Treating the menopause – the concept of risk and benefit

As medical practitioners, we are well aware of the benefits of menopausal hormone therapy (HT) for the treatment of menopausal symptoms and maintenance of bone density. However, in discussing this with patients we may find that the patient is focused on the risks, real or perceived, of the treatment. It therefore behoves us to be able to discuss the risks and benefits in a way that is understandable to the patient.

- Consider the following when assessing risk: the patient's years since menopause, the type of menopausal hormone therapy (combined or oestrogen alone), route of administration, duration of hormone use and the patient's individual medical factors and family history.
- Be guided by current best practice and the quality of evidence.

Level of evidence (strongest to weakest)	Type of information on which it is based
1	Double-blind, randomised, placebo-controlled trial (frequently called an RCT)
2	Observational studies which compare users and non-users but without the benefits of random assignment or the use of placebo
3	Observational studies, but does not compare users of the drug with non-users
4	Opinions from experts, non-experts (e.g. relatives, friends) and vested interest parties

Absolute vs. relative risk

- Absolute risk is the chance of an event, stated without any context and is not compared to any other risk. It is simply the probability of an event occurring e.g. like flipping a coin and having a 50% chance of getting heads.
- A change in absolute risk can be expressed either as an absolute number of events with treatment compared with the absolute number of events without treatment, usually expressed as per 10,000 women years; or a change in an individual's personal chance of having an event with a particular intervention.
- Relative risk is a comparison between risk e.g. the risk with treatment compared that risk without treatment, but does not tell us anything about the absolute risk of the event occurring.
- A relative risk of 2 means a 100 percent increase in the risk i.e. the risk gets multiplied by 2 (the incidence doubles). The level of concern with this increase in risk depends on the baseline risk. If, for example, the baseline absolute risk is 1/10,000 women per year and the relative risk of 2 doubles this to 2/10,000 women per year. Although this may be statistically significant, most of us would consider this is to be not clinically significant.

The risks and benefits of menopausal HT: a historical perspective

- The first major study of menopausal HT was the Nurses' Health Study, conducted in women aged 30 to 55 years at entry (1). The advantages of this study were that HT was used from the time of menopause. The disadvantage was that it was an observational study. However, the findings of this study, i.e. that HT is associated with reduced mortality, particularly that from cardiovascular disease, prompted the subsequent randomised controlled trials (RCT).
- The Women's Health Initiative (WHI) evaluated the impact of menopausal hormone therapy on cancer, cardiovascular disease, and osteoporotic fractures was conducted in women aged 50 to 79 years at entry. The study was terminated early (July 2002), as the researchers felt the risks outweighed the benefits. The study reports indicated that menopausal hormone therapy (specifically combination oral oestrogen and progestin) increased the risk of venous thromboembolic disease, stroke, breast cancer and myocardial infarction (2, 3). In particular, the finding of increased cardiovascular morbidity in the WHI tipped the perceived balance of risk and benefit toward risk.
- As a result of the findings of the WHI many doctors and their patients abandoned the use of menopausal hormone therapy.

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- Manson, in the 2013 follow up overview of the findings from the WHI, concluded as follows: "Menopausal hormone therapy has a complex pattern of risks and benefits. Findings from the intervention and extended post-intervention follow-up of the two WHI hormone therapy trials do not support use of this therapy for chronic disease prevention, although it is appropriate for symptom management in some women" (4).
- A recent Cochrane review of the studies of menopausal HT and its relationship to cardiovascular risk has concluded that there was no strong evidence for protection or harm from HT with respect to cardiovascular disease (5). However, in women who start HT less than 10 years post menopause, there was some evidence of protection for mortality (RR 0.70, 95% CI 0.52 to 0.95) and coronary heart disease (RR 0.52, 95% CI 0.29 to 0.96), providing support for the so-called "timing hypothesis"

Summary of WHI findings

The following table from Manson et al JAMA 2013 summarises the change in outcome in absolute numbers in the overall study by the intervention phase and the cumulative follow-up (4).

Events per 10 000 women per year – intervention v placebo

	Estrogen plus progestogen therapy		*Estrogen therapy*	
	Intervention phase	*Cumulative follow-up*	*Intervention phase*	*Cumulative follow-up*
Coronary heart disease	6	3	-3	-4
Breast cancer	9	9	-7	-7
Stroke	9	5	11	5
Pulmonary embolism	9	4	4	2
Colorectal cancer	-6	-3	2	2
Endometrial cancer	-1	-3	NA	NA
Hip fracture	-6	-5	-6	-2
All-cause mortality	-1	-1	3	-1

NA, not applicable

The above table does not convey fully the information about differences in different formulations and delivery of HT and of the age of the women who will use it. In particular some points to note:-

- Transdermal HT has not been associated with an increase in risk of venous thromboembolic disease whereas oral HT has (6, 7)
- Starting HRT in the first 10 years after menopause carries no increase in cardiovascular risk and may confer some cardiovascular protection
- The addition of progestogen reduces the risk of endometrial cancer but increases the risk of breast cancer
- Different progestogens have different risk ratios for breast cancer increase and some, e.g. micronized progesterone and dydrogesterone, may be "safer" than others (8).

Supporting women in making a decision

- For some women any extra risk will be unacceptable but others may feel that the benefits outweigh the risks.
- Management of menopausal symptoms should be individualised for each patient.
- Issues to consider with each patient contemplating menopausal hormone therapy include:
    - The impact of symptoms on Quality of Life (QOL) and functioning.
    - What lifestyle measures can be implemented?
    - The risks and benefits of management options, including the relative and absolute risk of menopausal HT options, and the reliability of the evidence.
    - Regular review of health and medication.

 ID: 2015-05-28

Key points

- **For the majority of symptomatic women the benefits of menopausal HT outweigh the risks**
- **Consider the risks and benefits of all menopausal hormone therapy in the individual prior to commencing treatment.**
- **Risks differ depending on the age of the woman and the route of administration.**
- **Recent information clarifies and refines the original findings of the WHI studies and these findings show that some women have been inappropriately discouraged from the use of menopausal hormone therapy.**
- **Utilise current evidence and be aware of the quality of the evidence you use to make a decision.**
- **Optimise lifestyle factors for each patient regardless of whether you will recommend hormone therapy.**

Recommended reading

1. de Villiers, T. J., Gass, M. L., Haines, C. J., Hall, J. E., Lobo, R. A., Pierroz, D. D., & Rees, M. (2013). Global consensus statement on menopausal hormone therapy. *Climacteric, 16*(2), 203-204. doi: 10.3109/13697137.2013.771520

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6. Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P-Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008 May 31;336(7655):1227-31.
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