisons against placebo and showed no effect in the other two comparisons. All 5 of the comparisons of HRT against another active treatment showed no difference between the groups.

**Depression**

In 2 RCTs (19,20) HRT was associated with improvements in symptoms of depression compared with placebo (table 3 in the data tables appendix).

**Other outcomes**

In 2 RCTs (3,21) comparing different preparations of HRT, oestrogen may be more effective than progestogen or conjugated equine oestrogen for improving hormone levels and acceptance by patients. In 1 RCT (17) patients using vaginal oestrogen may be more likely to use the product again when compared with placebo (table 4 in the data tables appendix).

**Adverse effects**

Adverse effects of HRT were reported in 3 Cochrane reviews (9,10,18) and 1 RCT (3) (table 5 in the data tables appendix). A range of preparations of oestrogen-only HRT, including oral, transdermal, and intranasal showed worse or no effects on adverse events compared with placebo (6 comparisons), or other preparations of HRT (1 comparison). Oestrogen tablets had no effect on endometrial thickness compared with placebo, but an oestrogen ring preparation increased endometrial thickness compared with oestrogen cream. Tibolone was associated with more bleeding than placebo but less than combined HRT.

**Intelligence gathering**

**Vasomotor symptoms**

Topic expert feedback noted that the terminology around ‘bioidentical hormones’ is confusing because it can be used to mean chemically identical to the hormones produced by the human body (such preparations are regulated), and preparations of
different hormones in ratios produced in the body (which are not regulated). The study of ‘bioidentical’ oestrogen (9) included regulated products.

Topic experts also suggested that recommendations for women with breast cancer (and other hormone-dependent cancers) should be expanded, for example how treatments for vaginal atrophy might differ for women on tamoxifen and those on aromatase inhibitors.

**Impact statement**

**Vasomotor symptoms**

The guideline recommends offering HRT for vasomotor symptoms after discussing the risks and benefits. The new evidence indicating that HRT improves vasomotor symptoms and quality of life is consistent with current recommendations.

The guideline does not currently recommend tibolone because it was associated with reduced quality of life compared with no treatment, and thus was not cost effective. The finding that tibolone was associated with worse vasomotor symptoms compared with conjugated equine oestrogens is therefore consistent with evidence considered during guideline development.

The guideline additionally noted that ‘the efficacy and safety of unregulated compounded bioidentical hormones are unknown’. One study assessed ‘bioidentical’ hormones but referred to regulated products rather than unregulated compounded bioidentical hormones are unknown’. However, new evidence suggested no difference in hot flushes between regulated bioidentical hormones and conjugated equine oestrogens, so no update to consider these treatments separately is necessary.

There is some overlap in recommendations on treatment of menopausal symptoms in women with or at high risk of breast cancer across NICE guidelines, particularly in the guidelines on early and locally advanced breast cancer and familial breast cancer. The guideline on menopause already has cross-references to the breast cancer guidelines. These guidelines have more detailed recommendations for women with or at risk of breast cancer who have treatment-related menopausal
symptoms. We did not find sufficient new evidence to support an update of the menopause guideline in this area.

**Vaginal symptoms**

The guideline recommends offering vaginal oestrogen to women with urogenital atrophy, including those already on systemic HRT. The new evidence that vaginal oestrogen improves vaginal symptoms and sexual function is consistent with current recommendations.

**Depression**

The guideline found evidence suggesting that HRT improved symptoms of depression, and recommends considering HRT to alleviate low mood, which is consistent with the new evidence identified in surveillance.

**Other outcomes**

New evidence indicated that HRT, particularly vaginal oestrogen, was acceptable and satisfactory for patients, and improved hormone levels. The guideline did not address these aspects of HRT use in depth, but the new evidence provides support for the current recommendation to offer intravaginal HRT for women with vaginal symptoms.

New evidence indicated that different hormone preparations may improve levels of follicle stimulating hormone, luteinising hormone and oestrogen. However, these physiological outcomes were not considered by the guideline and the new evidence does not indicate that changes in hormone levels are directly related to changes in symptoms. Therefore, an update to consider these outcomes is not necessary.

**Adverse effects**

The guideline notes that unscheduled vaginal bleeding is a common side effect of HRT in the first 3 months of treatment. Although study abstracts often did not define what adverse events were included, the new evidence did not highlight any unexpected adverse events. Prescribers should consult the summary of product characteristics for information on possible adverse effects associated with individual HRT products. The guideline should not be updated to consider additional adverse events of HRT at this time.
New evidence is unlikely to change guideline recommendations.

**Non-HRT treatments**

**2019 surveillance summary**

We identified 39 RCTs and 1 Cochrane review that assessed treatments other than HRT.

**Drug treatments**

We identified 11 RCTs of non-HRT drug treatments for menopausal symptoms (table 6 in the data tables appendix). All drugs were compared against placebo, except for 1 study that used a non-active control (vaginal moisturiser).

- In 3 reports from 2 RCTs, (22–24) intravaginal prasterone (dehydroepiandrosterone) was more effective than placebo or across a range of sexual outcomes, including vaginal dryness and dyspareunia, lubrication and orgasm. However, no difference between prasterone and vaginal moisturiser was seen for vaginal dryness or dyspareunia, although prasterone improved sexual health compared with vaginal moisturiser. Prasterone is licensed in the UK for treating vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.
- In 2 RCTs, (25,26) ospemifene improved sexual function, vaginal dryness and dyspareunia.
- In 2 RCTs, of melatonin, one trial suggested this treatment improved ovarian hormone levels, (27) but no effect was seen on low-density lipoprotein (28). No patient-oriented outcomes were reported in the abstracts for these studies.
- In 1 RCT, oxybutynin improved sleep quality and vasomotor symptoms and increased dry mouth (29).
- In 1 RCT, oxytocin vaginal gel improved dyspareunia (30).
- In 2 studies, venlafaxine improved insomnia, sleep quality and quality of life (2,4).

**Physical and psychological therapies**

We identified 9 RCTs that assessed the effects of physical and psychological treatments for menopause (table 7 in the data tables appendix).
Cognitive behavioural therapy (CBT) was assessed in 3 studies (31–33) with wait list and menopause education acting as controls. Self-managed, therapist-based and telephone-based CBT were associated with improvements in night sweats and insomnia, but inconsistent effects were seen on hot flushes with effects seen in one study (composite outcome of hot flushes and night sweats), but no effect was seen in another study.

New evidence for other physical and psychological therapies indicated that:

- device-guided slow-paced breathing showed inconsistent effects on hot flushes depending on the control group (34).
- exercise interventions had no effect on hot flushes or night sweats but may increase daily step counts and improve symptoms of anxiety or depression (35–37).
- foot reflexology was more effective than control aromatherapy for hot flushes, sweats and night sweats (38).
- health coaching had no effect on depression symptoms (39).
- self-directed learning improved menopausal symptoms (40).

**Alternative medicine and complementary therapies**

We identified 10 RCTs that assessed a variety of herbal remedies (14,41–51) such as extracts from lavender (and lavender aromatherapy), bitter orange, hops, soy, and homeopathic and ayurvedic preparations compared against mostly placebo controls (table 8 in the data tables appendix).

The trials assessed a range of outcomes including vasomotor symptoms, hot flushes, sleep quality and anxiety and depression. Most studies indicated a significant effect of the herbal remedy; however, the homeopathic remedy had no effect on hot flushes or quality of life compared with placebo.

**Chinese herbal medicine**

In 1 Cochrane review (52) and 1 RCT (53), Chinese herbal medicine compared with HRT, other drug treatments or placebo, had no effects on menopausal or vasomotor symptoms including hot flushes and night sweats or adverse events (table 9 in the data tables appendix).
Acupuncture

We identified 6 RCTs of acupuncture (table 10 in the data tables appendix) (54–59), 4 of which used a non-sham acupuncture control group (for example, self-care, wait list, or alprazolam).

The studies found improvements in sleep quality, vasomotor symptoms, and oestrogen levels, but no effect on luteinising hormone or follicle stimulating hormone levels. However, these studies may be at risk of bias because the control group was aware that they were not receiving acupuncture.

In 2 RCTs comparing acupuncture with sham acupuncture, inconsistent results were seen for hot flushes. Hot flushes were statistically significantly improved in 1 study, but the result was noted to be less than the minimum clinical difference. There was no effect on hot flushes in the other study. The study finding improved hot flushes also reported improved menopausal symptoms and menopause-related quality of life. However, these measures could be driven by effects on hot flushes to some degree, so they do not indicate a clear clinically important effect.

Intelligence gathering

Topic experts suggested that the guideline could cover more non-hormonal treatments, but the limitations of the evidence base were recognised. Topic experts also highlighted new evidence on CBT, ospemifene and prasterone.

We identified ongoing studies assessing the effects of:

- CBT on vasomotor symptoms of menopause – Can nurse delivered CBT reduce the impact of hot flushes and night sweats in women who have had breast cancer? (ISRCTN12824632).
- complementary therapies, including two doses of standardised black cohosh. The guideline noted ‘there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms…’ but that ‘multiple preparations are available, and their safety is uncertain, different preparations may vary and interactions with other medicines have been reported’. This ongoing study – Effect of Menopause Relief EP-40 in Women With Menopausal Symptoms (NCT03461380) – may provide further evidence in this area.
We will check the publication status regularly and evaluate the impact of the results on current recommendations as quickly as possible.

**Impact statement**

**Drug treatments**

The guideline did not consider melatonin, oxybutynin or oxytocin. The clinical importance of the results reported in the abstracts was unclear and the studies were generally conducted in small numbers of people. Larger studies are needed to clarify the role of these treatments in menopause. Therefore, the guideline should not include these treatments in an update.

The guideline assessed venlafaxine but made no recommendations on this drug. The authors of the study of venlafaxine noted that the effects on sleep were ‘modest’, and the change in quality of life was small and of borderline statistical significance. Overall, the clinical significance of the findings is unclear. Therefore, there is no clear indication that an update to the guideline to consider venlafaxine is needed.

The guideline did not consider prasterone although it was available as a supplement in some countries when the guideline was developed. A preparation of prasterone is now available (costing £15.94 for 28 pessaries) for treatment of vulvar and vaginal atrophy in postmenopausal women with moderate to severe symptoms in the UK. New evidence suggests that prasterone may reduce vaginal symptoms of menopause and improve sexual function over 3 months of treatment. One of the studies identified in surveillance was also highlighted by topic experts. However, the evidence suggested that prasterone was no more effective than vaginal moisturiser for vaginal dryness and dyspareunia. Further evidence on the effects with prasterone treatment longer than 3 months and longer-term safety data is needed before considering an update of the guideline to evaluate the role of prasterone for treating vaginal symptoms of the menopause.

The guideline assessed ospemifene but made no recommendations on this drug. At the time of guideline development, ospemifene had recently received marketing authorisation in the UK, but its cost was unknown, so it could not be considered alongside vaginal oestrogen in the evidence review. However, it is now available in
the UK (costing £39.50 for 28 tablets) and is licensed for use in postmenopausal women who are not candidates for local vaginal oestrogen therapy.

The evidence on ospemifene reviewed during guideline development included 7 studies, with analyses of the various outcomes including 331 to 1971 women. The quality of these studies ranged from very low to moderate quality. The evidence indicated that ospemifene improved dyspareunia and vaginal dryness. Ospemifene also affected several physiological outcomes, such as reducing parabasal and intermediate cells, increasing superficial cells, and reducing vaginal pH. Ospemifene treatment for up to a year was not associated with endometrial hyperplasia, but endometrial thickness was increased. It was associated with more adverse events than placebo, but women were not more likely to stop treatment over 12 weeks. The new evidence was consistent with these findings and indicated improvements in sexual function. However, the new evidence did not report on adverse events associated with ospemifene. It was not possible to tell from the abstracts whether the effects were clinically meaningful, or durable.

The cost of prasterone is comparable with available intravaginal oestrogen pessaries, and although ospemifene is more expensive, its use is restricted to a smaller group of women for whom intravaginal oestrogen is not suitable. Therefore, we do not expect these treatments to have a substantial impact on NHS resources. Additionally, we are not aware of any new safety issues relating to other treatments for vaginal symptoms of menopause. For these reasons, we decided that an update was not necessary at this time.

New evidence is unlikely to change guideline recommendations.

**Physical and psychological therapies**

The guideline recommended considering CBT to alleviate low mood or anxiety that arise as a result of the menopause. The new evidence suggests that CBT may be useful for coping with other menopausal symptoms. Additionally, topic experts indicated that an update should look at CBT. However, because of heterogeneity in the type of CBT intervention, and the lack of information on the clinical importance of the effects sizes reported in the abstracts, the evidence base for CBT does not
appear to have advanced sufficiently to indicate a need to update the guideline at this time.

Similarly, the evidence did not show a clear effect of device-guided slow-paced breathing health coaching and exercise interventions and foot reflexology and self-directed learning were each assessed in a single small trial. A larger body of evidence is needed to support considering these treatments in a guideline update.

New evidence is unlikely to change guideline recommendations.

**Alternative medicine and complementary remedies**

The guideline does not recommend the herbal remedies identified in the new surveillance evidence. However, it recommends explaining to women who wish to try complementary therapies that the quality, purity and constituents of products may be unknown. The new evidence consisted of relatively small RCTs (100–200 participants). Larger studies evaluating complementary therapies in preparations with standardised quality, purity and constituents are needed before considering an update in this area.

New evidence is unlikely to change guideline recommendations.

**Chinese herbal medicine**

The guideline does not have recommendations on Chinese herbal medicine. The new evidence found no effect of this treatment on any relevant outcomes, indicating that an update in this area is not necessary.

New evidence is unlikely to change guideline recommendations.

**Acupuncture**

The guideline does not recommend acupuncture and the new evidence, showing little clinically important effect of this treatment, indicates that an update to include acupuncture is not necessary.

New evidence is unlikely to change guideline recommendations.
Long-term benefits and risks of hormone replacement therapy

**Surveillance proposal**

This section of the guideline on long-term benefits and risks of hormone replacement therapy should not be updated.

**2019 surveillance summary**

We identified 66 studies looking at long term risks and benefits of HRT, usually compared with an inactive control (mostly placebo). The studies assessed different types of HRT (oestrogen-only, combined, and tibolone) and varying durations of use. Many abstracts did not include specific details about the type or duration of HRT. Additionally, dosage information was not reported in all abstracts so information on dosage was not considered in this surveillance unless the study specifically compared a single regimen at 2 different doses (1 such study identified).

**Coronary heart disease**

We identified 2 large cohort studies (60,61) that assessed the risk of coronary heart disease with intravaginal HRT use compared with no HRT (table 11 in the data tables appendix). The results were inconsistent, with one study finding no effect and another finding lower risk of coronary heart disease with HRT. One of the studies found lower risk of coronary heart disease mortality.

**Stroke**

We identified 7 cohort studies (61–67), 1 Cochrane review (68) and one other systematic review (69) that assessed risk of stroke (ischaemic or haemorrhagic) or stroke mortality (table 12 in the data tables appendix). Studies assessed various types and durations of HRT use, and differing lengths of time since stopping HRT.

The studies showed mixed findings:

- 6 analyses suggested increased risk of stroke with
  - Oestrogen-only HRT compared with placebo (68,69).
  - Combined oestrogen (cyclic or continuous) and progestogen HRT compared with placebo or no HRT (65,68).
HRT compared with no HRT (63,66).

- 1 analysis suggested increased risk of stroke mortality in the first year after stopping HRT compared with no HRT or current HRT use (67).
- 5 analyses suggested no effect on stroke (mostly haemorrhagic) with combined or oestrogen-only HRT, including analyses of whether HRT was started up to 5 years after menopause or more than 5 years (62,65,66).
- 6 analyses suggested lower risk of stroke with oestrogen-only HRT, intravaginal oestrogen, and combined HRT, compared with no HRT, which was analysed by whether HRT was started up to 5 years after menopause or after 5 years (62,64,65).
- 2 analyses suggested improved stroke mortality with 3–5 years of intravaginal oestrogen and more than a year after stopping HRT (67).

**Venous thromboembolism**

We identified 2 cohort studies (63,70), 2 Cochrane reviews (10,68), and 1 other systematic review (69) that measured the risk of venous thromboembolism with HRT (table 13 in the data tables appendix). Both oestrogen-only and combined HRT were associated with increased risk of venous thromboembolism. One of the Cochrane reviews (10) suggested no effect of tibolone on risk of venous thromboembolism. However, this result was uncertain, with the confidence intervals indicating that tibolone may be associated with less than half the risk as no HRT but could also nearly double the risk of venous thromboembolism.

**Diabetes**

We identified one systematic review (69) that suggested a reduced risk of diabetes with either oestrogen-only or combined HRT compared with placebo (table 14 in the data tables appendix).

**Other cardiovascular outcomes**

We identified 5 cohort studies, 4 RCTs and 2 Cochrane reviews that assessed the effects of HRT on other cardiovascular outcomes (table 15 in the data tables appendix). Preparations of HRT varied across the studies, including oestrogen-only, combined and unspecified HRT. Additionally, studies analysed differing time points, such as stopping in the past year or more than a year ago, having started HRT in the
past 3 years or more than 3 years ago. Results suggested possible inconsistent effects of HRT compared with no HRT including:

- increased risk of acute coronary syndromes (63)
- no effect or increased risk of cardiovascular events or coronary events (10,29,68,71)
- no effect on cerebrovascular events (10) but reduced arterial thromboembolic events (72)
- inconsistent effects on blood pressure (8,73)
- improved blood pressure in one study of combined HRT and increased risk of hypertension in one study of oestrogen alone or combined HRT
- improved blood lipid profile (74).

Cardiovascular mortality (61,67,75–77) showed inconsistent results. Across 9 analyses, 4 suggested a lower risk of cardiovascular mortality and 3 suggested no effect. Analyses suggested increased cardiovascular mortality in the first year after stopping HRT but no effects more than a year after stopping HRT.

A Cochrane review (10) suggested that, compared with combined HRT, tibolone had no effect on cardiovascular, cerebrovascular, or thromboembolic events.

**Breast cancer**

We identified 10 cohort studies (76,78–86), 2 RCTs, 2 Cochrane reviews (10,68) and 1 other systematic review (69) that addressed the risk of breast cancer (table 16 in the data tables appendix).

Lower risks of breast cancer were seen in 3 studies of oestrogen-only HRT or unspecified HRT (that is, no details about the preparation were reported in the abstract) compared with placebo or no HRT (68,87).

No effect on breast cancer risk was seen in 3 studies of oestrogen-only HRT or unspecified HRT compared with no HRT (79,85,86).

Higher risks of breast cancer were seen in 11 studies of HRT compared with placebo or no HRT including:
6 studies of combined HRT (68,69,78,85–87)
4 studies of unspecified HRT (76,79,80,84)
1 study of intrauterine progestogen (83).

Tibolone showed inconsistent effects on breast cancer with 2 analyses showing no association with breast cancer and 2 suggesting increased risk of breast cancer compared with placebo, no HRT, or combined HRT (10,85).

One study assessed the outcomes for women using HRT who were subsequently diagnosed with breast cancer. HRT was associated with lower breast cancer mortality and recurrence compared with not using HRT at diagnosis (82).

**Other cancers**
We identified 14 cohort studies (76,80,88–98), 5 RCTs (77,84,99–102), 3 Cochrane reviews (10,68,103) and 1 other systematic review (69) that addressed the risk of cancers other than breast cancer with HRT use compared with an inactive control (table 17 in the data tables appendix).

Overall, studies indicated that HRT use was associated with:

- a generally consistent reduced risk of gastrointestinal cancers, including colorectal cancers.
- an increased risk of ovarian cancer, melanoma and in any cancer
- no effect on risk of non-Hodgkin’s lymphoma or lung cancer.

**Osteoporosis**
We identified 2 cohort studies (104,105), 1 RCT (106), 1 Cochrane review (68) and one other systematic review (69) that addressed outcomes related to osteoporosis (table 18 in the data tables appendix). Overall 9 of 10 analyses showed a lower risk of fracture or increased bone mineral density with HRT use. The remaining analysis suggested no effect.

**Dementia**
We identified 1 cohort study (107), 4 RCTs (20,108–110), 1 Cochrane review (68) and 1 other systematic review (69) that assessed dementia and cognitive outcomes
 Overall, results were inconsistent across the 13 analyses:

- 6 analyses suggested worse cognitive outcomes with HRT; however, most analyses were of varying measures of cognitive function rather than diagnosis of dementia
- 6 analyses suggested no effect of HRT; again, most analyses were of varying measures of cognitive function rather than diagnosis of dementia
- 1 analysis suggested reduced risk of Alzheimer's disease with HRT.

**Long-term risks not currently covered in the guideline**

We identified 4 cohort studies (75,76,82,111), 1 RCT (77), and 1 Cochrane review (10), that measured the effects of HRT use on mortality (1 study specified the outcome as non-breast cancer mortality) (table 20 in the data tables appendix). In 7 analyses, HRT was associated with lower mortality, and 5 analyses found no effect. There was no indication that the results were dependent on population characteristics or type or duration of HRT use.

We identified 11 cohort studies, 4 RCTs, 2 systematic reviews and 3 Cochrane reviews that addressed other outcomes that were not considered in the guideline (table 21 in the data tables appendix). Results indicated:

- HRT was associated with increased risk of faecal incontinence, fibroids, gallbladder disease and gallstones, hearing loss, joint swelling, rheumatoid arthritis, and urinary incontinence (68,69,97,112–116).
- HRT was associated with improvements in albuminuria, anxiety, carpal tunnel syndrome, joint pain, lung function, and tinnitus (20,113,117–120).
- There may be no association between HRT and sudden sensorineural hearing loss (120).
- Inconsistent effects on intraocular pressure were seen, with improvement seen with conjugated equine oestrogen, but no effect seen with combined HRT (121).
One cohort study (122) compared 2 doses of conjugated equine oestrogen – less than 0.625 mg daily and 0.625 mg daily. Progestogen was also used in both groups. The occurrence of global index events (coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death) was lower with the lower dose. For the higher dose, duration of treatment of 5 or more years was associated with higher rates of global index events than a duration of less than 5 years.

Intelligence gathering
No topic expert feedback was relevant to this section of the guideline.

Impact statement

Coronary heart disease
The guideline considered the effects of HRT on coronary heart disease. Both the guideline and the new evidence found no or reduced risk with oestrogen-only HRT. Therefore, the new evidence is consistent with current recommendations to explain that HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease.

Stroke
Evidence identified in developing the guideline found possible increased risk of stroke with combined or oestrogen-only HRT. However, the effects were uncertain. The guideline recommends explaining to women that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke and that the baseline population risk of stroke in women aged under 60 years is very low.

The new evidence was mixed, with some new evidence indicating an increased risk of stroke with HRT and other studies finding no effect or reduced risk of stroke. Therefore, the uncertain risks of stroke with HRT noted in the guidelines are unlikely to change substantively.

Venous thromboembolism
The guideline recommended explaining to women that oral HRT was associated with an increased risk of venous thromboembolism, but there was no increased risk for
transdermal HRT. The new evidence also indicated an increased risk of venous thromboembolism with HRT, and an uncertain effect of tibolone on venous thromboembolism. Therefore, an update in this area is not necessary because the findings are consistent with the guidelines recommendations on oral HRT, and is unclear whether tibolone has a different risk profile to oral HRT.

**Diabetes**

The new evidence of reduced risk of diabetes with HRT is consistent with evidence considered in the guideline. However, in developing the guideline, the protective effects of HRT on type 2 diabetes appeared to last only until HRT was stopped. The recommendations therefore noted there to be no increased risk of type 2 diabetes, rather than a reduced risk of diabetes. The new evidence did not inform whether the effect on diabetes continues after stopping HRT, thus no update in this area is needed.

**Other cardiovascular outcomes**

The guideline recommended that HRT does not increase cardiovascular disease risk when started in women aged under 60 years and does not affect the risk of dying from cardiovascular disease. The new evidence showed inconsistent effects on other cardiovascular outcomes and cardiovascular mortality. The new evidence is thus unlikely to substantively change the guideline’s conclusions about risk of cardiovascular disease and mortality.

**Overall impact on cardiovascular outcomes**

Overall, the new evidence was generally consistent with the guideline’s conclusions about cardiovascular risks associated with HRT use. There was no clear indicator that any additional cardiovascular risks need to be considered by the guideline.

New evidence is unlikely to impact on the guideline.

**Breast cancer**

The guideline considered the effects of HRT on breast cancer. The effects differed depending on whether HRT use was current or historical, duration of treatment, and whether oestrogen-only HRT or combined HRT was used. The guideline recommended explaining to women around the age of menopause that ‘HRT with
oestrogen alone is associated with little or no change in the risk of breast cancer’ and ‘HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer’.

Overall the evidence identified in surveillance was consistent with these findings, with oestrogen-only HRT generally showing no or lower risks of breast cancer, and HRT containing progesterone generally showing an increased risk of breast cancer.

**Other cancers**
The guideline did not address risk of cancers other than breast cancer. Although the new evidence provides additional information on possible risks and benefits of HRT use, they do not substantively change the overall risk–benefit profile of using HRT. The increased risk seen for ovarian cancer is already recognised in the SPCs of hormone replacement therapy products. Evidence suggests a balance between increased risks of some cancers such as melanoma and reduced risks of other cancers such as colorectal cancers. However, the evidence mostly comes from observational studies, and as such, it is not possible to be sure of a cause and effect relationship. The observed cancer rates may be influenced by confounding factors that have not been recognised or measured. Therefore, the guideline should not be updated to address additional cancer risks at this time.

New evidence is unlikely to impact on the guideline.

**Osteoporosis**
The guideline recommends explaining to women that their risk of fragility fracture is decreased while taking HRT. The new evidence showing reduced risk of fracture with HRT is consistent with this finding.

New evidence is unlikely to impact on the guideline.

**Dementia**
The guideline recommends explaining to menopausal women that the likelihood of HRT affecting their risk of dementia is unknown. The new evidence showed inconsistent effects on dementia and cognitive function and thus is unlikely to substantially impact on the findings in the guideline.
New evidence is unlikely to impact on the guideline.

**Long-term risks not currently covered in the guideline**

The guideline did not cover overall mortality and the inconsistency of the new evidence suggests that a guideline update to consider these outcomes is not necessary.

New evidence is unlikely to impact on the guideline.

**Other outcomes**

The new evidence seems to show inconsistent effects across HRT-related outcomes, such as hearing or joint pain and swelling. The evidence mostly comes from observational studies, and as such, it is not possible to be sure of a cause and effect relationship. The observed effects may be influenced by confounding factors that have not been recognised or measured. Additionally, most of these other outcomes were identified in a single study and we are not aware of clinical or patient concerns on outcomes not covered by current recommendations. Therefore, a guideline update to consider additional outcomes is not necessary at this time.

New evidence is unlikely to impact on the guideline.
Diagnosing and managing premature ovarian insufficiency

**Surveillance proposal**

No new information on diagnosing and managing premature ovarian insufficiency was identified at any surveillance review.

**Research recommendations**

What is the safety and effectiveness of alternatives to systemic HRT as treatments for menopausal symptoms in women who have had treatment for breast cancer?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What is the impact of systemic HRT usage in women with a previous diagnosis of breast cancer for the risk of breast cancer reoccurrence, mortality or tumour aggression?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

How does the preparation of HRT affect the risk of venous thromboembolism (VTE)?

- New research relevant to the risk of venous thromboembolism was identified but does not clearly answer this research recommendation.

What is the difference in the risk of breast cancer in menopausal women on HRT with progesterone, progestogen or selective oestrogen receptor modulators?

- New research relevant to the risk of breast cancer was identified but does not clearly answer this research recommendation.
What is the impact of oestradiol in combination with the levonorgestrel-releasing intrauterine system (LNG-IUS) on the risk of breast cancer and venous thromboembolism (VTE)?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What are the effects of early HRT use on the risk of dementia?

- New research relevant to the risk of dementia was identified but does not clearly answer this research recommendation.

What are the main clinical manifestations of premature ovarian insufficiency and the short- and long-term impact of the most common therapeutic interventions?

- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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