

Considerations in blood pressure management

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The sudden onset of cardiovascular events in hypertensive patients belies the fact that the underlying vascular problems which lead to these events have been progressing relentlessly for decades. With this understanding of vascular disease progression, it seems erroneous that our medical education and consequent clinical practice focuses mainly on the emergency management of cardiovascular events. These events could have been effectively prevented if tackled in a timely fashion. As we are unable to visibly appreciate developing vascular problems, we are oblivious to their underlying dangers. We are also unaware how our daily choices are influencing disease development. However, are we really in the dark when it comes to our vasculature or are there tell-tale signs that problems are brewing?

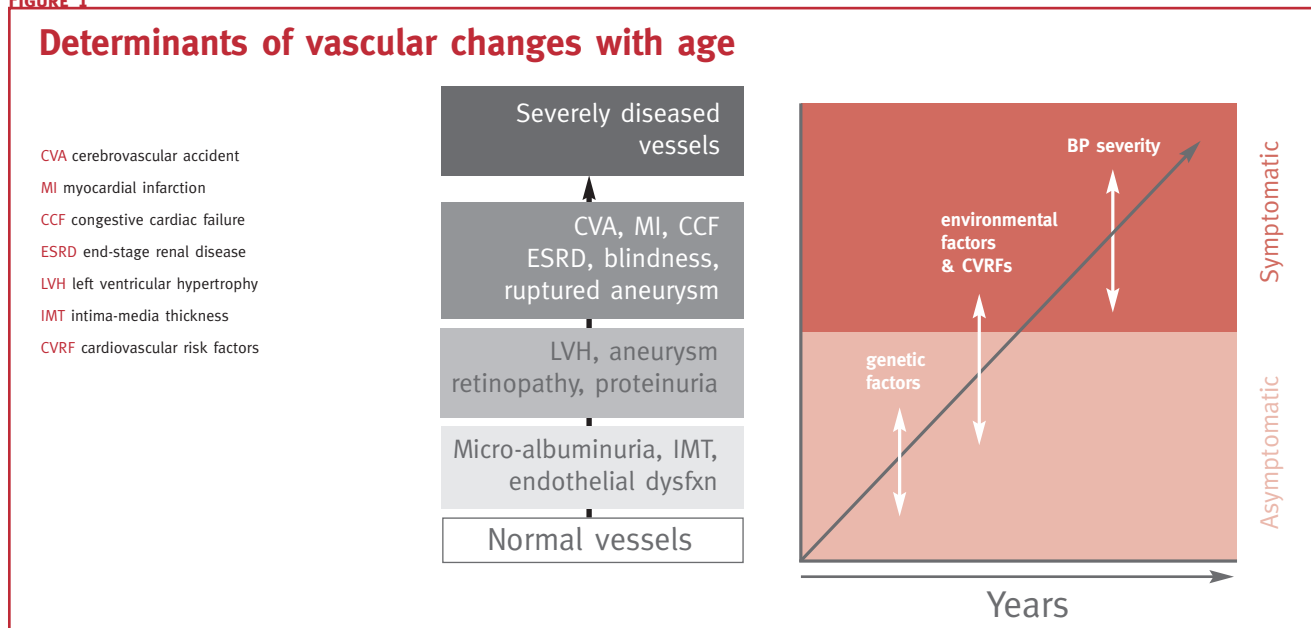
Disease development

Although it is not often that patients present with end stage hypertensive disease including severe retinopathy, cardiac failure and renal failure, it is not uncommon for hypertension

only to be recognised when a cardiovascular event has occurred. With increasing public awareness and screening programmes, it is possible to identify hypertensive patients earlier. However, they often have evidence of target organ damage (TOD) such as proteinuria, early retinopathy or left ventricular hypertrophy at the time of diagnosis. Many hypertensive patients have features of the insulin resistance syndrome which involves increased weight, central obesity, lipid abnormalities such as raised triglycerides, low levels of high-density lipoprotein cholesterol (HDLc), hyperinsulinaemia and an increased clotting tendency.

It is becoming increasingly recognised that many of these features are present much earlier, before overt hypertension develops. These patients in the pre-hypertension stage have underlying vascular changes. Thus, the vascular changes can pre-date hypertension. In susceptible individuals, there is a continuum whereby initial vascular changes that are not easily detectable progress to overt vascular abnormalities. The rate at which these vascular changes may develop is under genetic and environmental influences. In addition, the severity of hypertension will drive the rate of disease progression (Figure 1).

FIGURE 1



When faced with a patient, one must have some idea where they stand in terms of this vascular disease continuum. The reason for this is that in most disease states there is a period of time where changes can be totally reversed. In addition, there is a reduced potential to reverse disease change as disease advances. With this concept in mind, it would therefore be very important to try and recognise a person's vascular disease path as early as possible if one were to significantly influence their long term outcome.

The rate at which disease develops in individual organs may vary considerably, depending on genetic and environmental forces. Nonetheless, the underlying problem in all organs is related to vascular abnormalities.

Aggravating factors in hypertension

It is not uncommon to have patients present to your clinic who are slightly apprehensive about being reviewed. Anxiety is a well-known contributor to higher clinic blood pressure readings and must always be considered in your evaluation. This is the mechanism for white coat hypertension. Such problems are eliminated by the use of ambulatory blood pressure recordings. While acute anxiety temporarily raises blood pressure, chronic stress can lead to chronically elevated blood pressures.

Alcohol consumption a short while before blood pressure measurements will lead to higher readings. Excess alcohol intake is responsible for many patients presenting with hypertension. It is very important to recognise this before embarking on life-long drug treatment for a self-induced problem. Some individuals are very sensitive to alcohol and the criteria of 21 units of alcohol per week does not apply to individuals with alcohol-related illness. Abstinence for two months is recommended to confirm the diagnosis. Patients should then be restricted to less than 7 units per week if they are very reluctant to totally abstain from alcohol.

Salt has a variable impact on blood pressure. In salt-sensitive individuals there is a huge increase in blood pressure after the ingestion of salt. In contrast, there are a larger number of individuals who are salt resistant. Nevertheless, avoidance of added salt and restriction of salt content of food are important considerations in hypertensive patients.

Increasing body weight is directly related to increasing blood pressure levels. This is particularly true when the obesity is mainly centrally located. With this form of obesity, there is a large collection of visceral fat which is associated with the insulin resistance syndrome. There is an epidemic of obesity in most developed countries and Ireland has not been spared this problem, as the number of obese individuals has risen sharply over the last 10 years. Obesity contributes to hypertension through its effect on the sympathetic and renin-angiotensin-aldosterone systems. Weight reduction has a remarkable impact on blood pressure levels.

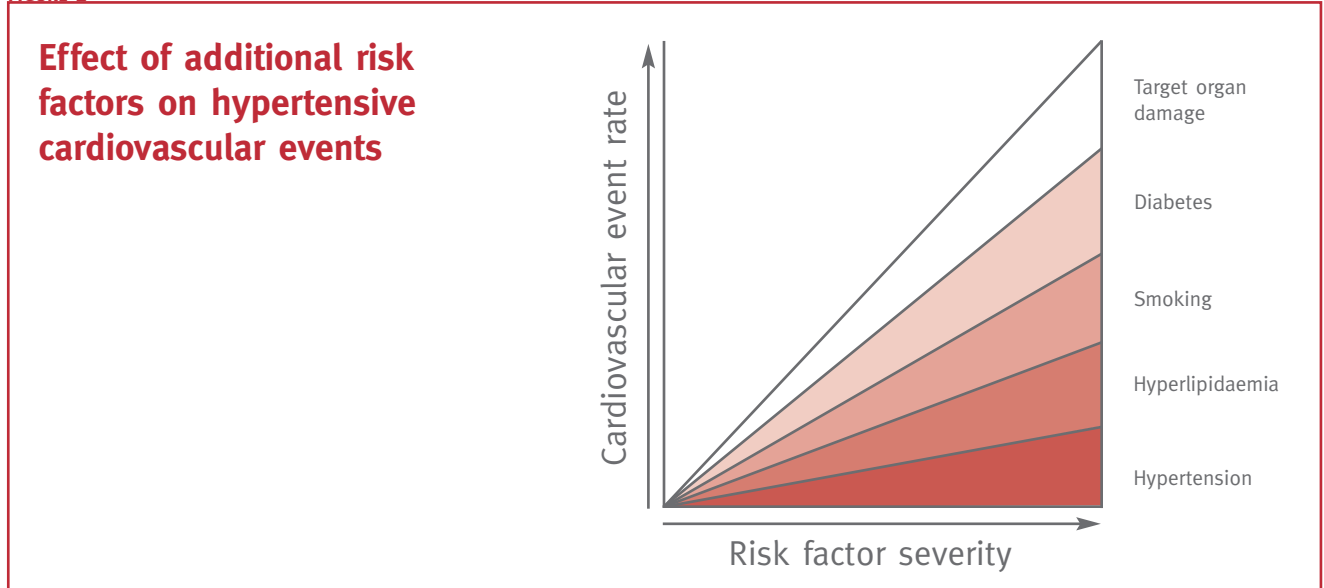
Concomitant risk factors

From studies in different populations, including the Framingham study, there has been a wealth of information which highlights that for any given level of blood pressure, the presence of concomitant risk factors magnifies its cardiovascular risk. In individuals with multiple risk factors, the risks are very high (Figure 2). However, with the fact that multiple risk factors add to the hypertensive vascular complications, it stands to reason that removal of these other risk factors will reduce the total vascular burden. It is therefore a very important exercise in all hypertensive patients to not only recognise the other features of insulin resistance, but to screen for concomitant cardiac risk factors.

Managing hypertension

It is now accepted that hypertensive vascular disease is a continuum, with the early vascular changes that are

FIGURE 2



evident in childhood progressing to full blown hypertensive vascular disease in adult life. The rapidity of this process is influenced by lifestyle, concomitant risk factors and genetic factors.

There are a number of steps to managing hypertension.

Step 1. Confirm your patient has hypertension

It is very important to have proof that a patient has hypertension before embarking on life-long medication that may cause many unwanted side effects. It is therefore important to arrange a 24-hour blood pressure recording on all patients suspected of having hypertension. This avoids the white coat effect or the impact of patients being stressed out from traffic or clinic waiting times.

Step 2. Are there any aggravating factors that could be removed?

Alcohol and salt excess are two readily correctable causes of hypertension. These should be searched for carefully and eliminated. Check liver function tests on your patients, so that if they are even slightly abnormal, it is easier to argue for alcohol reduction benefiting total health. Salt addition should be avoided and salt substitutes run the risk of excess potassium intake. A visit to the dietitian is essential so that food salt content can be considered.

Continuous stress has a major impact on blood pressure levels. It is important to recognise this contributing factor as its elimination (if possible), may totally correct a patient's hypertension.

Step 3. Assess blood pressure severity and TOD

Using a 24-hour recording, one can determine the degree and duration of hypertension throughout the day and night. Average readings are more closely linked to hypertensive organ damage than office blood pressure readings. In addition, it is normal to expect blood pressure levels to drop at night. In those patients in whom blood pressure does not drop at night, the so-called non-dippers, there is a greater degree of TOD. The non-dipping phenomenon should also increase suspicion of an underlying secondary cause for hypertension.

In recent times, the difference between systolic and diastolic readings, known as the pulse pressure, has been shown to be a major determinant of vascular problems. In patients with isolated systolic blood pressure, the lower the associated diastolic pressure, the worse the vascular risk. One should always look for evidence of TOD. In this regard, simple tests such as an ECG, which may reveal features consistent with left ventricular hypertrophy, a urinalysis to reveal proteinuria and fundoscopy to exclude retinopathy should be performed. Evidence of TOD should be a warning to instigate aggressive lifestyle changes and drug treatment.

Step 4. Is there a secondary cause for this patient's hypertension?

In 5% of subjects there is a secondary cause identified to explain the presence of hypertension. The secondary

causes include renal artery stenosis, coarctation of the aorta, Cushing's syndrome, Conn's syndrome, and a pheochromocytoma. Renal disease is also an important consideration and the use of the contraceptive pill can also cause hypertension in some women.

The usual indications to search for secondary causes are severe hypertension (>180/110), non-dipping of blood pressure on 24-hour recordings, onset before age 20 years or after 50 years, uncontrollable hypertension despite three medications, a renal artery bruit or severe hypokalaemia. The work-up for secondary causes is very important, as their correction may reduce or eliminate the need for anti-hypertensive treatment.

Step 5. Correct other risk factors

Before launching into hypertensive drug treatment, it must be realised that the reason for treating patients is to reduce their risk of hypertensive complications. With the large contribution to hypertensive risks from other risk factors, it would be very appropriate to get patients to stop smoking and reduce their cholesterol levels profoundly. With these two simple measures, one could markedly reduce the risk of hypertension without even reducing blood pressure by a single millimetre of mercury. Control of diabetes is also very important in reducing hypertensive nephropathy. Likewise, marked blood pressure reduction is essential to limit diabetic nephropathy.

Step 6. Lifestyle changes

Exercise raises blood pressure acutely and it is wise to avoid heavy physical exertion when blood pressure levels are very high and poorly controlled. In particular, upper limb exertion can cause marked increases in blood pressure.

However, regular physical exercise, through its impact on muscle vascularity, has a long-term blood pressure reducing effect. Walking, in particular, has a very positive effect on reducing blood pressure and should be practised by all hypertensive patients.

Weight reduction has major effects on blood pressure and should be an integral component of blood pressure management. By reducing obesity, sympathetic and angiotensin II-mediated effects are favourably modified. Reduction of perinephric fat levels will also improve renal perfusion, thus reducing this contribution to hypertension. Weight reduction has beneficial effects on people's ability to exercise, which has a knock-on effect on mood and then blood pressure. In obese subjects, there is increased fluid retention, so weight reduction will reduce plasma volume.

Step 7. Drug treatment

This review is too short to consider all the pharmacological choices available to treat hypertension. However, certain principles apply across the board. Drug treatment should be considered when hypertension persists, despite the above-mentioned treatment measures.

It is important to consider adding low doses of a number of drug classes to observe which have the greater impact on

blood pressure levels. With this information, one can then remove certain drugs which only make a very small contribution to blood pressure management. In the patient's interest, it is better to find the ideal drug choices through trial and then to use combination drug treatments to reduce their tablet burden. Most evidence is currently available for diuretic and beta blocker treatment. However, there are many smaller, and some larger, studies which suggest that ACE inhibition is an important component of blood pressure management. The rationale for the use of this class of drugs is that they tackle the underlying imbalance that occurs in the arterial wall between the vasodilating and growth-inhibiting nitric oxide and the vaso-constricting growth-promoting angiotensin II. Through ACE inhibition, there is a reduction in angiotensin II levels and an increase in nitric oxide levels. This leads to improved endothelial function and reduced vascular intima-media thickness. Long-acting calcium channel blockers are also very effective blood pressure-lowering agents and have been shown, in two very large studies, to reduce cardiovascular events when combined with other anti-hypertensive agents.

When dealing with refractory hypertension, volume overload and secondary hypertension should be considered. Some individuals respond dramatically to the introduction of diuretic treatment. Obese elderly subjects responded much more favourably to diuretic treatment than the slimmer, elderly

subjects and had a better impact on cardiovascular events.

Patient considerations are vital to ensure good compliance and effective long-term treatment of hypertension. One should obviously inform patients of potential side effects and enquire regularly about known drug-specific side effects. It is also important that medicines are tailored to meet other patient needs, such as using beta blockers or calcium channel blockers in patients with associated angina or tachyarrhythmias. ACE inhibitors and diuretics are very valuable in hypertensive patients with mitral regurgitation or evidence of left ventricular dysfunction.

Step 8. How low should blood pressure be reduced?

At present, European and American guidelines would favour reducing blood pressure levels below 140/90 in non-diabetics and 130/85 in diabetics. In diabetics with nephropathy, it may require much lower blood pressure targets, <110/70 for example, to achieve a significant reduction in proteinuria.

However, it is very important not to lose sight of the importance of multiple risk factor management in reducing vascular events.

How should we monitor hypertension?

This is a very important question, as it asks how adequately blood pressure is controlled on the one hand and how effective

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Indications: Treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction \leq 35%, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides. **Dosage:** The patients should have stable chronic heart failure without acute failure during the past six weeks and a mainly unchanged basic therapy during the past two weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure. **Warning:** The treatment of stable chronic heart failure with bisoprolol has to be initiated with a titration phase. **Adults:** Starting dose of 1.25mg a day for one week, then gradual up-titration, if well-tolerated, in defined steps, to a maximum dose of 10mg once daily. **Elderly:** No dosage adjustment required. **Children:** Not recommended. After initiation of treatment with 1.25 mg, the patients should be observed over a period of approximately 4 hours (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening of heart failure). During the titration phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of bisoprolol, or to stop immediately if necessary (in case of severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block). Treatment with bisoprolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should gradually be decreased. There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired liver or renal function. Up-titration of the dose in these populations should therefore be made with additional caution. **Contra-indications:** Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy, cardiogenic shock, second or third degree AV block, sick sinus syndrome, sinoatrial block, bradycardia with <60 beats/min before the start of therapy, hypotension, severe bronchial asthma or severe chronic obstructive pulmonary disease, late stages of peripheral arterial occlusive disease and Raynaud's syndrome, untreated phaeochromocytoma, metabolic acidosis, hypersensitivity to bisoprolol or to any of the excipients. **Precautions:** Bronchospasm, bronchial asthma, obstructive airways disease, concomitant treatment with inhalation

anaesthetics, diabetes mellitus, strict fasting, ongoing desensitisation therapy, first degree AV block, Prinzmetal's angina, peripheral arterial occlusive disease, psoriasis, thyrotoxicosis. Allergic reactions may be worsened. **Pregnancy and lactation:** Bisoprolol should not be used during pregnancy unless clearly necessary. Use during breastfeeding is not recommended. **Drug interactions:** Calcium antagonists, clonidine, monoamineoxidase-A inhibitors, class-I and class-III antiarrhythmic drugs, parasympathomimetic drugs, other β -blockers, insulin and oral antidiabetic drugs, anaesthetic agents, digitalis glycosides, prostaglandin synthetase inhibiting drugs, ergotamine derivatives, sympathomimetic agents, tricyclic antidepressants, barbiturates, phenothiazines, other antihypertensive agents, rifampicin, mefloquine. **Side effects:** **Common:** Coldness or numbness in the extremities, tiredness, dizziness, headache, GI disturbances. **Uncommon:** Muscular weakness/cramps, bradycardia, AV-stimulus disturbances, worsening of heart failure, orthostatic hypotension, sleep disturbances, depression, bronchospasm. **Rare:** Nightmares, hallucinations, hypersensitivity reactions, increased liver enzymes, hepatitis, increased triglycerides, potency disorders, hearing impairment, allergic rhinitis, dry eyes, psoriasis-like rash, alopecia. **Presentations:** Cardicor film-coated tablets contain either 1.25mg, 2.5mg, 3.75mg, 5mg, 7.5mg or 10 mg bisoprolol fumarate (2:1). Calendar Pack 28 tablets. Price in Republic of Ireland: 1.25mg E6.90; 2.5mg E6.39; 3.75mg E7.88; 5mg E8.28; 7.5mg E9.55; 10mg E10.58. **Product licence no.:** PL 0493/0179-84. **Product authorisation no.:** PA654/7/1-6. **Legal category:** POM. **Date of preparation:** November 2000. Full prescribing information available on request from: Merck Pharmaceuticals, (A Division of Merck Ltd), Harrier House, High Street, West Drayton, Middlesex UB7 7QG, United Kingdom. Distributed in Ireland by Allphar Services Ltd., Belgard Road, Tallaght, Dublin 24. Tel: 01 4041600. **Reference:** 1. CIBIS II, *Lancet* 1999; 353 (9146): 9-13.



blood pressure management is in reversing or stabilising TOD.

Office readings are useful if one is sure that the white coat effect is not an issue and that due consideration is taken to ensure accurate blood pressure recordings. Self measurements are very helpful when the patients is well informed on their utility and careful to avoid becoming obsessive about measurements. Twenty-four hour blood pressure readings are a vital component of long-term blood pressure management and should be used as often as necessary to ensure satisfactory blood pressure management.

However, the bottom line is to avoid TOD and hypertensive complications. It is in this regard that we need to develop reliable measurements to assess changes in TOD. For instance, carotid intima-media thickness is easily measured and its change with time may reflect future risks of vascular events. This has not yet been proven for hypertensive complications, but a similar approach in coronary atherosclerosis has definitively proved that disease progression on angiography over a two-year time interval is a strong predictor of future cardiac events. Following ECG changes over time may also be a useful guide to the changes in ventricular hypertrophy.

Measurement of 24-hour urinary protein levels has been shown to correlate with renal damage, so monitoring changes in this regard may be a useful way to determine if the anti-hypertensive measures being employed are effective.

Finally, routine ophthalmological examinations should

help monitor retinal changes and again assess the value of the interventions being employed.

While many of the above-mentioned monitoring approaches appear to be very time consuming, they will yield the best long-term results for patients. Ideally, the simpler the method employed to monitor vascular changes, the better. In this regard, the use of a device called a sphygmocor, currently being researched in many centres in Ireland, will give us a possible window on changes in vascular stiffness which relates to arterial wall changes. It is a simple, non-invasive technique that is reproducible and may help monitor blood pressure management in the future.

In summary, blood pressure management requires much more attention than simple drug prescribing. The results of lifestyle modification can be very rewarding. We need to know if the efforts we are making to treat our patients are translating into clinical benefits. When we have useful reproducible tools to monitor the impact of our treatment strategies, we may be able to treat patients holistically, without the need for marked blood pressure reductions.







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