COUNCIL ON HIGH BLOOD PRESSURE OF THE IRISH HEART FOUNDATION

Practice Statement

ARE CALCIUM CHANNEL BLOCKERS SAFE IN HYPERTENSION?

Calcium channel blockers have been extensively used for many years in the treatment of hypertension and ischaemic heart disease. Their popularity is largely based on their potent anti-hypertensive effect and their considerable efficacy as anti-anginal agents, and their purported lack of side-effects.

However, in the past year, several articles have appeared in the medical literature, casting doubt on the safety of calcium channel blocker drugs, initially in patients with cardiovascular disease, and subsequently in the patient population in general. These papers sparked a series of critical reviews and somewhat emotive correspondences, regarding the subject matter of the articles, and in some cases, personal criticisms of the authors. The primary result of this has been to highlight in the minds of the public and the prescribing physician a question-mark regarding the safety of these drugs.

The controversy, which has been the subject of a number of reviews, has centered on whether or not the use of these drugs might be associated with an excess cardiac mortality, gastrointestinal bleeding and cancers of various kinds. An extensive review of the literature on this controversial subject permits at least the formulation of recommendations which it must be acknowledged may change in the light of evidence from a number of on-going trials.

Firstly, with regard to the risks of cancer and gastrointestinal hemorrhage with calcium channel blockers, the evidence as presented to date is speculative at best. The studies which have investigated the issue are of dubious merit with regard to methodology and have substantive flaws in their design. Accordingly, it would not seem appropriate to accept the evidence to-date as constituting a rational basis for not prescribing calcium channel antagonists, at least in regard to the cancer threat.

The data with respect to treatment of patients with cardiovascular disease is more impressive, if lacking the evidence to prove the argument. However two large studies using long-acting calcium channel blockers in hypertension - the STONE and Syst-Eur Studies - both showed a large reduction in the occurrence of stroke and heart attack without any apparent adverse effects from treatment. The follow-up period in these studies was relatively

short and studies using these drugs over longer periods, which are underway, are awaited. The large clinical trials performed to-date permit the following recommendations:

- There is little evidence that the long-acting calcium channel blockers cause any adverse cardiovascular or other effects in uncomplicated hypertension

- Erring on the side of caution, the best policy may be to reserve calcium channel blockers for those patients whose blood pressure fails to respond treatment with well proven first-line therapeutic agents, such as beta-blockers and diuretics

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Practice Statement

WILL MERCURY SPHYGMOMANOMETERS SOON BE OBSOLETE?

After a century of clinical use, the mercury sphygmomanometric technique of blood pressure measurement is under threat. There are a number of reasons for this:

- Mercury is a non-degradable, bioaccumable toxic substance, which is a serious threat to marine biology and there is mounting pressure has from environmentalists to have it banned from use in hospitals. Mercury has already been banned from medical use in Scandinavian countries and the Netherlands; in the rest of Europe the move to ban mercury from hospital use has been resisted for the moment on the grounds that the once common alternative, the aneroid sphygmomanometer, becomes inaccurate with use and should not, therefore, be substituted for the mercury instrument. Furthermore, automated devices have not proved themselves sufficiently accurate for clinical use and have not been recommended as a replacement for the mercury sphygmomanometer. Whereas this has indeed been the case in the past, accurate automated devices for home measurement of blood pressure have been described recently, and these could be modified for broader clinical use. However, further studies are needed to assess the durability and performance of such instruments in busy hospital practice.
- Though the mercury sphygmomanometric technique has served us well, it is inherently fraught with many sources of error, paramount among which are the biases and inaccuracies introduced by the observer. If the fallible observer could be replaced by an automated instrument, the errors of measurement would undoubtedly be greatly reduced, provided the automated device did not introduce errors of its own, a phenomenon that might only become apparent as the device aged with use.
- Profiles of blood pressure measured by automatic devices in the home and at work, or over the entire day, lead to more accurate diagnosis and facilitate the management of hypertension. As a consequence,

manufacturers have turned their attention to satisfying a large market with a daunting array of automated systems.

These considerations lead to the almost inevitable conclusion that it is only a matter of some short time before the Riva-Rocci/Korotkov technique disappears from clinical practice. This being so, it is likely that the millimeter of mercury will in time be replaced by the Système International (SI) kilopascal as the unit of measurement for blood pressure. The argument that clinical practice would be adversely affected by such a change in unitage will be no stronger than that voiced when SI units were introduced to other measurements affecting clinical practice.

The message would therefore seem to be that we should begin to prepare for inevitable change. Perhaps a first step might be that when our mercury sphygmomanometers need replacement we should opt for an accurate independently validated automated device. Manufacturers are likely shortly to begin providing both the mercury and kilopascals scales and we might begin to familiarize ourselves with the latter in anticipation that it will be ultimately adopted as the unit for measurement of pressure in medicine.

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IS WHITE COAT HYERTENSION AN INNOCENT CONDITION?

White coat hypertension is the term used to describe a transient hypertensive state whereby blood pressure is elevated when measured by medical personnel - classically in a hospital clinic or doctor's surgery - but normal on 24-hour ambulatory monitoring when the subject has left the medical environment.

Two questions among many raised by this intriguing condition have important implications for clinical practice. Firstly, is the white coat phenomenon normal, and, secondly, are subjects with the condition at any risk?

Though white coat hypertension was recognized shortly after the technique of blood pressure measurement was introduced at the beginning of the century, it was the advent of techniques for measuring blood pressure over 24-hours that demonstrated the condition to be common - some 20% of so-called hypertensive patients - and a potential cause for mislabeling patients and of overtreating them.

There is now a substantial literature on the condition examining its prevalence, the possible mechanisms governing the phenomenon and whether or not subjects with white coat hypertension are at increased risk from cardiovascular disease.

A study of the available evidence permits some conclusions to be drawn. First, it is necessary to be clear on definition. The term white coat hypertension should be reserved for those subjects whose blood pressure is elevated when measured in the medical environment but then settles to normal throughout the remainder of the 24-hour period. This condition should be differentiated from the white coat response that occurs in patients with hypertension in whom blood pressures are higher when measured by the conventional technique and though pressures are lower when measured by ambulatory techniques they do not return to normal levels. This white coat response occurs in the majority of hypertensive patients.

In attempting to answer the important question as to whether or not subjects with white coat hypertension are at increased risk from the cardiovascular complications of hypertension, it should be borne in mind that white coat hypertension is a recently recognized

clinical entity and that the necessary longitudinal outcome studies necessary to answer this question are now proceeding. However, there is interesting evidence emerging from a number of studies which have examined the impact of white coat hypertension on surrogate end-points, such as left ventricular mass on echocardiography. These studies show in general that subjects with white coat hypertension are indeed at risk of developing target organ involvement, albeit at a much lesser rate than patients with sustained hypertension.

The message from the literature would seem to be this: Subjects with white coat hypertension are not 'normal', and though they may be at risk from the cardiovascular complications of hypertension, this risk is very much less than in subjects with sustained hypertension. Whereas the non-pharmacological means of managing hypertension should be instituted in subjects with white coat hypertension, antihypertensive medication is often not required. Finally, subjects with white coat hypertension should be followed at yearly or two yearly intervals to ensure that sustained hypertension does not develop and to control other relevant risk factors, such as obesity and hyperlipidaemia.

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NOCTURNAL BLOOD PRESSURE MAY BE MORE IMPORTANT THAN BLOOD PRESSURE DURING THE DAY.

There is a growing interest in the hypothesis that hypertensive patients with a non-dipping nocturnal profile may have a worse prognosis than the majority of hypertensive and normal patients with a dipping pattern of nocturnal blood pressure. Should on-going longitudinal studies show that this so is four important clinical conclusions would follow: *first,* non-dipping is a risk factor in hypertensive patients; *second,* non-dippers are therefore at greater risk than dippers; *third,* the identification of non-dippers must, as a consequence, become a goal of good practice, and *fourth,* clinical trials should be initiated in order to investigate whether restoring the normal nocturnal profile reverses risk for cardiovascular morbidity.

There is considerable evidence from the literature that 24-hour blood pressure or components of the awake or sleep periods, are superior to conventional measurement in predicting indices of left ventricular structure. Hypertensive subjects with an attenuated nocturnal dipping pattern have increased left ventricular mass. Of all the target organs at the mercy of the hypertensive process, the brain has to endure the most devastating vascular consequences of ineffectively managed elevation of blood pressure. The presence of periventricular white matter lesions is best correlated with sleep blood pressure suggesting that cerebrovascular disease may be more closely related to sleep than awake pressure. Circadian blood pressure variation has been shown to be

significantly decreased after haemodynamic infarction, and patients with involvement of the insular cortex showed a nocturnal rise of blood pressure more frequently than patients without involvement of the insular cortex. In elderly hypertensive patients dipper status as shown by 24-hour ABPM may allow prediction of cerebrovascular target organ involvement. Nocturnal blood pressure may also affect the arterial target organ. For example, a reduced nocturnal fall in systolic and pulse blood pressures has been observed following endartrectomy.

The relationship of nocturnal ABPM to the risk of heart attack, stroke and death in longitudinal studies is needed to confirm the suggestive evidence that a non-dipping nocturnal profile is a risk factor. Recently, ABPM has been shown to stratify cardiovascular risk independently of other traditional risk markers including echocardiographic left ventricular hypertrophy. A number of longitudinal studies which are now underway should provide information that will determine if a non-dipping pattern of nocturnal blood pressure is predictive of cardiovascular morbidity and mortality. Such studies include the OvA (Office versus Ambulatory), the Syst-Eur trial, another multicentre longitudinal study being conducted in Europe to determine the value of treating isolated systolic hypertension in the elderly, the APTH (Ambulatory Blood Pressure and Treatment of Hypertension) study, and the Italian Pamela study in Monza, which should permit correlations to be made between ABPM and measures of target organ involvement as well as longitudinal data in relation to outcome.

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Ambulatory Blood Pressure Measurement improves drug prescribing in hypertension

Proponents of ambulatory blood pressure measurement (ABPM) have often postulated that the technique should lead to improved prescribing of antihypertensive drugs. Their argument has been based on the fact that ABPM gives the prescribing doctor information that cannot be obtained with conventional measurement. First, ABPM identifies those patients with a white coat response, many of whom will not need treatment and therefore the amount of drugs prescribed should be reduced. Second, in those patients who need treatment, ABPM identifies patients in whom the blood pressure lowering effect of drugs is being excessive, again allowing a reduction in the amount of drug prescribed, and finally, ABPM allows adjustment of medication according to the profile of blood pressure over the 24-hour period.

However, these plausible arguments remained unproven until recently, when the results of the APTH (Ambulatory Blood Pressure Monitoring and Treatment of Hypertension) Study were published in the *Journal of the American Medical Association* *. This study, which involved collaboration between Belgium, Ireland, the Netherlands and Luxembourg, had the objective of determining if patients with high blood pressure who needed blood pressure lowering drugs would be prescribed less drugs using ABPM to monitor their blood pressure, rather than relying on the old standard technique of conventional blood pressure measurement (CBPM).

419 hypertensive patients were randomised to treatment according to either the average of many daytime ABPM blood pressures or their office CBPM. In the ABPM managed patients, 26% were not given drugs compared to 7% in the CBPM managed group, and whereas 43% of the CBPM patients progressed to multiple drug therapy, only 26% of the ABPM patients did so. Moreover the reduction in drug treatment in the ABPM patients did not result in any increase in heart size (a measure of the toll hypertension has had on the cardiovascular system), thereby supporting the concept that withholding drug treatment was not harmful. As might be expected with less drug prescribing, general well-being was greater in the ABPM than CBPM patients.

The savings in drug treatment ($100 per patient per year) was offset by the cost of ABPM. However, this is unlikely to hold true for the future as ABPM devices become cheaper, or as less expensive strategies, such as automated self-measurement of blood pressure, are devised. Indeed a similar study is presently being conducted (by the investigators of the APTH Study) in which self-measurement of blood pressure is being assessed against CBPM to determine if this less expensive technique might confer the same advantages to the prescribing doctor as ABPM.

The important message for clinical practice from the APTH Study is that patients were treated better with less drugs using ABPM rather than CBPM. How then should we incorporate this message into our day-to-day practice? There would now seem to be a very strong case for not initiating antihypertensive drugs (which are usually for life) without being sure that the patient really requires treatment. In other words, white coat hypertension, which more often than not does not require drug treatment, should be excluded by ABPM. In those patients already on medication in whom control of blood pressure appears to be inadequate, ABPM should be performed to ascertain the true state of blood pressure behaviour over 24-hours before adjusting drug treatment.

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The other side of the coin: Hypotension – a forgotten illness

For the past century attention has been focussed on the pathological sequelae of hypertension, but what of the other extreme, low blood pressure? On mainland Europe, and in France and Germany in particular, there may be as many drugs available for the treatment of hypotension as for hypertension. Yet in Ireland and the UK, medical science has tended to concentrate on the latter while playing down the role of low blood pressure as a cause for symptoms or morbidity. Should we not be giving more attention, therefore, to the hypotensive states? The answer would appear to be in the affirmative. *

Broadly, one can categorise hypotensive manifestations into two groups: chronic constitutional hypotension, and orthostatic hypotension. The former has been associated with non-specific symptoms of fatigue and light-headedness in a primarily younger female population. More likely to occur in non-smokers and those of a tall and thin body habitus, there is some evidence that it may not be such a benign finding. Some workers have found a higher level of psychiatric morbidity (particularly depression) in these subjects, and subtle disorders of autonomic vaso-regulation have also been described. There also exists data showing an increased mortality in patients at the very low end of the blood pressure distribution.

Orthostatic hypotension is a more striking finding for the clinician, and is manifest in older age groups, and in patients with a predisposing pathological condition, such as diabetes mellitus or Parkinson's disease. Varying from mild, sub-clinical presentations only detectable using provocative tilt-table-testing, to a debilitating total lack of orthostatic reflexes, it continues to be a very difficult clinical management problem. Approaches to management vary, and simple physical measures may be as helpful as pharmacological intervention. An additional feature that complicates management is the occurrence of supine (usually nocturnal) hypertension, which, though asymptomatic, is frequently a greater threat to the patient's life than the troublesome daytime hypotension, because of end-organ damage leading to stroke and heart attack.

Evaluation of hypotension is best achieved by 24-hour ambulatory monitoring which allows not only a time dependent examination of blood pressure thorough the course of a full day, but the opportunity of documenting episodes of hypotension and associating these with symptoms. Furthermore, nocturnal hypertension, which may be a frequent accompaniment of autonomic failure, can be demonstrated.

Treatment can be difficult as it must often take cognisance of both extremes of blood pressure. The symptoms of daytime hypotension are what concern the patient but it is the nocturnal hypertension that may give rise to an adverse cardiovascular event. Treatment of the latter may aggravate the former. Short-acting anti-hypertensives at night may reduce night-time pressures, while pressor agents such as methylxanthines and α-agonists given in the morning may reduce symptoms referable to hypotensive episodes. Simple physical measures such as elevation of the head of the bed at night, which ameliorates nocturnal intra- and extra-vascular compartment fluid shifts, and the use of lower limb compression garments may help. Finally, one must consider hypotensive events that occur in the context of arterial disease. Many of the vaso-active medications given for treatment of vascular disease are hypotensive agents. It is known that administration of blood pressure lowering drugs to patients with cerebrovascular disease can induce ischaemic cerebral events, and likewise, in patients with coronary artery disease, perfusion related coronary ischaemic events can be induced.

The message for clinical practice would seem to be that where a patient's symptoms suggest hypotension these should be assessed by 24-hour ambulatory blood pressure measurement, and in all cases careful attention should be given to drug treatment, but most especially in elderly patients in whom autonomic function may be impaired.

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CALCIUM CHANNEL BLOCKERS; SAFE OR UNSAFE IN HYPERTENSIVE DIABETICS

For the past five years there has been concern over possible adverse effects of the dihydropyridine calcium antagonists in the treatment of hypertension. (1) It has been suggested that the dihydropyridines might cause such diverse events as myocardial infarcts, stroke, cancer, bleeding, depression and suicide.

These accusations were extensively reviewed in 1997 by a subcommittee from the World Health Organisation and the International Society of Hypertension. Their conclusions may be summarised as follows:

- There is not good evidence for any important adverse effects of calcium channel blockers.
- There is a deficiency of completed large randomised clinical trials.
- No change in current guidelines or clinical practice is advised.

Three recent publications, suggesting increased myocardial infarcts in hypertensive diabetics treated with calcium antagonists, have re-ignited the "calcium channel blocker controversy".

A reanalysis of MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study) reported that hypertensive patients with a glycosylated haemoglobin greater than 6.6% and randomised to isradipine had more than double the risk of a vascular event than those randomised to hydrochlorothiazide (15/199 vs 6/216; $p = 0.04$).

In FACET (Fosinopril Amlodipine Cardiovascular Events Trial) hypertensive patients with non-insulin dependent diabetes receiving amlodipine had a significantly higher rate of cardiovascular events than those receiving fosinopril (27/191 vs 14/189, $p = 0.03$).

ABCD (Appropriate Blood Pressure Control in Diabetes) is an ongoing trial comparing moderate control of blood pressure with more intensive control on the incidence and progression of diabetic nephropathy. Secondary end-points include cardiovascular events, retinopathy, clinical neuropathy, urinary albumin excretion, and left ventricular hypertrophy. The study also compares nisoldipine with enalapril as first-line antihypertensive agents in diabetes. In response to greater numbers of myocardial infarctions amongst the hypertensives treated with nisoldipine than amongst those treated with enalapril (25/235 vs 5/235, $p < 0.001$), the ABCD data safety and monitoring board recommended termination of nisoldipine treatment in the hypertensive diabetic sub-group.

The 3 trials do not provide definitive evidence of deleterious effects of calcium antagonists in hypertensive diabetics, because:

- In both MIDAS and ABCD cardiovascular events were secondary end-points, and the apparent adverse effects were only identified by subgroup analyses.
- In both ABCD and FACET long acting calcium channel blockers were compared against ACE inhibitors. It is impossible to say whether these studies show harmful effects of calcium antagonism or beneficial effects of ACE-inhibition.
- Most importantly, the trials were very small - in total there was only 92 cardiovascular events amongst 1,265 patients. In Syst-Eur, (Systolic hypertension in the Elderly Europe n = 4695) the protection by calcium antagonism was almost doubled amongst diabetic hypertensives by comparison to non-diabetic hypertensives (unpublished data).

There are two important trials currently underway of sufficient size and duration to reliably detect any modest harm or benefit of calcium antagonists in hypertensive diabetics

- ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), in the USA, is a comparison of first line antihypertensive therapy with amlodipine, lisinopril, doxazosin or chlorthalidone in 40,000 high risk hypertensives. In the light of recent publications from MIDAS, FACET and ABCD, the ALLHAT Data Safety and Monitoring Committee examined their current end-point data, including approximately 80,000 patient years. Since the committee have not recommended any premature discontinuation of the calcium channel blocker arm in the diabetic hypertensive cohort, it may be deduced that no worrying trends have been seen.
- ASCOT (Anglo Scandinavian Coronary Outcomes Trial) is a trial comparing a calcium antagonist +/- ACE inhibitor regimen versus a beta-blocker +/- diuretic regimen on heart attack in 18,000 hypertensives, many of whom will also be diabetic. ASCOT is being conducted in centres in Scandinavia, UK and Ireland*.

The message for practice is: overall the currently available evidence would suggest that calcium channel blockers are probably as safe as any other blood pressure lowering agent in hypertensive diabetics. For non-diabetic hypertensive patients, the conclusions of the 1997 ISH and WHO committee remain valid - prior to any large-scale change in clinical practice, we must have the results of large randomised trials such as ALLHAT and ASCOT

(1) Stanton A,

* The Blood Pressure Unit at Beaumont Hospital is the regional centre for ASCOT in Ireland. For further information concerning ASCOT please contact; The ASCOT team, The Blood Pressure Unit, Beaumont Hospital, P.O. box 1297, Beaumont road, Dublin 9, Telephone 8092750.

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ROLE OF SALT IN HYPERTENSION

The contribution of dietary factors such as salt to the rise in blood pressure with age and the development of essential hypertension has been difficult to elucidate due to the poor precision (or reliability) with which dietary exposures are measured in free living subjects and the limited range of dietary exposures in most populations. Despite these difficulties however, the evidence that salt intake plays a critical role in blood pressure regulation is now overwhelming. (1) The evidence from a number of sources, from observational epidemiological studies, animal models, and randomised controlled trials in hypertensives and normotensives, all points in the same direction.

In the INTERSALT study, a study of over 10,000 subjects in 52 different population groups in 32 countries, positive associations between urinary sodium excretion (a marker of salt intake) and blood pressure were observed within and between populations. Within populations, individuals with higher sodium excretion tended to have higher blood pressure and in the across population, ecological analyses, populations with higher mean sodium excretion had higher mean blood pressures. A key finding from this study was a consistent and highly significant association of sodium excretion across populations with the slope or rise of blood pressure with age.

There is a considerable amount of evidence in other mammals that salt plays a critical role in the regulation of blood pressure. In virtually all mammals, high blood pressure is caused or aggravated by a high salt intake. For example, it has been shown in chimpanzees that that an increase in salt intake from 0.5 grams daily (their usual intake) to a level between 9 and 15 grams daily (our usual intake), leads to a substantial increases in blood pressure.

The best evidence for the role of salt in blood pressure comes from randomised control trials and from a classic community intervention trial in Portugal. For example, in a randomised control trial involving 500 newborn infants in the Netherlands, it was found that

infants given formula milk and solids with reduced salt content had significantly lower blood pressure at six months of age relative to a control group on a standard infant diet. Intriguingly, on re-examination of a subgroup of these children at age 15 years, there was evidence that the beneficial effects of early salt restriction on blood pressure persisted into adolescence. Law and colleagues, in a meta-analysis of 78 trials of the effect of sodium intake on blood pressure, reported that the effect of sodium restriction of at least 5 weeks duration were consistent with the observational epidemiological data. It was estimated that in people aged 50 – 59 years, a reduction in daily salt intake of about 3 grams, attainable by moderate dietary salt reduction, will lower systolic blood pressure by an average of 5 mmHg. An average reduction in blood pressure of this magnitude in the general population in a country such as Ireland would reduce the incidence of stroke by 25% and the incidence of ischemic heart disease by 15%. Thus the potential clinical and public health impact of relatively modest salt restriction is substantial.

Reductions in salt intake may be of particular benefit in the elderly. In a recent UK study it was shown that a reduction in salt intake from 10 grams to 5 grams daily over one month in a group of men and women aged 60 – 78 years, was associated with an average fall in systolic blood pressure of 7 mmHg. These effects, which were seen in normotensive and hypertensive subjects, translate into an estimated 36% reduction in stroke risk over a 5 year period in this age group. Given the high underlying incidence of stroke in the elderly, a reduction in stroke incidence of this magnitude (more than one third), would represent a public health triumph. In this, as in other similar studies, there was no evidence of a distinct subgroup of so called salt-sensitive subjects. The latter concept, much favoured by the salt industry, that a minority of the population may be salt-sensitive, with the rest relatively immune, has now been discredited.

In the community intervention trial in Portugal, the salt intake of an entire village was reduced by reducing salt in cooking and in processed food, including bread. At the end of the observation period, blood pressure was significantly lower than in a control village.

These data have clear implications for both clinical practice and public health. Patients with diagnosed hypertension or with high normal blood pressure can be advised, on the basis of good evidence, to reduce their salt intake. We need also to reduce salt intake at the population level. Small shifts in mean population blood pressure translate into sizeable reductions in the incidence of stroke and coronary heart disease. The achievement of population wide reductions in salt intake is difficult and ultimately will depend on public

pressure and political action. Most salt in our diet is hidden in processed foods such as bread, biscuits and Corn Flakes. It is not widely known that the salt concentration of many processed foods approaches or exceeds that of sea water. Unfortunately, the food industry is keen on salt as it makes unpalatable food edible. However, the sensitivity of the salt taste receptors depends on an individual's habitual intake and once salt intake has been reduced for a month or more, highly salted food becomes distasteful. Thus, the case for gradually reducing the salt content of processed food, particularly bread, which is the single largest source of salt in our diet, is strong.

A rise in blood pressure is not an inevitable consequence of aging. Dietary sodium, together with low dietary potassium intake, excess alcohol intake and obesity contribute to the increase in blood pressure with age, seen in Western countries and to the associated burden of stroke and heart disease. We now have enough knowledge to act on salt, both in advising our patients and in the formulation of public policy on food and health.

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The Multifactorial Approach to Hypertension

One of the problems associated with recommendations about the management of risk factors such as hypertension is that they may encourage consideration of such factors in isolation. Yet, physicians deal with whole people in whom modest elevations of a number of risk factors may interact multiplicatively with important effects on risk (Table. This is why the European Society of Hypertension joined with the European Atherosclerosis Society and the European Society of Cardiology to produce Recommendations on the Prevention of Coronary Heart Disease in Clinical Practice.[1]

The risk charts produced by the First Task Force of the European Societies in 1994 were widely circulated in Ireland. The Second Task Force announced updated recommendations at the European Society of Cardiology meeting in Vienna in August of this year. These revised recommendations will be circulated to health professionals in Ireland when they become available.

The concepts of risk assessment will by retained and reinforced in the forthcoming publications of the Task Force. 'As coronary heart disease is multifactorial in origin it is important in healthy individuals to estimate absolute risk .... by taking into account all the major risk factors. ..... Physicians should always use absolute coronary heart disease risk when making a clinical judgement about using drugs to treat blood pressure, and blood lipids, rather than just considering the level of any one risk factor alone.'

Randomised controlled trial data and observational epidemiology both suggest that the benefits of treatment are greatest in high risk subjects. For this reason the European Recommendations suggest a particularly active approach to risk factors in subjects whose 10 year coronary heart disease risk exceeds 20% or will exceed 20% if projected to age 60. If this level of risk is sustained despite professional lifestyle intervention, then risk is sufficiently high to justify the selective use of proven drug therapies.

Targets: As a general rule one would aim for a blood pressure level of less than 140/90 mmHg and a blood cholesterol level of less than 5 mmol/L in most subjects; such targets are helpful in encouraging intensive preventive efforts. Focusing on overall risk also helps the patient and doctor to recognise the extent to which risk of atherosclerotic disease is increased by smoking. A patient who smokes can be shown the extent to which their overall risk would be reduced if they quit.

In addition to making sense from a clinical perspective, management of risk may be particularly useful in patients with hypertension. Compliance with treatment can present challenges when the patient is asymptomatic. However, when the patient is encouraged to view the treatment as a component of on-going risk reduction, compliance with lifestyle changes and with medication may improve.

An important benefit of assessing and managing overall risk is that both patient and doctor consider the various risk factors in the context of the patient's lifestyle and environment. Attention is drawn to the potential for risk reduction through non-pharmacological means.

Diet and Lifestyle: Patients with increased risk should receive advice on food choices to provide a diet which reduces risk of coronary heart disease and other atherosclerotic disease. Diet is important in relation to weight reduction, lowering

blood pressure and blood cholesterol, and in the control of diabetes in diabetic patients.

An important aspect of diet for patients with raised blood pressure is a reduction in salt intake. Diets rich in complex carbohydrates and in vegetables and fruit increase the intake of potassium and magnesium which may play a role in limiting the rise in blood pressure, as well as improving the sodium to potassium ratio of the diet.

A weight reducing diet together with regular physical activity can lower blood pressure and improve lipid profiles. Avoidance of excessive alcohol intake is important for patients with raised blood pressure and will also aid weight reduction and reduce raised triglyceride levels.

Perhaps the greatest benefit from approaching the management of hypertension as an exercise in risk reduction is that structures can be established within which all patients with increased risk of atherosclerotic disease may be managed. Improved access among those at increased risk to health professionals skilled in supporting risk reduction is likely to improve outcome in all such patients, including those in whom raised blood pressure contributes to the increase in risk of cardiovascular disease.

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Table 1. The effect of modest changes in risk factors on overall CHD risk.

Sex	Age	Plasma Cholesterol (mmol/L)	Systolic Blood Pressure (mmHg)	Smoking	Clinical CHD	Estimate of 10-year risk
Male	50	7	120	--	--	10%
Male	50	6	140	+	-	20%

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Managing pre-eclampsia

Hypertension during pregnancy is an unsolved mystery. While it may reflect an existing condition (essential hypertension, secondary hypertension), hypertension in pregnancy is largely due to pre-eclampsia characterised by late onset and associated proteinuria. Curiously, pre-eclampsia occurs more commonly in the first pregnancy, complicating 4% of primigravid deliveries in the National Maternity Hospital but only 1% of multiparous patients. * The underlying defect is impaired placental implantation which ultimately restricts placental blood flow and foetal nutrition. In affected individuals foetal trophoblasts fail to express adhesion receptors that direct their invasion into the maternal tissue. In part, this could reflect a disordered immunotolerance so that the mother fails to recognise the foetal tissue as 'self'. The immune system, however, 'learns' immunotolerance in the first pregnancy, hence the lower rate of pre-eclampsia in subsequent pregnancies. This may explain why pre-eclampsia occurs at a higher than expected rate during second and third pregnancies if these result from a second partner. However, there is also evidence for a defect in maternal vasoregulation. Affected mothers have an exaggerated vasoconstrictor response to angiotensin and have higher carrier rates of a polymorphism in the angiotensinogen gene, which may explain the tendency for the condition to run in families. Low levels of prostacyclin and nitric oxide, two endogenous vasodilators, are also reported. It is possible that as a result maternal perfusion of the placenta is impaired.

With this confused and unresolved pathogenesis, it is not surprising that treatment has progressed little. The only antihypertensive drug that has clearly been shown to be safe for the foetus is methyldopa. Beta-adrenergic blockers such as atenolol are also effective in reducing blood pressure. However, in one trial where these were administered from early pregnancy birthweights were reduced. Although this study is flawed (it was discontinued early for administrative reasons), there is

anecdotal evidence confirming its findings. The use of atenolol in the third trimester however, appears to be safe.

Labetalol and nifedipine are effective antihypertensives in pre-eclampsia, but it is not known what effect they have on foetal outcome and they are not approved for use in pregnancy. One concern is that potent vasodilators, such as nifedipine, would 'shunt' blood away from the placenta and aggravate the foetal hypoperfusion. However, their use may be mandated if the blood pressure is difficult to control using methyldopa or atenolol alone. Pareneteral hydralazine is often used to gain rapid control of blood pressure, but this is usually a short term measure prior to urgent delivery. It is worth emphasising that antihypertensive therapy has no effect on the gestation at delivery or foetal outcome. Moreover, antihypertensive therapy may fail to control blood pressure and ultimately urgent delivery may be the only way to prevent progression to eclampsia.

Several approaches have been used to modify the disease process rather than simply control the symptom, hypertension. Based on evidence of increased platelet activation in pre-eclampsia, aspirin has been extensively studied and although the trials are to some extent flawed, there is no evidence that aspirin prevents the disease, prolongs gestation or improves foetal outcome.

Hypertension should resolve following delivery, although it may persist for up to 12 weeks. In general, this is easily controlled with standard antihypertensive agents, such as atenolol or nifedipine. Occasionally, hypertension following delivery may be very resistant to treatment and it is worth emphasising that patients may develop eclamptic seizures as late as one week post-partum. Rapid titration of triple therapy (angiotensin-converting enzyme inhibitor, beta-adrenergic blocker, calcium channel blocker) is important in this setting. Premature infants are highly sensitive to angiotensin converting enzyme inhibitors, so that the mother should not breast feed if these drugs are used. However, it is usually possible to withdraw them 1-2 weeks after delivery.

In conclusion, antihypertensive therapy of pre-eclampsia only influences matrenal blood pressure, not foetal outcome. Indeed, overly aggressive therapy may impair foetal growth. Evidently, we have a lot to learn about this condition.

* Data from Professor Desmond Fitzgerald, Cardiovascular Clinic, National Maternity Hospital, Dublin.

A SERIES OF MONTHLY ARTICLES ON ISSUES OF IMPORTANCE TO THE CLINICAL PRACTICE OF HYPERTENSION FROM THE COUNCIL ON HIGH BLOOD PRESSURE OF THE IRISH HEART FOUNDATION

IMPORTANCE OF THE SYST-EUR STUDY FOR CLINICAL PRACTICE

For fifty years or more diastolic blood pressure was considered to be more important than systolic blood pressure as a risk factor for cardiovascular disease. Antihypertensive therapy in many controlled clinical trials was directed against either diastolic blood pressure alone or at patients with combined systolic and diastolic hypertension. In the last decade or so attention began to focus on isolated systolic hypertension (ISH).

ISH is extremely common in older people with a prevalence of approximately 8% in people aged 70 and older rising to more than 25% among those aged 80 years or older. In 1989 the European Working Party on High Blood Pressure in the Elderly began a placebo controlled double blind trial; systolic hypertension in Europe (Syst-Eur). Active treatment commenced with the calcium channel blocker Nitrendipine with the potential addition of Enalapril, Hydrochlorothiazide or both. In 1991 the systolic hypertension in the elderly (SHEP) trial demonstrated that diuretic based treatment prevented stroke, myocardial infarction and congestive heart failure. Because of the remaining doubts about the treatment of ISH in the elderly the Syst-Eur trial continued after the SHEP results were published. In addition, controversy

surrounding the use of calcium channel blockers as first line antihypertensive agents highlighted the need for evidence that these drugs reduce cardiovascular risk.

The morbidity and mortality results of the Syst-Eur trial were reported in the *Lancet* on September 13th 1997, * the trial having been discontinued in February of that year after the second interim analysis because the primary end point of a significant benefit for stroke had been reached.

In the Syst-Eur Trial the antihypertensive agents used were the Dihydropyridine calcium channel blocker Nitrendipine, the converting enzyme inhibitor Enalapril and the thiazide diuretic Hydrocholothiazide. These drugs reduced the risk of stroke and the incidence of a number of other cardiovascular complications. The benefit of active treatment became clear soon after randomisation when the majority of patients were still on monotherapy with Nitrendipine. Given the rates observed in the placebo group, treatment of 1,000 elderly patients with isolated systolic hypertension for five years could prevent 29 strokes or 53 major cardiovascular events.

Furthermore, given the controversy surrounding the safety of calcium channel blockers, information from the Syst-Eur study is very reassuring. Compared with the placebo group, no differences occurred in non cardiovascular death and the rate of cancer or bleeding. Patients in the Syst-Eur Trial have remained in open follow up (Syst-Eur 2) to assess the safety of dihydropyridines in the long term management of ISH.

In conclusion therefore, the Syst-Eur study provides a number of important messages for clinical practice. Firstly, isolated systolic hypertension in the elderly is very common and is an important risk factor for cardiovascular disease. Secondly, treatment with a dihydropyridine based regimen significantly reduces the risk of

stroke and other major cardiovascular events. Finally, the study provides reassuring information on the safety of this class of antihypertensive agent.

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Irish Heart Foundation

COUNCIL ON HIGH BLOOD PRESSURE

STATEMENT ON BLOOD PRESSURE MEASUREMENT

Conventional blood pressure measurement

- Conventional blood pressure measurement (CBPM) is the most effective screening blood pressure

- White coat hypertension occurs in 20% of individuals with apparent elevation of blood pressure with CBPM and this measurement should not dictate diagnostic or treatment decisions

- Mercury is toxic to the environment and mercury sphygmomanometers should be replaced by accurate alternative devices

- Non-mercury sphygmomanometers are available but have not yet been independently validated

- Two automated devices have fulfilled the accuracy criteria of the British Hypertension Society (BHS) and the Association for the Advancement of Medical Instrumentation (AAMI); these are:

  A & D UA 767 monitor

  Omron HEM-705CP monitor

- The inflatable bladder of the sphygmomanometer should encircle at least 80% of the arm and preferably the entire arm; a new cuff – the Adjustacuff , which encircles all arms regardless of arm circumference , is now available and is recommended

- If blood pressure is high with CBPM consideration should be given to obtaining 24-hour ambulatory blood pressure measurement (ABPM) before making a diagnostic and certainly before antihypertensive medication is prescribed

Ambulatory blood pressure measurement (ABPM)

- ABPM is a useful technique for obtaining information on blood pressure behaviour away from the medical environment
- ABPM is the most accurate technique for measuring blood pressure provided certain technical procedures are followed and the device used has been validated for accuracy according to the BHS and AAMI protocols
- The most common indications for ABPM are:
    - Identification of white coat hypertension
    - Clarification of borderline hypertension
    - Assessment of resistant hypertension
    - Identification of hypotension

Determination of efficacy of drug treatment

Determination of duration of effect of drug treatment

Identification of nocturnal dipper/non-dipper status

Diagnosing and characterising patterns of hypertension in the elderly

Diagnosing hypertension in pregnancy

Self measurement of blood pressure (SBPM)

SBPM can be used for the same indications as for ABPM other than for obtaining nocturnal blood pressures, and SBPM has not been studied as well as ABPM

Wrist and finger recording devices are not recommended because the influence of arm position on recorded blood pressures makes the accuracy of the measurement questionable

Only devices which have been independently validated according to the BHS and AAMI protocols should be recommended (most devices on the market have not been validated). The most reliable devices are :

A & D UA 767 monitor

Omron HEM-705CP monitor

Recommended reading

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