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Pre-hypertension: how low to go and do drugs have a role?

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People with pre-hypertension (high blood pressure but below the conventional threshold for intervention with antihypertensive drugs) undoubtedly have increased risk of cardiovascular and other complications. However, the vast majority has low absolute risk and whether treatment would be beneficial is uncertain. While pharmacotherapy has attractions from a public health perspective, clinicians and crucially those with pre-hypertension require robust evidence that drug treatment will lead to short term as well as long term gains. Any changes in recommendations should await adequately powered outcome studies which provide solid evidence of the magnitude of absolute risk reduction in treating pre-hypertension and assessment of the cost-effectiveness.

Introduction

Blood pressure exhibits a continuous association with cardiovascular outcomes. A meta-analysis of individual blood pressure data from 1 million adults in 61 prospective studies demonstrated a log-linear relationship for coronary heart disease and stroke mortality rates in each decade of age (40–89 years) *vs.* usual blood pressure at the start of that decade [1]. This finding was true for both systolic and diastolic blood pressure and in all age groups. There was no indication of a threshold below which blood pressure was not associated with risk. In all ages, death rates declined progressively down to a mean usual systolic blood pressure of 115 mmHg and a diastolic blood pressure of 75 mmHg.

Confronted with such data, it has been proposed that the term hypertension is now redundant [2]. When making therapeutic decisions, the focus should be on blood pressure level and the associated risk. Since antihypertensive therapy appears to be beneficial across the blood pressure range, a case can be made for initiating treatment at levels lower than currently recommended, certainly in those with appreciable cardiovascular risk [3].

Current British recommendations [4] set a threshold for intervention with drugs when blood pressure is sustained at levels of at least 160 mmHg systolic and/or 100 mmHg diastolic. A lower threshold of 140 mmHg systolic and/or 90 mmHg diastolic is recommended for people identified as being at high risk of cardiovascular events by virtue of having established cardiovascular disease, target organ damage or diabetes mellitus. Furthermore, the same threshold is proposed for otherwise healthy people with a cluster of other clinical and demographic characteristics which predicts a risk of at least 20% of suffering a cardiovascular event over the next 10 years.

Hypothesis

Epidemiological data from the general population confirm that cardiovascular risk is not restricted to those in the above categories. There is a graded increase in risk moving from optimal blood pressure (<120/80 mmHg) through normal blood pressure (120–129/80–84 mmHg) to high-normal blood pressure (130–139/85–89 mmHg) in the Framingham population [5]. Over 10 years, high-normal blood pressure at baseline is associated with an approximately 10% cumulative incidence of cardiovascular events in men (over 8% in woman). The incidence in men with normal blood pressure is 8% (4% in women).

In westernized populations, longitudinal studies indicate age-related changes in blood pressure [5, 6]. Diastolic blood pressure rises progressively until the sixth decade of life and then declines quite steeply. In contrast, systolic blood pressure rises progressively throughout life.

Recognition that people with normal or high normal blood pressure already have appreciable cardiovascular risk and that many such people will progress to conventional

hypertension over one to two decades led to a proposal that those with blood pressure 120–139 mmHg systolic and/or 80–89 mmHg should be categorized as having pre-hypertension [6]. This was intended as a 'wake-up' call to alert the public and practitioners of the need to take action to reduce risk and prevent progression of hypertension. Since 'hypertension' represents the upper part of a slightly skewed normal distribution, pre-hypertension is common: 40% of the adult US population [7]. American guidelines [6] recommend lifestyle modification to prevent progression based on evidence from short term studies [8, 9]. Antihypertensive drugs are reserved for those with compelling indications; people with cerebrovascular disease or coronary heart disease might qualify [10].

Supporting evidence

There is remarkably little evidence to support intervention in pre-hypertension. Studies of life-style measures have been of short duration. Although meta-analysis indicates that the proportional benefit of antihypertensive therapy is independent of starting blood pressure [3], outcome trials in people in the pre-hypertension range have been exclusively in high risk individuals. One large study [11] suggested that treatment of people with high normal blood pressure delays the development of incident hypertension for up to 2 years after discontinuation of antihypertensive therapy. However, the data analysis in this trial has been heavily criticized [12, 13] and a further study in normotensive offspring of hypertensive patients was unable to demonstrate a persistent effect on blood pressure when treatment was discontinued [14]. Thus, management of pre-hypertension must be for life and, if adopted, reflects a major step shift in the working definition of hypertension (i.e. the level of blood pressure above which the benefits of treatment are worthwhile [15]).

Insights into whether or not treatment of pre-hypertension is likely to be worthwhile might be gleaned from examining the evidence which supports rigorous blood pressure control. In keeping with other national and international guidelines [6, 16], the British Hypertension Society recommends tight blood pressure targets for treated hypertension [4]. In uncomplicated hypertension, the target is less than 140/85 mmHg and <130/80 mmHg in people with diabetes, target organ damage and chronic kidney disease. The reader will note that these targets are higher than the proposed threshold for individuals with pre-hypertension.

The evidence in support of such targets is not strong. The best effort at establishing goal blood pressure, the Hypertension Optimal Treatment (HOT) study [17], failed to provide a clear answer. Despite enormous investment, no clear difference in cardiovascular event rate was found between the groups randomized to achieve diastolic blood pressures 90 mmHg or less, 85 mmHg or less or 80 mmHg or less. A *post hoc* observational analysis indicated that, in people with mild to moderate hypertension, the minimum blood pressure around which the maximum benefits of treatment can be expected are systolic 130–140 mmHg and diastolic 80–85 mmHg.

Within the HOT population of around 19 000 participants, 1501 (about 8%) had a diagnosis of type 2 diabetes at randomization. These patients exhibited a step-wise reduction in cardiovascular event rate amounting to 51% for those randomized to target diastolic blood pressure 80 mmHg or less *vs.* 90 mmHg or less. In fact, the difference in achieved diastolic blood pressure between those groups was only 3 mmHg (82 mmHg *vs.* 85 mmHg). Thus, small differences in achieved blood pressure appear to be very important in people with diabetes, a finding confirmed in other studies [18]. No such benefit was seen in the non-diabetic population in the HOT study [17].

Rigorous blood pressure control has also been shown to reduce adverse outcomes in other high risk populations. In people with renal impairment [19] the rate of decline of glomerular filtration rate appears to be directly proportional to the achieved mean arterial pressure. Renal function appears to be best preserved at a blood pressure less than 130/85 mmHg, although it must be remembered that the main cause of nephropathy is diabetes.

Modest blood pressure reduction has been shown to protect against further cerebrovascular events and coronary heart disease events in individuals who have suffered from stroke [20]. Proportional benefit is independent of blood pressure at randomization. Thus, antihypertensive drug therapy appears capable of reducing cerebrovascular risk in high risk patients who would usually be considered normotensive.

The lower the better?

Although individual trials support the policy of more intensive blood pressure control compared with less intensive control, a comprehensive meta-analysis [21] suggested significant advantages only for stroke and a composite of major cardiovascular events, including stroke. There were non-significant trends favouring rigorous control for other cause-specific outcomes including coronary heart disease and mortality. Again, the benefits appear to be restricted to patients with type 2 diabetes.

The view from meta-analysis of blood pressure lowering trials [3] in an epidemiological context [1] that 'the lower the blood pressure the better' has been challenged by the results of recent reports. A series of trials of rigorous blood pressure control in high risk individuals including people with diabetes [22–28] were unable to demonstrate extra benefit from low achieved blood pressure.

One interpretation of these findings is that there is a level of blood pressure below which further reduction provides no additional reduction in cardiovascular events. An

analysis of trials of antihypertensive treatment in diabetes suggests little additional gain in protection at achieved systolic blood pressure much below 140 mmHg [29]. Optimal systolic blood pressure appears to be around 135 mmHg.

Other explanations for these findings are equally possible. Although the recent trials of rigorous blood pressure control failed to demonstrate a statistically significant advantage over less rigorous control in outcomes, 95% confidence intervals for differences were wide and benefits predicated from epidemiological considerations [1, 3] and prior drug studies [30] for the observed blood pressure difference cannot be excluded. Recent trials were hopelessly underpowered probably because of the failure to recognize the influence of the increasing use of concomitant cardioprotective agents in both the treatment and control groups. This is illustrated by the use of concomitant therapy and event rates in two very similar trials HOPE [30] and TRANSCEND [27] conducted a decade apart; concomitant cardioprotective therapy was prescribed much more frequently in participants of TRANSCEND, where event rates were much lower. The annual risk of myocardial infarction was over 3% in the placebo group in HOPE [30] but only 1% on placebo in TRANSCEND [27].

The J-curve controversy

While trials comparing rigorous against less rigorous blood pressure control have failed to demonstrate convincingly the optimal target blood pressure, no increased cardiovascular risk was observed in those randomized to the lower achieved blood pressure. Thus, there appears to be no benefit but at least no harm from tight blood pressure control.

Risk associated with low achieved blood pressure has been suggested from observational studies mainly in those with clinical evidence of coronary heart disease. Since the coronary circulation is perfused during diastole it is plausible that low diastolic blood pressure might predispose to myocardial infarction in people with critical coronary artery occlusion. One widely cited study [31] described a J-shaped relationship between on-treatment blood pressure and coronary death rate in hypertensive people with evidence of ischaemic heart disease. The rate was lowest in those with achieved diastolic blood pressure of 85–90 mmHg and highest in those with diastolic blood pressure over 90 mmHg; those with achieved diastolic blood pressure less than 85 mmHg had an intermediate level of risk. In contrast, those with no evidence of prior ischaemic heart disease exhibited a progressively declining coronary death rate across the same levels of diastolic blood pressure. These observations have been taken to indicate that rigorous lowering of diastolic blood pressure may be dangerous in those with coronary artery disease. However, numbers of subjects were small and unintended biases of observational studies confound interpretation. It cannot be inferred that low diastolic blood pressure causes coronary mortality; reverse causality is just as likely.

There have been few randomized trials of blood pressure lowering therapy in a population restricted to people with coronary heart disease prior to treatment. INVEST compared treatment based on atenolol and verapamil in such patients. No difference in cardiovascular outcomes was found but in the whole population a J-shaped relationship between achieved diastolic blood pressure (but not systolic blood pressure) and the incidence of myocardial infarction (but not stroke) was identified in a retrospective analysis [32]. The nadir diastolic blood pressure for the primary outcome was 84.1 mmHg.

Further analysis of the INVEST database [33] suggested a J-shaped relationship between achieved systolic blood pressure and outcomes in participants aged 70 years and older. Similarly, a J-curve effect between on treatment systolic blood pressure, cardiovascular and stroke complications was observed in the high risk populations in ONTARGET [34]. The nadir of the J-curve was around 130 mmHg for all outcomes other than stroke. For any given level of systolic blood pressure, the risk of the primary composite cardiovascular outcome was higher with the lowest diastolic blood pressure [34].

What is the prescriber to make of this conflicting evidence? It should be noted that in trials where drugs which lower blood pressure were compared with control treatment in patients, most of whom had established coronary heart disease and who did not have elevated blood pressure at randomization, reduction in diastolic blood pressure to levels of 80 mmHg or less was associated with a dramatic reduction in coronary heart disease risk [30, 35, 36]. In investigations of the J-curve, the nadir levels of systolic and diastolic blood pressure have shown considerable variability (112–169 mmHg for systolic blood pressure and 72–94 mmHg for diastolic blood pressure) [29]. These differences do not appear to depend on differential baseline levels of cardiovascular risk, which was usually high, or on average blood pressure at randomization or on average achieved blood pressure. In many of the study cohorts, regardless of the blood pressure range and whether antihypertensive treatment was given those patients with blood pressure in the lowest part of the range appeared to be prone to a higher incidence of outcomes. Not all of these studies were on people with hypertension and not all used antihypertensive medication. In the Treatment to New Targets (TNT) study [37], although antihypertensive treatment was unlikely to have been intensified in patients with lower blood pressure, these patients showed a small but consistent decrease on systolic and diastolic blood pressure during follow-up, while blood pressure increased slightly in all other patients, suggesting worsened general health in patients with the lowest blood pressure.

This observation strongly supports the conclusion that reverse causality is responsible for the relationship

between increased event rate and low diastolic blood pressure. It must be remembered that the retrospective analyses upon which the J-curve hypothesis depends are inherently weak since, even when treatment is initially randomized, this protection against bias is lost and the consequence is essentially observational data. Such data are susceptible to error due to regression to the mean and regression dilution bias [38]. There is a strong possibility that the J-phenomenon is an artefact and that low blood pressure is a marker for existing disease rather than a cause of events [39, 40].

Of course, there must be a J- or U – shaped relationship between blood pressure and mortality since a blood pressure of zero is incompatible with life. The point of inflection (nadir) of this relation is unknown and probably varies in different populations. Low pressure may be hazardous in a few patients with severe occlusive coronary artery disease but is unlikely to be of general importance and should not influence guidelines for management.

Concerns about treatment of pre-hypertension

Despite the epidemiological support for blood pressure reduction across the population, the negative results of trials exploring rigorous control and concerns that low blood pressure may not be without risk has persuaded the European Society of Hypertension [41] to amend its guidelines. Whereas previously these recommended drug treatment of high normal blood pressure (systolic 130–139 mmHg and/or diastolic 85–89 mmHg in those at high cardiovascular risk, it is now acknowledged that there is no trial evidence of treatment benefit except for delayed onset of hypertension [11]. Further trials are needed before drug treatment of pre-hypertension can be recommended.

There are other reasons why use of drugs in pre-hypertension may be problematic. Although early intervention should maximize lifetime cardiovascular risk reduction, it appears that late intervention is as effective [42]. Cardiovascular risk reduces rapidly after drug treatment is started. Clinical trials provide only short term answers and most treated subjects gain no benefit [43]. Unlike public health specialists, people want short term gain and few asymptomatic individuals are motivated to enter a life long intervention programme and even fewer are willing to take drug treatment. This is an example of the 'prevention paradox, a preventive measure that brings much benefit to the population but which offers little to each participating individual', first described by Geoffrey Rose [44]. Most people with pre-hypertension are young and have low short term absolute risk, making compliance with treatment even less likely.

UK guidelines for the management of hypertension [4] and cardiovascular risk [45] are based on accepted principles of risk factor management. The relative risk reduction per intervention is usually constant. Absolute risk reduction per intervention is determined by baseline absolute risk. The decision about the level of cardiovascular disease risk at which to intervene is based on evidence, economics and population attitudes.

For hypertension, the absolute risk reduction following antihypertensive drug treatment is proportional to absolute risk [10] and relative risk reduction is constant across the blood pressure range [3]. Current thresholds for intervention in the UK [4, 45] reflect the evidence base and cost. These appear to be readily accepted by prescribers and consumers.

The key challenge of cardiovascular risk management is to identify those likely to benefit from intervention. This should allow the development of a high benefit strategy with better differentiation between winners (those who gain from treatment) and losers (those who are treated without gain or who are not treated at all).

A general focus on pre-hypertension is unlikely to meet this challenge since identification of high risk individuals who will gain high benefit from treatment will be difficult. Lowering the threshold of blood pressure for intervention will turn more people into patients. Society is unlikely to be ready for this challenge. A policy based on risk may be more acceptable. Risk scores for the eventual development of hypertension have been developed. For instance, in the STRONG Heart Study [46], baseline systolic blood pressure, diabetes and increased left ventricular mass were predictive. More work is needed.

Current dilemma

In the meantime, the prescriber is left to decide on the optimal target blood pressure for an individual. Controversy about the J-curve has created a dilemma. In general, rigorous control of systolic blood pressure is beneficial with greater benefit in high risk individuals who should be targeted for drug therapy. If the J-curve hypothesis is correct, however, rigorous control of diastolic blood pressure may cause myocardial infarction or death if the high risk is due to coronary heart disease.

Advocates of the J-curve phenomenon issue a warning against excessive lowering of diastolic blood pressure in individuals with coronary heart disease [10]. The clinician may have to face the dilemma that lowering the risk of cerebrovascular events could concomitantly increase the risk of coronary events in a susceptible patient.

The concerns have influenced the way that high blood pressure is managed. Traditionally, the management of hypertension can be described as 'start low, go slow'. This conservative approach is driven by concerns about side effects and the J-curve phenomenon, and is endorsed by the latest European recommendations [41]. Rigorous control of blood pressure (<130 mmHg systolic) in diabe-

tes and cardiovascular disease is not supported by trial evidence, although the J-curve phenomenon is unlikely except perhaps in advanced occlusive disease. Such negative advice is unhelpful when, even in clinical trials, blood pressure targets are rarely achieved [47].

A further complication has arisen. In ASCOT [48] and VALUE [49], early blood pressure control in one treatment arm was superior to that in the other. Despite more additional drug therapy, blood pressure control 'never caught up' in that arm. Furthermore, it appears that early blood pressure control is associated with better eventual cardiovascular outcomes [49, 50].

Whether early blood pressure control does indeed determine eventual blood pressure control is under evaluation in the PATHWAY study programme designed by the British Hypertension Society and funded by the British Heart Foundation. The programme is also testing the most appropriate treatment in people with refractory hypertension and investigating the influence of diuretic (and potassium haemostasis) on new onset diabetes.

Conclusions

The desirability of drug treatment for pre-hypertension remains uncertain. The costs are likely to be high and the benefits are speculative. The focus should be on high risk rather than high blood pressure in an attempt to identify those who are likely to gain long term benefit. Further outcome trials are needed to determine optimal blood pressure.

Competing Interest

There are no competing interests to declare.

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