Clinical opinions in general medicine

The second issue of clinical opinions for 2004 looks at two papers each concerned with the treatment and prevention of thrombosis and thromboembolism. Which thrombolytic to use in acute myocardial infarction is clearly an important decision and it is thought provoking, to say the least, to note that there is such wide variation in the interpretation of trial data.

If more reason for advocating smoking cessation and healthy eating were necessary, and it at this point in time surely it is not, the review of the paper by Tosetto *et al.* highlighting the association of both with venous thromboembolism is important. The third paper addresses the thorny issue of HRT in post-menopausal women and, in the opinion of Purdie, suggests that Estradiol is a safe and effective treatment when given in an appropriate dose. No doubt the debate will continue. As always we welcome comments regarding clinical opinions and especially welcome contributions from our readers.

Clinical opinion: Which thrombolytic in acute myocardial infarction?

TITLE: Superiority and equivalence in thrombolytic drugs: an interpretation.
KEYWORDS: Thrombolytic agents, interpretation of clinical trials, choice of agent.
AUTHORS: Walley T, Dunbar Y, Hill R *et al.*
JOURNAL: *Q J Med* 2003; **96:**155–60.

SUMMARY

The authors discuss the rationale of trials designed to show that one drug or regimen is better than another (superiority) as opposed to those that set out to show that a new strategy is as good as an established one (equvalence). In the context of the trials of thrombolysis in acute myocardial infarction (AMI) Walley *et al.* explore the different approaches of method and of definitions of efficacy and therefore the limits of confidence in defining benefit versus harm. They go on to describe how their own meta-analysis (published in the same journal) coped with the problem of different levels of mortality of the AMI populations across trials – and indeed such wide differences between the placebo treatment arms of AMI trials have always been a challenge to understanding how to apply results to clinical practice.

There follows a critical statistical review of the reported comparisons of alteplase and streptokinase (SK); alteplase and reteplase; reteplase and SK; and alteplase and tenecteplase. Conclusions are drawn in a summary of comparisons and they discuss contexts in which regimen choices have to be made.

OPINION

It has always seemed remarkable that so many different conclusions have been made from the results of the thrombolysis trial data, resulting in so many different coronary care unit protocols. Some claim that the trials have shown a clear superiority of alteplase over SK and therefore only use alteplase in their practice; others claim that the trials have shown a clear additional benefit from alteplase in anterior infarcts or in younger patients with ventral infarcts even to the point, in early days, of suggesting that treating inferior infarcts was unnecessary. Yet no clinical trial set out to compare the results in anterior infarcts against inferior infarcts, or in younger patients against older ones and statisticians have often warned against *post hoc* subgroup analysis. The European and British guidelines including those from the National Institute for Clinical Excellence do not specify what drug should be employed, only that a thrombolytic should be used in ST elevation infarcts presenting within the time window of efficacy.

My own practice, as a participant in most of the major trials, has therefore been to use SK as first line treatment and to use alteplase only in those who have previously been exposed to SK and therefore have antibodies to it. (More recently we have substituted reteplase because it comes in prefilled syringes and is now significantly cheaper than alteplase.) I believe that this critical review is helpful and it makes me comfortable with my own approach. No doubt others will interpret even this differently but Professor Walley and his group have done us a great service in laying out the ground rules for decision making and provide excellent information from which to work.

RH Smith, Consultant Cardiologist, Stockton-On-Tees

Clinical opinion: Preventing non-fatal venous thromboembolism

PAPER: Prevalence and risk factors of non-fatal venous thromboembolism in the active population of the VITA project.
KEYWORDS: Epidemiology, risk factor, venous thrombosis.
AUTHORS: Tosetto A, Frezzato M, Rodeghiero F.
JOURNAL: *J Thromb Haemost* 2003; **1:**1724–9.

SUMMARY

This study describes a cross-sectional evaluation of the prevalence, distribution and risk factors for non-fatal venous thromboembolism (VTE) in an active population of 15,055 subjects. The subjects, who constitute the population of the VITA project, were randomly selected from the census list of the district of Vicenza, Italy, were white and aged between 18 and 65 years. Those with severe physical or mental disease or a history of active cancer in the past year were excluded. Appropriate clinical data were collected by direct interview and examination, validated questionnaire and review of medical notes in subjects diagnosed as having VTE. The sensitivity of identifying cases correctly was estimated at almost 80% with a specificity of 99%. Smoking history, family history of VTE, previous superficial venous thrombosis (SVT), oral contraceptive use and body mass index (BMI) at the time of the VTE were ascertained as well as any specific circumstances such as pregnancy, trauma or surgery, or none (idiopathic). The overall prevalence of non-fatal VTE in this population was 1 in 130 with the most common being lower limb VTE (61·1/10,000), then pulmonary embolus (13·9/10,000) and then upper limb VTE (1·9/10,000). After sex and age adjustment, identifiable risk factors were SVT (odds ratio (OR), 6·8), oral contraceptive use (OR 4·7), family history (OR 4·5), BMI (upper- versus mid-tertile OR 2·9) and smoking (OR 1·7). A history of SVT and BMI in the upper-tertile were associated with VTE in all circumstances. A positive family history was associated with an increased risk in pregnancy and idiopathic VTE, and oral contraceptive use in idiopathic but not trauma or surgery associated VTE. It was concluded that in 30% of cases of VTE, two easily recognisable risk factors were present and in an active population VTE was potentially preventable in 56% of cases.

OPINION

Venous thromboembolism in active people <60 years of age is rarely fatal but can cause significant morbidity and this group constitutes 30% of all cases of VTE. Strategies for identifying subjects at risk in this population would help determine in whom primary prophylaxis might be of benefit. Much emphasis recently has been placed on identifying genetic predisposition to thrombosis by testing for factor V Leiden and prothrombin G20210A mutations, for example. These tests are poorly predictive in a healthy population, invasive and require specialised laboratories. This paper describes five risk factors that are easily determined either by clinical examination or history and relates their influence on thrombotic risk in two situations, pregnancy and trauma or surgery, or none (idiopathic). Of note, a history of hormone replacement therapy (HRT) was not taken although it is known to be associated with an increase in thrombosis and information on whether heparin was given during trauma or surgery was also lacking. Although risk varies with factor and situation, in the population as a whole, increasing numbers of risk factors were associated with an increasing prevalence of VTE. The authors postulate that the 56% of cases that occur in association with pregnancy and trauma or surgery are potentially preventable, presumably by primary prophylaxis but this is not stated; prospective studies would be needed. Although the increased risk with individual factors is low, their prevalence is high in the population and 12% of subjects had two risk factors and a five-fold increased risk of VTE compared to those with none. Overall, if clinicians are aware of risk factors in a healthy population, they can advise patients how to reduce risk and trials of primary prophylaxis for those in the highest risk groups in particular circumstances can be considered. Unfortunately, some of the advice such as to lose weight and not smoke is not easy to take.

AE Thomas, Consultant Haematologist, Edinburgh

Clinical opinion: Whither now for HRT?

TITLE: Risks and benefits of oestrogen plus progestin in healthy post-menopausal women; principal results from the Women's Health Initiative randomised controlled trial.

KEYWORDS: Oestrogen, progestogen, cardiovascular disease, breast cancer, osteoporosis, post-menopausal women.

AUTHORS: Rossouw JE, Hsia J, Johnson KC *et al*.

JOURNAL: *JAMA* 2002; **288:**321–33.

SUMMARY

The oestrogen plus progestogen (E+P) and the oestrogen-only (E) arms of the Women's Health Initiative (WHI) were the first large-scale randomised controlled trials to test the hypothesis – generated by positive observational studies – that oestrogen replacement would prevent myocardial infarction (MI) and stroke. The only primary endpoint, set out in the Trial Protocol, was cardiovascular disease (CVD) events – all other endpoints being secondary. A total of 8,506 post-menopausal women were randomised to receive 0·625 mg conjugated equine oestrogens (CEE) plus 2·5 mg medroxyprogesterone acetate (MPA) daily, with 8,102 patients being randomised to placebo. The study was halted prematurely at 5·2 years by its Data and Safety Monitoring Board (DSMB) since the confidence interval surrounding the hazard ratio (HR) for breast cancer had trespassed into its preset termination lower limit of 1·00 – the point estimate being 1·26 (1·00–1·59). Overall, the null hypothesis was proved, there being no cardiovascular protection and indeed an excess of both MI, HR 1·29 (1·02–1·63) and stroke, HR 1·41 (1·07–1·85). On the positive side there were reductions in the incidence of colon cancer, HR 0·63 (0·43–0·92) and femoral neck fracture, HR 0·66 (0·45–0·98). The E-only arm continued until March 2004 when it too was terminated – after 6·8 years – apparently due to loss of statistical power due to withdrawals. This study, just published, confirmed the absence of cardiovascular system protection but, interestingly, found no excess of breast cancers in the oestrogen-treated group.[1]

OPINION

This study was well-conducted and is extremely valuable in itself. It answers the question posed in its protocol – will CEE and MPA prevent CVD in post-menopausal women. The answer is No, it will not. However, practising physicians in the UK must enquire into the relevance of this study to this country. Hormone replacement therapy was never, and likely will never be licensed for prevention of CVD. The combination of CEE and MPA used in the WHI is not available here – although other combinations are. The authors in their conclusions properly caution that their data 'do not necessarily apply' to other forms, or combinations of E+P. Furthermore, the commencement of HRT here is almost universally restricted to women in their fifties. When the WHI data are stratified, women in their fifties showed no excess of CVD over controls. Finally, the E-only arm of the recently terminated study has most surprisingly not shown in MI, although the excess of strokes (8/10,000 per year) found in the combined study was confirmed. The WHI study was billed as a primary prevention study. I leave it to my colleagues to judge whether the test groups with, as reported by the authors, high prevalence of obesity, cigarette consumption, hypertension and statin use, could constitute a primary prevention trial. I believe it was a secondary prevention study or, at best, a hybrid. The ability of oestrogen to prevent CVD remains untested – and is now likely never to be tested. Oestrogens have been associated – except inthe WHI E-only arm – with a small but quantifiable increase in the risk of breast cancer, that tumour most feared by our patients. We should now capitalise on the WHI results by continuing to lower the dose of estradiol in oestrogen regimens and continuing the development of analogues such as raloxifene and tibolone. These agents retain the ability to arrest bone loss while minimising, or deleting, adverse effects upon the reproductive tract and the cardiovascular system. Estradiol is a natural steroid bioregulator. It is inherently unlikely that such a compound, evolved over not less than 500 million years by natural selection to regulate human female fertility, will prove to be harmful or lethal to women if given in appropriate regimens and under medical direction.

REFERENCES

1 The Women's Health Initiative Steering Committee. Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy: The Women's Health Initiative Randomized Controlled Trial. *JAMA* 2004; 291:1701–12.

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