General Practice

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Introduction

The remarkable rate of development of medical knowledge and pharmacology affects all medical specialties and in particular general practice, since the latter embraces various aspects of different medical fields.

Certain areas of medical practice, such as Hormone Replacement Therapy (HRT), hypercholesterolaemia and drugs affecting the Renin Angiotensin System (RAS) feature in a vast amount of literature which is constantly being updated. The increasing awareness of the previously unknown effects of HRT on one side, and the widespread prevalence of cardiovascular disease in the case of hypercholesterolaemia and drugs affecting the RAS have contributed to this large amount of studies.

On the other hand, certain areas of practice such as atopic eczema and anti-thrombotic therapy have been rather quiescent as far as developments are concerned, but revolutionary treatments have recently been introduced in both areas, namely the calcineurin antagonists and ximelagratan. The latter is a very promising drug which can replace warfarin, while the former are the first steroid-sparing medications which effectively control atopic eczema.

Keeping abreast with recent developments is a further hurdle which the modern general practioner has to contend with in order to offer valid treatment options, and to be able to answer questions by increasingly well-informed patients.

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Hormone Replacement Therapy (HRT)

The issues surrounding HRT are controversial. Some of the benefits ascribed to it include the relief of troublesome menopausal symptoms, a decrease in the incidence of cardiovascular disease and the prevention or treatment of osteoporosis. However, the Women's Health Initiative Trial (WHI)[1] and the Million Women Study (MWS)[2] cast doubt on the validity of these claims.

The WHI was aimed to identify strategies that could potentially lower the incidence of heart disease, breast and colonic cancer, and fractures in healthy women. The study consisted of two arms, namely the oestrogen/progesterone component, and the oestrogen alone component. The latter component is due to report in March 2005, but the former component had to be stopped prematurely after there was an excess of breast cancer disease and cardiovascular events in the treatment group. The combined hormone therapy resulted in absolute excess risks of 7 more coronary events, 8 more strokes, 8 more episodes of pulmonary embolism, and 8 more invasive breast cancers per 10,000 person years.

The findings of the WHI with respect to the effect of HRT on the cardiovascular system have been supported by other recent trials which have been carried out across different categories of women.[3,4,5]

The Million Women Study was aimed at describing the effects that different types of HRT had on the increase in incidence of breast cancer.

Over one million females were recruited between 1996 and 2001. The study concluded that current users of HRT have a relative risk of 1.66 of developing breast cancer and of 1.22 of dying from it. This relation was particularly evident in the combined oestrogen-progestagen combination.

The above two studies have re-dimensioned the role of HRT and the claims on its cardiovascular benefits are being questioned, despite the observed beneficial effect HRT has on the lipid profile.

HRT is effective in increasing bone mineral density and reducing fractures in osteoporosis. But given the associated increase in incidence of breast cancer, and above all the availability of better alternatives such as bisphosphanates[6], the use of HRT for the treatment of osteoporosis is being re-defined. Further more, after stopping HRT, there is a rapid decline in bone mineral density which is not observed when

Table 1: *Major Results of the Heart Protection Study*[8]

	Placebo	*Simvastatin*	*Relative Risk Reduction*
First event rate of non-fatal MI or coronary death	1212 (11.8%)	898 (8.7%)	26.3%
Non-fatal or fatal Stroke	585 (5.7%)	444 (4.3%)	24.6%
Need of Coronary Revascularization	1205 (11.7%)	939 (9.1%)	22.2%

bisphosphonates are stopped. In addition the results of studies on new treatment options such as strontium ranelate are promising[7].

Hypercholesterolaemia

Since the publication of the Scandinavian Simvastatin Survival Study (4S) in 1994, there has been an extraordinary increase in interest concerning hypercholesterolaemia. The Heart Protection Study[8] (HPS) is only one of many important studies published recently.

The aim of the HPS was to study the effects of using simvastatin in high-risk individuals, irrespective of whether they suffered from dyslipidaemia or not. Over twenty thousand adults suffering from some form of vascular occlusive disease or diabetes were randomly assigned to receive simvastatin 40 mg daily or placebo. A summary of the more important results is provided in Table 1.

This was the first time that statins were used on people without overt dyslipidaemia. In addition, the study population included adults up to the age of 80 years as well as a substantial number of women. Both of these population sub-types have been understudied or excluded in previous trials on statins.

The compliance rate for treatment in the HPS is claimed to be 82%, with a special emphasis being made by the authors that this is primarily attributable to the low incidence of side effects. Although this high adherence rate may be true in the controlled setting of a trial, it cannot be transferred to the community setting, where adherence rates may fall down to about 25-40%.[9] This study does not consider the fact that there are other issues involved in compliance other than the side effect profile.

The HPS concludes that simvastatin is beneficial for people at high risk of cardiovascular disease, even without dyslipidaemia or actual evidence of vascular disease, by reducing the incidence of new vascular events by nearly 25%. These findings have been further supported by the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)[10] and PROSPER (PROspective Study of Pravastatin in the Elderly at Risk)[11] studies, where the same risk reductions were observed.

A meta-analysis[12] published this year reviewed the benefit of using statins in diabetic patients, and the Numbers Needed to Treat (NNT) quoted are impressive:

- In Primary Prevention the NNT's is 34, while
- In Secondary Prevention the NNT's drops to just 13.

The publication of the HPS created some controversy and offered issues for discussion. It was the first time that people without dyslipidaemia derived benefit from an anti-lipid agent, and further confirmed the current trend of delivering treatment to reduce overall cardiovascular risk and not merely treating abnormal blood tests. In addition, it has raised an issue about the financial implications of giving statins to all people at high risk of cardiovascular disease.

Finally there is always the dilemma over the desirable cholesterol profile that clinicians should aim for. Specific guidelines have been provided by official bodies (Table 2), however apart from a 35% reduction from the starting low density lipoprotein (LDL) level, there is no universally accepted threshold.

Headache

Headache is a common complaint especially Tension Type Headache (TTH) and migraine. The major underlying reasons for consultation are reassurance about possible underlying serious disease and relief of pain.

The diagnosis of headaches is mostly based on history taking (Table 3). The British Association for the Study of Headache (BASH) guidelines for Tension-Type Headaches (TTH) and Migraine[13], released in 2003, are laid down in a clear manner and are very helpful when dealing with this type of complaint.

In the case of migraine, when symptoms become troublesome and frequent, the issue of prophylaxis arises. There are numerous drugs which are used as prophylactic agents, but none of them is 100% effective.

A recent study suggests that Angiotensin Receptor Blockers (ARBs) may be an effective prophylactic agent[14]. This

Table 2: *Guidelines of the European Society of Cardiology*

1. For asymptomatic patients, aim for TC = 5mmol/L or LDL = 3mmol/L, with the intent of lowering the CVS risk to <5%.
2. For patients with clinically established CVD and patients with diabetes treatment goals should be lowered to TC = 4.5mmol/L or LDL = 2.5mmol/L. {TC = Total Cholesterol; LDL = Low-density Lipoproteins}

Adapted from *European guidelines on cardiovascular disease prevention in clinical practice* Eur J Cardiovasc Prev Rehabil 2003; 10(Suppl 1): S1-S78

randomized double blind, placebo controlled cross-over trial was carried out in a neurology outpatient clinic, and recruited 60 adults known to suffer from migraine. The 12 week treatment period was divided into two phases. 30 patients received placebo in the first phase and 16 mg candersartan cilexitil in the second phase. The other thirty received the candersartan followed by placebo.

The number of days with headache was 18.5 in the placebo group as opposed to 13.6 in the candersartan group. Also, there was considerable amelioration of secondary endpoints in the candersartan group.

Although carried out on a small scale, the conclusions of this study follow on a previous one using lisinopril. Despite the need to carry out further larger studies, these findings open new horizons on the prophylactic treatment of migraine.

Alternative medicine in the form of acupuncture is also being explored as a relief to chronic headache. A recent study[15] carried out in a number of general practices in UK randomized 400 patients suffering from migraine or TTH to receive either acupuncture or routine care from their GP. The latter obviously excluded referral for acupuncture. Follow-up was for one year. There was a 36% reduction in headache scores in the acupuncture groups, and 22 % reported a reduction of more than 35% of the original score.

Atopic Eczema

Atopic eczema is very common, and results in frequent consultations at primary care level, in adults and children alike.

The mainstay of treatment includes a combination of steroid creams/ointments, emollients and patient education in the avoidance of allergens.

Table 3: *British Association for the Study of Headache recommendations for history taking and examination in TTH and Migraine (2003)*[3]

History

1. How many different types of Headaches are experienced
2. Time Questions (onset, frequency)
3. Character Questions (intensity, quality, associated symptoms)
4. Cause questions (predisposing, aggravating and alleviating factors)
5. Response questions (activity limitation and medications used)
6. State of health in between attacks

Examination

1. Check Optic fundi and blood pressure
2. In children check Head circumference and plot it
3. A thorough examination already reassures patient and this is of benefit

Although steroids are the treatment of choice when dealing with "flare-ups" of eczema, they can have adverse side-effects if used over a prolonged period of time. Recently two potentially revolutionary drugs, tacrolimus and pimecrolimus, have come on the market.

These drugs are topical immuno-suppressants and function by inhibiting inflammatory cytokine transcription in activated T cells through inhibition of calcineurin. Unlike steroids, they do not affect other cells such as fibroblasts so they can be used indiscriminately on any body area. However, they may cause a slight burning sensation. Both of these agents are also licensed for use in children above the age of two. There is currently an application with the Food and Drug Administration (FDA) for pimecrolimus to be licensed for children above 3 months of age.

A double blind study was also carried out to assess whether early treatment with pimecrolimus could influence long term outcome by preventing flare-ups.[16] A random sample made up of 713 patients between 2 and 17 years of age were prescribed either pimecrolimus based treatment or conventional treatment. After one year, the proportion of children in the control group experiencing "flare-ups" was nearly twice as high as in the pimecrolimus group (61% vs. 34.2%). Fewer "flare-ups" implies that the need to use steroids as rescue medication decreases.

Being new, there is still some debate as to the exact place of these drugs in the management of atopic eczema. The British Association of Dermatology Guidelines[17] (2003) suggest that they be used as second line treatment when conventional therapy has failed or is not tolerated by the patient. In addition, it is recommended that tacrolimus be reserved for specialist use.

However, in certain particular situations, notably facial eczema and diffuse eczema in children, it may be wiser to initiate first-line treatment with these drugs.

Dyspepsia

Patients consulting family doctors because of dyspepsia usually seek alleviation of symptoms and reassurance about the possibility that their symptoms might be due to benign disease. This consideration usually results in GPs referring patients for endoscopy. In fact, it is estimated that 1% of the UK population undergoes gastroscopy each year. Gastroscopy is an expensive tool, and not devoid of side effects.

The role of the GP is to "triage" patients (Table 4) referring only those suspected of having serious disease on triage or who

Table 4: *"ALARM" symptoms in dyspepsia*

1. **A**naemia
2. **L**oss of weight
3. **A**ge (>55 years)
4. **R**ecent onset of progressive symptoms (<3 months)
5. **M**elaena
6. dysphagia

Adapted from *ABC of the upper gastrointestinal tract*
BMJ 2001; 323: 675

fail to respond to treatment. A policy of *Testing and Treating* (without using endoscopy) after triage is safe and effective, as a recent study has shown.[18]

The trial was carried out in a hospital gastroenterology unit and included a random sample of 586 patients. Patients suspected of serious disease were immediately excluded. The rest were referred to either endoscopy or breath testing. After one year, the reduction in dyspepsia score was equal in both groups. In addition, patient satisfaction was equal in both groups. No potentially serious pathology was missed and only 8.2% of patients who underwent *Testing and Treating* eventually required or asked for a gastroscopy.

The findings of this study have been confirmed in the Scottish Intercollegiate Guideline Network (SIGN) Guidelines for the Management of Dyspepsia issued in 2003.[19]

Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARBs)

Since the landmark study SOLVD (Study Of Left Ventricular Dysfunction) was published, the role and importance of ACEI has changed. Initially they were regarded as merely anti-hypertensive medications, but recent studies have unraveled an array of added beneficial effects, ranging from reduction in cerebro-vascular accidents and progression of diabetic nephropathy, to increase in survival in patients with left ventricular systolic dysfunction after myocardial infarction[20]

Recently the EUROPA[21] (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) assessed whether the use of ACEI (perindopril) reduced the cardiovascular risk in a low-risk population with stable coronary heart disease and no apparent heart failure.

This randomized controlled double blind study divided 12218 patients to receive either perindopril or placebo. The mean follow-up was 4.2 years. No details are given of the left ventricular function of the patients, but it seems likely that most had a normal ventricular function. There was a 20% relative reduction in attainment of the primary end point in the perindopril group (603 vs. 488). The benefit shown by ACEI on the CVS system may be beyond simple blood pressure reduction, and possibly also dependent on dosage.[22]

ARB's have seen a dramatic surge in popularity and two trials highlighting the significant role of ARBs have recently been published.

The CHARM[23] (Candersartan in Heart failure Assessment of Reduction in Mortality and Morbidity) was specifically designed as three independent randomized controlled trials, comparing the effects of candersartan in three different but complementary populations of patients with symptomatic heart failure.

- CHARM Alternative (n=2028) enrolled patients intolerant of ACEI. Candersartan significantly reduced both the risk of hospitalization or death, with an overall risk reduction of 23%.
- In CHARM Added (n=2548) patients already stabilized on ACEI had Candersartan added to their treatment. In contrast with previous studies, there was a reduction in death or hospitalization of 15%
- In CHARM Preserved (n=3025) patients with heart failure and preserved left ventricular systolic function, candersartan did not demonstrate a significant reduction in death.

The results of the individual trials have been grouped together in the CHARM-Overall programme.

The VALIANT[24] (Valsartan in Acute Myocardial Infarction) trial assessed the effect of valsartan, captopril or a combination of both over mortality in 14,703 patients with a myocardial infarct complicated by heart failure or left ventricular systolic dysfunction. The primary endpoint was death. In the valsartan group the reduction in the risk of death was 25%, equivalent to the captopril group. No benefit was seen in using a combination of ACEI and ARB; in fact this group reported most drug-related side-effects.

Anti-thrombotic treatment

The role of anti-thrombotic therapy in the prevention and treatment of cardiovascular disease has long been established and the more frequently used drugs are aspirin and warfarin.

The Anti-Platelets Collaboration of 1994 reviewed 145 studies, and unequivocally showed the benefit of using aspirin to prevent serious vascular events in a range of high risk patients (unstable angina, myocardial infarction, transient ischaemic attacks, peripheral vascular disease, and after vascular procedures). In fact the reduction in adverse vascular events was around 25%.

A new review of 287 trials was published in 2002[25], with the aim of addressing certain areas which were left unanswered by the previous meta-analysis. The findings of the first meta-analysis have been confirmed. New information added includes:

- The recommended dose of aspirin is 75-150 mg daily. The first meta-analysis had failed to identify an adequate dosage and suggested a range from 75-325 mg daily.
- Clopidrogel is an effective alternative to aspirin in people intolerant of aspirin.

Warfarin has long been used as the only oral anti-coagulant in a variety of clinical scenarios to reduce systemic embolic events and stroke. Unfortunately, its efficacy is shadowed by the numerous drug interactions and the need of regular INR monitoring. People who are at low risk and could be managed in a community setting are still being followed up in secondary care due to these undesirable effects. However things may change with the advent of ximelagratan.

Ximelagratan is an oral direct thrombin inhibitor. After oral administration it is rapidly metabolized to its active form melagratan. Potential benefits of ximelagratan are adminstration on a fixed twice daily schedule without the need

of altering the dosage and it does not need any type of blood monitoring. It is practically devoid of any relevant interactions and the main mode of excretion is via the kidneys.

Two phase III trials[26] compared the effect of ximelagratan to warfarin in preventing stroke in patients with atrial fibrillation deemed to be at high-risk. The pooled results showed that ximelagratan is as effective as warfarin while there was a lower incidence of major and minor bleeds with ximelagaratan. The only problem with this new drug is that elevation of liver enzymes was noted in 6% of the study population.

Ximelagratan was also studied in the secondary prophylaxis of myocardial infarction[27] and patients who suffered a myocardial infarction were given aspirin and randomized to different dosages of ximelagratan. The combined therapy, irrespective of which dose of ximelagratan was used reduced the primary end point of all cause mortality, non fatal MI or recurrent ischaemia from 16.3% to 12.7%.

The role of ximelagratan has still to be defined, and may be more appropriate in low risk scenarios. Certainly more studies need to be carried out to confirm its efficacy and review the potential side effects. However, it provides a new exciting tool for the general practitioner and also a less cumbersome treatment for the patient.

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