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Managing big issues on lean evidence: treating obesity hypertension

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Introduction

Obesity, defined as a body mass index (BMI) greater than 30 kg/m^2, is an important risk factor for hypertension, and excess adiposity is believed to account for 70% of hypertension in men and 60% in women [1,2]. There is now accumulating evidence that adipose tissue may itself be involved directly in the pathogenesis of hypertension, not only by contributing to an increase in sympathetic activity [3], but also to sodium and volume retention [4].

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Obesity—a risk factor neglected by current guidelines

Current guidelines for the management of hypertension provide specific recommendations for a variety of special patient populations, including patients with diabetes mellitus, coronary artery disease, renal dysfunction and the elderly [5,6]. Surprisingly, however, these guidelines do not provide specific recommendations for managing the obese hypertensive patient that go beyond recommending weight loss. Thus, for example, the JNC-VI guidelines [5] include only one paragraph on the specific management of hypertension in obese patients, with a focus on non-pharmacological weight reduction. Similarly, in the recent WHO/ISH guidelines [6], obesity is listed as a risk factor adversely influencing prognosis and weight reduction is recommended, but no specific recommendations are made for the pharmacological management of obese hypertensive patients. Apparently, most guideline bodies do not consider obese patients as

'special' populations and are under the impression that all that these patients need to do is to lose weight.

Antihypertensive treatment of the obese—beyond weight loss

While, in theory, weight loss may indeed be the most effective measure for the treatment of hypertension in obese patients, in practice, long-term maintenance of weight loss is notoriously unsuccessful, even in the context of controlled clinical trials [7]. Thus, as most obese patients will either not lose weight or fail to maintain any relevant weight loss in the long run, we have no option but to use antihypertensive medications in the majority of obese patients. Unfortunately, current guidelines do not tell us which drugs to use [8].

One reason for this glaring lack of specific recommendations for obese patients is perhaps the even more glaring lack of antihypertensive trials in such patients. Thus, even rather recent intervention trials appear to have excluded obese patients, as the average BMI of patients in these trials barely exceeds 30 kg/m^2 (Figure 1). Clearly, the results of these trials are more applicable to non-obese patients than to patients with a BMI of 35 kg/m^2 (grade II obesity) or above. Although some of these large trials may have included substantial numbers of overweight or obese patients, sub-analyses for these patients have not been presented so far.

Why specific recommendations for obese hypertensive patients?

The lack of specific recommendations for the obese hypertensive patient is far from trivial. Firstly, compared to hypertension in non-obese patients, obesity-related hypertension is characterized by volume expansion, increased cardiac output, and a decrease rather than an increase in total peripheral resistance [9,10]. Secondly, obese patients often have metabolic abnormalities that can be exacerbated by commonly used antihypertensive agents [11,12].

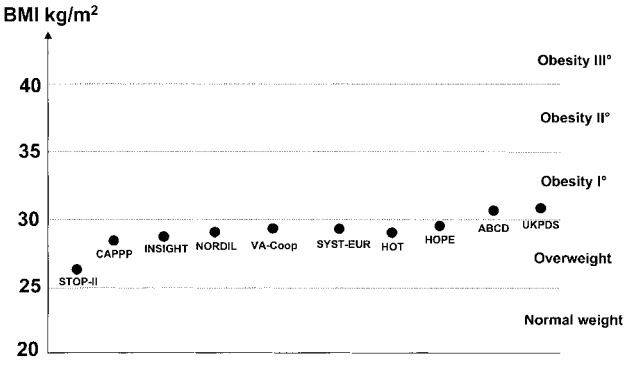

Fig. 1. BMI levels in recent intervention trials.

Thirdly, obesity *per se* is often associated with end-organ damage, including eccentric left ventricular hypertrophy [9], glomerular hyperfiltration and microalbuminuria [13], congestive heart failure [14], or sudden cardiac death [15,16]. Thus, obese patients, even when presenting with apparently uncomplicated hypertension, may require more aggressive blood pressure control, similar to that now recommended for patients with diabetes.

On the other hand, certain classes of drugs, such as β-blockers, that are clearly indicated in patients with coronary artery disease or congestive heart failure, might cause weight gain or make it more difficult for patients to lose weight [17]. These drugs should, therefore, perhaps be avoided in young obese hypertensive patients with uncomplicated hypertension.

An increase in adipose mass may also be important as a potential determinant of response to treatment, possibly reducing the effectiveness of antihypertensive therapy. Thus, patient surveys clearly indicate that overweight hypertensives are less likely to achieve normal blood pressure on treatment than non-obese patients [2,7]. Other issues, related to pharmacokinetics of lipophilic drugs [18,19] or increased prevalence of liver abnormalities [20,21] in obese patients, may also warrant attention.

Selection of antihypertensive agents in the obese

Based on the currently available data, recommendations for the pharmacological therapy of obese hypertensive patients can perhaps best be described as grade C or B. While there is some evidence that monotherapy with β-blockers or angiotensin-converting enzyme (ACE) inhibitors may be more effective than calcium channel blockers or diuretics in lowering blood pressure in obese patients [22,23], these data are based on trials that have included less than 100 patients in each group. No hard-endpoint studies in obese hypertensive patients have been reported to date.

Clearly, where antihypertensive therapy is necessary, the aim should be to use agents that have effects beyond blood pressure lowering and benefit the conditions most commonly linked with obesity-associated hypertension, such as hyperlipidaemia, type 2 diabetes, left ventricular hypertrophy, coronary artery disease, or congestive heart failure. Based on their favourable metabolic profiles, it would appear that ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and α-blockers can lower blood pressure without worsening the metabolic abnormalities that accompany hypertension in obese patients. However, calcium channel blockers and diuretics, apart from being less effective, may further accentuate the already increased neurohormonal parameters in obese patients.

On the other hand, recent studies indicate that high sodium intake is strongly and independently associated with an increased risk of cardiovascular disease and all-cause mortality in overweight persons [24,25].

These studies raise the intriguing question whether a diuretic-induced reduction in total body sodium may have additional benefits in obese hypertensives that go beyond blood pressure reduction.

Conclusion

There is clearly an urgent need for extending the available evidence-base to address the pharmacodynamic and pharmacokinetic aspects of treating obesity-associated hypertension. Perhaps as a first step, investigators of large intervention trials should be encouraged to provide sub-analyses regarding outcomes in obese participants. Nevertheless, future studies should specifically address this issue in a prospective setting. The treatment of obesity *per se*, using newer anti-obesity drugs to encourage long-term weight reduction and maintenance must also be examined.

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