Menopausal therapy and protection against coronary heart disease

To the Editor: The South African Menopause Society (SAMS) statement on menopausal therapy[1] varies little from their previous publication,[2] except for proper definition of the indications and contraindications, and some changes in the position statement. It now includes a statement that hormone therapy (HT) may offer primary protection against coronary heart disease (CHD) if started soon after menopause. They base this 'on the assumption that estrogen offers protection only when the arterial endothelium is still intact' and state that this 'is supported by epidemiological studies, animal models and the ET arm of the WHI'. SAMS is trying to promote a concept that may not be true. Epidemiological and animal studies do not always predict or correlate with the outcomes of proper controlled double-blind clinical trials, and no such trial confirms this proposal.

It is folly for SAMS to promote this concept. The recent Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update[3] does not mention using HT for prevention, once again classifying it as a class III intervention (not useful/effective and may be harmful), and states that hormone therapy and selective estrogen-receptor modulators should not be used for the primary or secondary prevention of cardiovascular disease.

A misconception among the medical fraternity is the notion of 'an intact arterial endothelium'. Atherosclerosis is a process that starts early in life and tends to be detected only when patients present with complications, women being no exception. Not every patient is subjected to invasive tests to determine whether they have an 'intact' arterial endothelium or not. Recently two 'cardioprotective' drugs (both involved in properly controlled clinical outcome trials) have been discredited. The first was torcetrapib, a cholesterol ester transfer protein inhibitor that significantly raises high-density lipoprotein cholesterol (HDL-C). It showed no advantage in limiting coronary disease progression as ascertained by intravascular ultrasound, and was associated with worse cardiovascular and mortality outcomes than statin monotherapy.[4] Of note is that the pattern of cholesterol change seen with this drug is similar to the profile in women on HT, i.e. an increase in HDL-C and a decrease in low-density lipoprotein cholesterol (LDL-C), which brings up the question of what is good HDL-C. All the hormone therapy trials achieved this lipid profile, but none have shown corresponding positive clinical outcomes – irrespective of whether they were secondary or primary prevention studies. The second discredited drug group is the glitazones, used in the treatment of diabetes mellitus, which have shown similar trends in cholesterol lowering. However, recently the US Food and Drug Administration warned that they cause increased fractures in women on long-term therapy. There is also concern that one of these agents, rosiglitazone, may be associated with a potentially significant increase in the risk of heart attack and heart-related deaths.[5]

Risk stratification of women is a problem. The Reynolds Risk Score[6] validated and demonstrated highly improved accuracy of two clinical algorithms for global cardiovascular risk prediction in women. It reclassified 40 - 50% of women, who on traditional risk scoring were deemed to be at intermediate risk, into higher- or lower-risk categories, but predominantly into a higher-risk group. The main difference compared with the Framingham Risk Score is the addition of high-sensitivity C-reactive protein (hs-CRP) and family history. A concern associated with HT is that it causes an increase in hs-CRP, which itself may be a risk factor for the development of CHD.

One of the cornerstones of medical treatment is to 'do no harm'. Until there is solid evidence that HT is protective in the primary prevention of CHD, colleagues are strongly advised to not follow the advice of the recent consensus position statement.

Naomi Rapeport
Specialist Physician
Milpark Hospital
Johannesburg
cscham@global.co.za

1. De Villiers TJ, Bagratee JS, Dalmeyer JP, *et al*. South African Menopause Society Council Revised Consensus Position Statement on Menopausal Hormone Therapy. *S Afr Med J 2007*; 97: 354-357.
2. De Villiers TJ. South African Menopause Society Council Consensus Statement on Menopausal Hormone Therapy. *S Afr Med J* 2004; 94: 760-762.
3. Mosca L, Banka CL, Benjamin EJ, *et al*. Evidence-Base Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update. *Circulation* 2007; 115: 1481-1501.
4. Nissen SE, Tardif JC, Nicholls SJ, *et al*. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007; 356: 1304-1316.
5. US Food and Drug Administration FDA safety alerts 03/09/2007; 02/20/2007; 05/21/2007. www.fda.gov/opacom/7alerts.htm.
6. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women. *JAMA* 2007; 297: 611-617.

Dr De Villiers replies: Dr Rapeport disagrees with the statement that HT may offer primary protection against CHD if started soon after menopause. She does not, however, offer any facts based on clinical trial evidence to support her argument. Since submission of the revised SAMS statement in January 2007, two new publications by none other than the Women's Health Study (WHI) investigators strongly support our viewpoint.

A secondary analysis of the combined estrogen alone (ET) and combination therapy (EPT) arms of the WHI concluded that women who initiated hormone therapy closer to menopause tended to have reduced CAD risk compared with the increase in CAD among women more distant from menopause.[1] The same investigators revealed in a secondary analysis of the ET arm of the WHI that patients treated with estrogen in the age group 50 - 59 years, when compared with

placebo-treated patients, were 42 - 61% less likely to have significant arterial calcification (as measured by computed tomography).[2] These publications are in stark contrast to earlier publications by the same investigators that implied HT as a cause of CAD, without taking into account that this did not apply to the typical patient, who initiates HT at the age of 50 - 59 years.[3]

Dr Rapeport further falsely assumes that SAMS promotes the use of HT for the prevention of CAD, even though it is not included in the list of approved indications in the revised guidelines. We maintain our position that if the only aim of treatment is protection against CAD, HT is an inappropriate choice in view of other proven methods. However, it is important to be able to assure the patient in the age group 50 - 59 years, who starts HT for the control of vasomotor symptoms or the prevention or treatment of osteoporosis, not only that HT will not cause CAD, but that protection can be expected. This also needs to be taken into account when deciding on termination of treatment.

We stand by our statement that the initiation of HT for the indications as provided is safe for the patient in the age group 50 - 59 years and that the small risk of any complication can be further reduced by using the lowest effective dose.

1. Rossouw JE, Prentice RL, Manson JE, *et al*. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; 297: 1465-1477.
2. Manson JE, Allison MA, Rossouw JE, *et al*. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007; 356: 2591-602.
3. Rossouw JE, Anderson GL, Prentice RL, *et al*. for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321-333.

'Opi-phobia' among doctors leads to unnecessary suffering

To the Editor: Francois Venter and Chris Bateman are to be commended on this piece.[1] Basic training of South African doctors and nurses in palliative care has been poor. Therefore few have raised their voices to improve palliative care, despite the great need for it in a developing country where many patients present with far advanced disease. This applies particularly to people with HIV because of denial and stigma.

An important step towards the development of good general palliative care in Australia and the UK has been the formation of departments of palliative care in teaching hospitals, through which all students must rotate during their training. I suggest that pharmacology students also have a short rotation. With the enormous need for such care, it seems an urgent priority to establish such departments in all our teaching hospitals. These should also bring past graduates up to speed in this discipline.

Another serious public sector hospital problem is the lack of effective links between district hospitals and community structures offering home-based care. Too often, medical staff end up saying to patients, 'There is nothing more that we can do for you', because the doctor has decided cure is not possible. In most cases, no thought is given to linking patients to community carers, or to empowering the carers with medications to reduce the suffering of their last days. No help in controlling symptoms is provided to home-based carers who appeal to district clinics when the scheduled drugs needed are not available to clinic staff. This has two effects. Firstly, hospital staff are never really confronted with the patient's palliative care needs, so they never grow in that expertise. Secondly, there is an assumption that palliative care in HIV is simple (which it is not), just as the rest of the medical care of people with HIV is difficult and requires considerable experience and expertise.

A solution to this problem could be the development of palliative care facilities in every district hospital, staffed by medical and nursing staff who are part of the training team of home-based carers in the district. They could assess the patient's palliative needs, access the necessary medications, and link the patient and family to a designated carer, or non-governmental organisation. They should also identify patients with HIV wrongly consigned to terminal care when they have a manageable infectious condition. Such a facility could have regular follow-up clinics in each of the district clinics, and be empowered to carry and dispense the necessary scheduled drugs. This should be a high-priority project for co-operation between district health services and the medical staff of every district hospital, including those in metropolitan centres serving rural communities.

J V Larsen
181 Amberfield
Private Bag X010
Howick, KZN
jonvl@netactive.co.za

1. 'Opi-phobia' among doctors leads to unnecessary suffering [Izindaba]. *S Afr Med J* 2007; 97: 399-406.

Achieving the Millennium Development Goals in sub-Saharan Africa

To the Editor: The UN has released a mid-term report on progress towards achieving the Millennium Development Goals (MDG), eight pro-poor goals contained in the Millennium Declaration of 2000, to be achieved by 2015.[1] It paints a gloomy picture of health in sub-Saharan Africa. Child mortality rates declined globally, but the improvement was uneven, with sub-Saharan Africa recording the highest rate and the slowest pace of progress. In 1990 and 2005 in sub-Saharan Africa, 185 and 166 children respectively died, mainly from preventable causes, before their 5th birthday for