LETTERS

NICE GUIDELINES ON THE MENOPAUSE

Authors' reply to Sarri and colleagues

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The current combined evidence from conventional and from network meta-analyses of randomised controlled trial (RCT) data is that menopausal hormone therapy (MHT) is effective for the relief of vasomotor symptoms.^{1 2} We noted this in our editorial and agree with the National Institute for Health and Care Excellence (NICE) guidelines on this matter,³ so we are unsure why Sarri and colleagues considered this a point of contention.⁴

We also agree that women differ in their priorities and information needs, and that it is important to provide summary evidence on the risks and benefits of MHT according to each outcome separately. However, an overall assessment of whether MHT is likely to be harmful or beneficial for health in terms of serious potentially life threatening conditions is also important information for many women and their healthcare professionals. We remain concerned that the NICE guidelines do not present women and healthcare professionals with appropriate and useful summary estimates on the risks of MHT for serious disease. In particular:

1. It is inappropriate to restrict RCT data to those from women aged 50-59 years at trial entry. We did not misunderstand Sarri and colleagues on this point. It is a statistical principle that, where effects in study subgroups such as age do not differ significantly, the relative risks from the study as a whole should be assumed to apply to these subgroups.⁵⁻⁷ The relative risks for the association between MHT and cardiovascular disease and global health outcomes from RCTs do not differ significantly by age,⁸ so the relative risks found in RCTs for all age groups combined should be considered to apply to each age group. The only exception to this is breast cancer, where the effects of MHT on the relative risk are greater the closer women are to the menopause⁸—that is, in younger age groups. Hence, it would be conservative to use the relative risk estimates across all age groups. Restricting data to women aged 50-59 years at trial entry has the effect of excluding a large proportion of the relevant RCT data on MHT (see NICE guidelines, appendix G), inappropriately increasing

uncertainty and reducing statistical power to detect the risks and benefits of MHT.

2. The guidelines use observational data to estimate the effects of MHT on coronary heart disease and stroke, despite the acknowledged major problems in interpreting such data.

3. Although it is clear that predefined protocols were followed closely, the relative risk and absolute risk summaries presented do not seem to include all relevant studies and do not apply the data in a way that maximises its usefulness to women and their healthcare professionals. For example, the data on cohort studies estimating the association between current versus ever use of combined MHT and breast cancer risk seem to come from only three studies. Most of the relevant studies were excluded for various reasons that mostly seem to relate to the age or menopausal status of women included (see NICE guidelines, appendices G and J).

As well as excluding much relevant data, the NICE data synthesis, designed to inform clinicians and consumers on the association between MHT use and the absolute risk of disease, does not apply the best of what is known about the relative risk and associations with duration of use to the background absolute risks. If data from observational studies have been shown to be unreliable, as is the case for MHT and coronary heart disease and stroke, then RCT data should be emphasised. Where there is clear evidence that risk varies according to MHT type, data on risk for each of these types should be presented separately. However, where they do not differ, data should be combined to maximise statistical reliability.⁹ Whether or not the relative risks vary by duration of use should be taken into account, based on the summary of the best evidence. All of these data should then be brought together and applied to data on the background risk of the particular outcome, for different durations of use.⁹

For example, the Medicines and Healthcare Products Regulatory Agency (MHRA) summary of the association between current MHT use and stroke (the most recent independent and comprehensive quantitative assessment of the evidence) from

RCTs shows a 25% increase in risk (95% confidence interval 10% to 43%), consistent for oestrogen-only (relative risk 1.27, 1.05 to 1.53) and combined oestrogen-progestogen MHT (1.24, 1.03 to 1.50; P(heterogeneity between MHT types)=0.9) preparations.⁹ No clear variation in the relative risk according to duration of use has been established.¹⁰ Hence, the best current evidence on the association between MHT and stroke for different durations of use is obtained by applying the summary relative risk to the background risk of stroke for women of different age groups. The MHRA estimates that five years of MHT use among 1000 women will lead to one extra stroke in women aged 50-59 and three extra strokes in women aged 60-69; corresponding figures for 10 years of use are two and five extra strokes.⁹

By contrast, the NICE guidelines present separate absolute risk estimates for randomised and observational studies on oestrogen-only MHT, combined MHT, and unspecified MHT exposure, leading to six estimates for current use alone. More importantly, despite Sarri and colleagues' statement that "disease risk associated with different durations of HRT use has been presented," the estimates for absolute risk according to duration (<5 years and 5-10 years) are virtually all listed as "no data available"; for stroke, only one of 12 potential estimates is provided, from observational data.¹ It is clinically unhelpful that around 70% of the 40 MHT duration or disease categories in the guideline as a whole are listed as "no data available," and only one of these 40 categories has an estimate from RCT evidence.¹ Table 1 illustrates this point in relation to stroke.

In summary, we congratulate the authors of the NICE guideline on menopause for their focus on individualised care, but

re-emphasise that the best available data on overall risks are also key to informed decision making by women and their healthcare providers.

Competing interests: None declared.

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Table

Table 1 | Absolute risk of stroke (95% CI) for different types of HRT versus no HRT (or placebo) according to duration of HRT use and time since stopping HRT in menopausal women*

Source of risk estimate	Current HRT users	Treatment duration <5 years	Treatment duration 5-10 years	>5 years since stopping treatment
Women on oestrogen alone				
RCT estimate†	0 (–5 to 10)	No available data	No available data	1 more (–4 to 9)
Observational estimate‡	3 more (–1 to 8)	No available data	No available data	No available data
Women on oestrogen + progestogen				
RCT estimate†	6 more (–2 to 21)	No available data	No available data	4 more (–1 to 13)
Observational estimate‡	4 more (1 to 7)	No available data	No available data	No available data

*HRT=hormone replacement therapy; RCT=randomised controlled trial.

†For women aged 50-59 years at entry to the RCT.

‡Observational estimates are based on cohort studies with several thousand women.