Current Hypertension Reports (2019) 21: 6
https://doi.org/10.1007/s11906-019-0912-4

ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (MICHAEL E. ERNST, SECTION EDITOR)

Management of "Hypertension" Based on Blood Pressure Level Versus an Absolute Cardiovascular Risk Approach

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Published online: 18 January 2019

Abstract

Purpose of Review To address the tension between guideline recommendations and the evidence from clinical trials supporting them and clinician concerns of overtreatment of elevated blood pressure.

Recent Findings Systolic Blood Pressure Intervention trial (SPRINT) demonstrated lower blood pressure targets provided robust clinical benefit (reduced all-cause mortality) but also expected adverse events due to hypotension. Treatment thresholds for systolic blood pressure in the latest US guidelines have been lowered to 130 mmHg, although this has not been adopted elsewhere. These guidelines specify that treatment in the 130 s should be considered in the setting of absolute risk, i.e. treatment should be directed to those at high risk. This review argues that this hybrid approach, treatment thresholds in the 130 s based on absolute risk and above 140 mmHg on blood pressure level alone is a compromise, and that risk stratification should be the basis of drug treatment decision-making unless blood pressure is very high.

Summary Who receives blood pressure lowering medication is best determined by who is most likely to have a heart attack or stroke in the intermediate period rather than medicalising individuals who have a mildly elevated blood pressure.

Keywords Hypertension · Risk stratification · Clinical decision-making

Introduction

The recognition of elevated blood pressure as a risk factor for early death belongs not to clinicians or epidemiologists but the more hardnosed actuaries employed by life insurance companies in the first half of the twentieth century. Physicians of the day were want to say "there is some truth in the saying that the greatest danger to a man with a high blood pressure lies in its discovery, because then some fool is certain to try and reduce it" [1] and "hypertension may be an important compensatory mechanism which should not be tampered with, even if we were certain that we could control it" [2] and "people with 'mild benign' hypertension ... [defined as blood pressures up to levels of 210/100 mm Hg] ... need not be treated" [3]. When treatment did became available, which included open surgical renal sympathectomy, it was limited and laced with patient risk and intolerance.

From the days of the Framingham study and the availability of efficacious and safe medications such as thiazide diuretics from the late 1950s and beta-blockers from the 1960s, these earlier physician biases were turned on their head. When levels were very high and high blood pressure effects on target organs such as the retina and kidneys and major cardiovascular disease events were prevalent, the need for treatment was obvious. The evidence supporting lower treatment thresholds has been amassed by clinical trialists by their recognition that those with more modestly elevated blood pressure needed a cluster of other risk factors to ensure sufficient cardiovascular disease events, most trials are event driven to ensure adequate power, for example conducting such trials in older populations. However, as blood pressure medications have been given to persons with lower and lower thresholds for treatment, physicians' concerns have started rising again as such thresholds are approaching near universal

This article is part of the Topical Collection on *Antihypertensive Agents: Mechanisms of Drug Action*

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medication recommendation in adults. The publication of the National Institutes of Health sponsored Systolic Blood Pressure Intervention Trial (SPRINT) has brought this to a head as treatment targets reach down to "normal" blood pressure levels [4••]. The benefits seen in this study are not trivial with an all-cause mortality reduction of one third in the lower target, intensive treatment group compared with the less aggressively managed comparator. Thomas Kuhn famously spoke of a scientific idea holding sway until accumulating evidence meant an alternate explanation was needed, the so-called paradigm shift [5]. We have long ago reached this juncture with the concept of "hypertension" for the therapeutic reduction of blood pressure based on blood pressure alone.

A Brief History of Absolute Cardiovascular Disease Risk

An alternative approach to primary prevention of CVD is a more recent phenomenon. Critical cohort studies such as the Framingham study identified the multiple risk factors for the condition beyond just raised blood pressure. Risk algorithms that better predicted who was likely to have a myocardial infarction or stroke were developed from these observations and operationalised in New Zealand through their risk charts and inclusive guidelines [6••].

Absolute risk is calculated as the probability of a stroke, transient ischaemic attack, heart attack, angina, peripheral arterial disease or heart failure occurring over a specified period of time, usually 5 or 10 years. Five years has been adopted in Australia and New Zealand due to patient preference, discounting means that they are more likely to change behaviour or accept drug therapy if they are at immediate rather than long-term risk, but elsewhere 10 years is utilised. The rationale behind this strategy is outlined in Table 1.

Table 1 Rational for absolute risk stratification for thresholds for drug therapy of elevated blood pressure

- Medication is best given to those most likely to have covert cardiovascular disease that will become evident in the intermediate future
- Those at highest risk have a most favourable risk to benefit ratio
- It is more cost effective than intervention on single risk factors
- It avoids medicalisation of the low risk population
- It identifies those most likely to have covert CVD avoiding costly additional investigations
- Therapeutic agents can be initiated at a level above the ideal rather than at an arbitrary threshold
- Individuals at high CVD risk can be identified and treated in circumstances where other chronic disease management may lead them to be neglected (e.g. in the setting of diabetes or a mental health problem)

Is There Evidence for the Absolute Risk Approach in Deciding Who Needs Therapy?

Using the absolute risk approach younger patients and those with elevated blood pressure and no other risk factors will not be treated with blood pressure lowering agents. This approach does not mean that such patients are left unmanaged. Attention to risk factors for elevated blood pressure such as alcohol intake and other cardiovascular disease risk factors such as smoking and sedentariness are indicated through behavioural modification and other strategies. Such a strategy, rather than just writing a script, will have benefits for other prevalent diseases such as cancer. However, many clinicians will be uncomfortable with this approach as they fear that delayed drug treatment will lead to inferior outcomes in the long-term, a so-called legacy effect. They will therefore need to be reassured about the intermediate and long-term safety of such an approach.

It is very unlikely that there will be a randomised controlled trial of the absolute risk versus the individual risk factor approach to provide the highest level of evidence because of the enormous sample size and the time required to accumulate cardiovascular endpoints in a low-risk population. However, individual patient data (IPD) meta-analyses of blood pressure lowering trials have shown that the relative risk reduction of cardiovascular events is consistent regardless of baseline blood pressure levels. An IPD meta-analysis of blood pressure trials showed that the relative risk reduction was constant down to the lowest levels observed in the trials (110 mmHg systolic and 70 mmHg diastolic) and results were consistent in trials of patients with a prior history of coronary heart disease, stroke and no prior history of vascular disease [7]. The same result has been observed in cohort studies [8].

What Do the Guidelines Say?

Guideline writers who maintain a "hypertension" approach to the management of elevated blood pressure, have like the clinicians they serve, been placed in a quandary. How do they respond to the evidence of indisputable hard outcome benefits of blood pressure lowering at any level in high risk patients but dealing with clinician concerns that treatment goals are unobtainable and the results are not generalisable to my "real" patients and that we are medicalising the whole general population? All guidelines have some form of recommendation to conduct risk stratification but usually such an approach is not preferred over the blood pressure level per se. The US guidelines have taken a hybrid approach recommending treatment in the 130 s based on absolute risk to avoid the general population medicalisation but 140 mmHg and above on the old paradigm [9•]. It takes a lot of courage to loosen blood pressure treatment thresholds for low-risk individuals and less so to adopt lower ones for high-risk individuals. Contemporary

European guidelines have remained cautious moving from awaiting further evidence for treating those in the 130 s to "Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD" [10]. Thus, the high-risk primary prevention thresholds remain unchanged.

Conclusions

The move to an approach based on absolute risk for the primary prevention of cardiovascular disease is likely to improve the effectiveness and cost-effectiveness of treatment. The absolute risk approach targets the patients who are most likely to benefit and reduces the medicalisation of patients at low risk.

Compliance with Ethical Standards

Conflict of Interest The author declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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