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REVIEW

From Blood Pressure Control to Weight-Centered Hypertension Management: The Emerging Role of Incretin-Based Therapies

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ABSTRACT

Obesity and hypertension often coexist in the same person and reinforce each other. Treatment of hypertension in people with obesity has been based mainly on lifestyle changes and the gradual addition of antihypertensive drugs. The development of GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists has transformed the treatment of obesity, with implications beyond weight loss. These therapies can produce significant weight loss, but they also lower blood pressure and improve several other cardiometabolic risk factors. Recent data suggest that the reduction in blood pressure is largely related to weight loss, but is not necessarily fully explained by it. Effects on natriuresis, endothelial function, inflammation, neurohormonal activity, and circulating volume may represent additional mechanisms. In practice, this creates a new situation: a patient who loses significant weight may need less antihypertensive therapy. We aim to examine the relationship between obesity and hypertension, the clinical evidence on semaglutide, tirzepatide, and newer incretin-based therapies, as well as the possible transition from an approach focused solely on blood pressure toward management that also addresses adiposity as part of the disease mechanism.

Keywords: arterial hypertension; obesity; GLP-1; semaglutide; tirzepatide; incretins; weight loss; cardiovascular risk.

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Introduction

Obesity is not simply a condition associated with arterial hypertension (HTN). In many patients, it is one of the factors that drives and sustains high blood pressure. Increased visceral adiposity is associated with activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, sodium retention, insulin resistance, chronic low-grade inflammation, and changes in renal function. Obesity-related hypertension is often associated with type 2 diabetes, dyslipidemia, obstructive sleep apnea, chronic kidney disease, and increased cardiovascular risk [1,2].

The 2024 ESC guidelines continue to recommend weight reduction, physical activity, and dietary improvement as core interventions for patients with elevated blood pressure or hypertension [1]. However, in everyday practice, weight loss through lifestyle interventions alone is often modest and difficult to maintain. The introduction of new anti-obesity therapies has expanded the possibilities for achieving clinically meaningful and sustained weight loss. GLP-1 receptor agonists and newer incretin-based therapies can achieve a degree of weight loss that until a few years ago was mainly associated with bariatric surgery. For the internist and cardiologist, the question is no longer just how many kilograms the patient loses, but what happens to blood pressure, the need for antihypertensives, and overall cardiovascular risk.

This approach is gradually shifting the discussion from "treatment of hypertension in patients with obesity" to a broader concept: treatment of adiposity as one of the drivers of hypertension. Recent literature has increasingly supported this idea, although there are still no well-defined algorithms for integrating incretin-based therapies into the routine management of hypertension [2-4].

The clinical contribution of this article lies in linking the treatment of obesity to the daily management of arterial hypertension. Special attention is paid to monitoring arterial pressure and re-evaluating antihypertensive therapy during significant weight loss.

Why does obesity increase blood pressure?

The relationship between weight and blood pressure is consistent, but the mechanism is not just mechanical. Adipose tissue, especially visceral adipose tissue, is metabolically active. Increased leptin and other signals from adipose tissue may increase sympathetic nervous system activity. In parallel, the renin-angiotensin-aldosterone system is activated, renal sodium reabsorption increases, and volume expansion may occur. Hyperinsulinemia and insulin resistance may further favor sodium retention and vascular dysfunction [2,3,4].

Fat distribution also matters. Visceral adiposity and fat deposition around the kidneys are associated with renal hemodynamic changes, increased intrarenal pressure, and neurohormonal activation. At the same time, chronic inflammation, oxidative stress, and decreased nitric oxide bioavailability impair endothelial function. Obstructive sleep apnea, which is common in people with obesity, increases sympathetic activation and is an important factor in resistant hypertension [2,3,4].

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These mechanisms explain why weight loss can lower blood pressure even without directly changing antihypertensive therapy. But they also explain why substantial weight loss can change a patient's therapeutic needs. When visceral adiposity, insulin resistance, volume expansion, and neurohormonal load are reduced, the same antihypertensive regimen may have a greater blood pressure-lowering effect than before.

From weight loss to blood pressure reduction

Available data on GLP-1 agonists show a consistent, although not dramatic, reduction in blood pressure. A meta-analysis of 30 randomized trials with over 37,000 participants reported a mean reduction in systolic blood pressure of about 3.4 mmHg and diastolic blood pressure of about 1.0 mmHg compared with placebo [5]. Although these reductions are modest, they may still be clinically relevant, particularly at the population level, where small reductions in blood pressure can reduce the risk of stroke and coronary events. Greater blood pressure reductions have been reported with newer incretin-based therapies that also produce substantial weight loss [6].

Analyses of the STEP trials showed that semaglutide 2.4 mg improves not only weight and waist circumference, but also blood pressure, glucose, insulin resistance, and lipid profile. A net reduction in the use of antihypertensive and lipid-lowering drugs was also observed in patients treated with semaglutide in STEP 1 and STEP 4 [7]. This is clinically relevant: the benefit is not limited to a statistical change in blood pressure, but may also be reflected in a lower medication burden.

A meta-analysis of three large studies of semaglutide specifically assessed this issue in people with hypertension. The difference in systolic blood pressure versus placebo was about -5 mmHg in the general population and -4.8 mmHg in participants with hypertension [8]. At the same time, the intensity of antihypertensive therapy was reduced. This means that the full effect on blood pressure may be underestimated if antihypertensive medications are reduced during the study as blood pressure improves.

Tirzepatide and its effect on blood pressure

The dual GIP/GLP-1 receptor agonist tirzepatide has shown a greater effect on blood pressure. In the SURMOUNT-1 analysis, after 72 weeks of treatment, the net reduction compared with placebo was approximately 6.8 mmHg for systolic blood pressure and 4.2 mmHg for diastolic blood pressure [9]. At the end of the study, 58.0% of participants treated with tirzepatide had blood pressure in the normal range, compared with 35.2% in the placebo group [9].

Mediation analysis is particularly relevant to the question addressed in this review. About 68% of the reduction in systolic blood pressure and 71% of the reduction in diastolic blood pressure were explained by weight loss [9]. Thus, weight loss appears to be the main driver, but not the only one. This leaves room for other effects, such as changes in natriuresis, vascular function, inflammation, and circulating volume.

A substudy of SURMOUNT-1 used 24-hour ambulatory blood pressure monitoring and confirmed that the effect of tirzepatide is not limited to office measurements [10]. ABPM provides a more reliable assessment of blood pressure throughout the day and night. In another analysis of the SURPASS program in patients with type 2 diabetes, the reduction in systolic blood pressure was greater in those with higher baseline values, and weight-independent effects were also observed in some analyses [11]. The main clinical evidence on the blood pressure effects of incretin-based therapies is summarized in Table I.

Is Blood Pressure Reduction Explained by Weight Loss Alone?

Based on current evidence, the answer is: mostly, but not completely. Weight loss reduces metabolic load, improves insulin sensitivity, reduces obstructive sleep apnea, and

Table I. Effects of incretin-based therapies on blood pressure and antihypertensive treatment.

Therapy / Evidence	Population	Blood pressure effect	Antihypertensive therapy	Main clinical relevance
GLP-1 RAs - meta-analysis [5]	Overweight/obesity; >37,000 participants, 30 RCTs	SBP -3.4; DBP -1.0 mmHg, placebo-adjusted	Not specifically assessed	Consistent, modest BP reduction
Semaglutide 2.4 mg - STEP 1/4 [7]	Adults with overweight/obesity	BP reduction; numerical estimate not reported here	Net reduction in antihypertensive medication use	Lower medication burden
Semaglutide - IPD meta-analysis [8]	Overweight/obesity, including hypertension	SBP -5.0 mmHg overall; -4.8 mmHg in hypertension, placebo-adjusted	Treatment intensity decreased	Medication reduction may mask part of BP effect
Tirzepatide - SURMOUNT-1 [9]	Adults with overweight/obesity	SBP -6.8; DBP -4.2 mmHg, placebo-adjusted	-	68% of SBP and 71% of DBP reduction mediated by weight loss
Tirzepatide - SURMOUNT-1 ABPM [10]	Adults with BMI ≥27 kg/m²	BP reduction confirmed by 24-h ABPM	-	Confirms effect beyond office measurements
Tirzepatide - SURPASS [11]	Patients with type 2 diabetes	Greater SBP reduction at higher baseline BP	-	Weight-independent effects suggested in some analyses
CagriSema - REDEFINE 1 [19]	Adults with overweight/obesity, without diabetes	From baseline: SBP -10.9; DBP -5.4 mmHg. Placebo: SBP -2.8; DBP -1.7 mmHg	39.6% reduced/stopped treatment vs 18.8% with placebo	BP reduction and lower medication burden

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; ABPM = ambulatory blood pressure monitoring; IPD = individual patient data; RCT = randomized controlled trial.
Note: Blood pressure changes are reported as placebo-adjusted differences or changes from baseline, as indicated. These estimates should not be directly compared across studies.

reduces sympathetic activity and sodium retention. This explains a large part of the effect. GLP-1 receptors are also involved in processes that go beyond appetite control. Increased natriuresis, improved endothelial function, reduced vascular inflammation, and changes in neurohormonal regulation have been proposed as additional mechanisms [4]. However, the contribution of these mechanisms to the reduction of arterial pressure remains unclear and requires confirmation through further clinical studies.

This distinction between weight-mediated and potentially weight-independent effects is clinically important. If the benefit depended solely on the number of kilograms lost, then any method that produced the same weight loss would be expected to have the same cardiovascular effect. The SELECT data suggest that the story may be more complex. In 17,604 patients with overweight or obesity, established cardiovascular disease, and no diabetes, semaglutide 2.4 mg reduced the relative risk of the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 20% [12]. Subsequent analyses have suggested that the cardiovascular benefit is not fully explained by changes in weight or adiposity [13].

Lowering blood pressure and reducing cardiovascular events are two distinct effects, which are not necessarily explained by the same mechanisms. The results of SELECT suggest cardiovascular benefits that are not entirely dependent on weight loss, but they do not prove that these benefits are mediated by a direct effect on arterial pressure.

Semaglutide or tirzepatide are not antihypertensive drugs in the traditional sense and they are not meant to replace renin-angiotensin system inhibitors, calcium channel blockers, diuretics or other drugs when these are indicated. What they can do, in patients with obesity-driven hypertension, is to target one of the factors contributing to hypertension itself.

From Blood Pressure Reduction to Cardiovascular Protection

SELECT changed the way we view the pharmacological treatment of obesity. For the first time, a therapy used for weight management showed a clear reduction in major cardiovascular events in people without diabetes [12]. This result is particularly important for patients with hypertension and obesity, who often have several risk factors at the same time. In this context, blood pressure reduction is only part of the benefit. In practice, semaglutide and tirzepatide improve weight and waist circumference [14], alongside glycemia, insulin resistance, dyslipidemia, and markers of systemic inflammation [15,16]. Benefits have also been documented in selected patients with heart failure with preserved ejection fraction associated with obesity [17,18]. This supports a more integrated approach to risk, rather than treating each factor in isolation.

An important distinction must be made: the strong evidence for reducing cardiovascular events is not the same for every agent and every population. SELECT provides strong data for semaglutide in patients with established cardiovascular disease, overweight/obesity, and without diabetes [12]. For newer agents, the results on weight and cardiovascular risk factors are very promising, but these improvements should not automatically be interpreted as a reduction in MACE.

A New Clinical Challenge: What Do We Do with Antihypertensive Therapy When Weight and Blood Pressure Fall?

This is perhaps one of the most practical issues in clinical practice. A patient with obesity and hypertension may have been on two or three antihypertensive drugs for years. After starting modern anti-obesity therapy, the patient may lose 15-20% of body weight and have blood pressure of 105-110/65-70 mmHg, sometimes accompanied by orthostatic symptoms or fatigue. At this point, automatically continuing the same regimen is not necessarily the right choice.

Data from the use of semaglutide suggest that the intensity of antihypertensive therapy can be reduced during treatment [7,8]. More recent data come from REDEFINE 1 with the semaglutide/cagrilintide combination (CagriSema). At week 68, systolic blood pressure decreased by 10.9 mmHg from baseline in the CagriSema group, compared with 2.8 mmHg in the placebo group; for diastolic blood pressure, the changes were -5.4 and -1.7 mmHg, respectively. Among participants taking antihypertensives, 39.6% of those on CagriSema reduced or discontinued antihypertensive therapy, versus 18.8% on placebo [19].

These data do not yet constitute a deprescribing protocol. There is insufficient evidence to establish a universal order of which antihypertensive drug should be tapered first. The decision should take into account other drug indications: an ACE inhibitor or ARB may be needed for nephroprotection, a beta-blocker for coronary artery disease or arrhythmias, and a mineralocorticoid receptor antagonist for heart failure. In patients without other indications, low blood pressure, orthostatic symptoms, or volume depletion should prompt reassessment of doses, especially of diuretics and multidrug regimens.

In patients with dizziness or orthostatic symptoms, blood pressure should also be measured in the standing position. In cases of hypotension or signs of reduced circulating volume, the diuretic dosage should be re-evaluated, taking into account renal function and electrolytes.

Home blood pressure monitoring and, when there is uncertainty, ABPM can help to avoid both hypotension and unnecessary reduction of therapy. Particular attention is needed during the titration phase of incretin therapy, when weight loss and changes in food intake may be more rapid. A small increase in heart rate has been reported with GLP-1 agonists and should be considered in the overall assessment [4].

Gastrointestinal side effects, particularly nausea, vomiting, and diarrhea, can cause dehydration and a reduction in circulating volume. This requires special attention in patients taking diuretics or certain antihypertensive medications, due to the risk of hypotension and deterioration of renal function [20]. Practical considerations for reassessing antihypertensive therapy during substantial weight loss are summarized in Table II.

Future Therapies and New Treatment Perspectives

Dual and triple incretin receptor agonists are now being developed. Tirzepatide has been shown to provide greater weight loss and blood pressure reductions than earlier GLP-1 receptor agonists [21,22]. Other therapies under investigation include triple receptor agonists and CagriSema, a combination of the GLP-1 receptor agonist semaglutide and the amylin analogue cagrilintide [3,19].

Table II. Clinical considerations for antihypertensive therapy during substantial weight loss.

Clinical situation	What should be reassessed?	Practical consideration
Low BP or orthostatic symptoms	BP levels, symptoms, home BP readings, current antihypertensive regimen	Antihypertensive doses may need reassessment
Volume depletion or reduced oral intake	Volume status, renal function, electrolytes, and diuretic use	Particular attention may be needed for diuretic therapy
Multiple antihypertensive drugs	Number and doses of medications and their individual indications	The previous regimen may need adjustment after substantial weight and BP reduction
Antihypertensive drugs with additional indications	ACE inhibitors/ARBs for kidney protection; beta-blockers for coronary disease or arrhythmias; MRAs for heart failure	Decisions should consider indications beyond BP control
Uncertain BP control	Home BP monitoring and/or 24-h ABPM	May help distinguish persistent low BP from isolated measurements and avoid unnecessary treatment reduction
Titration of incretin therapy	BP, symptoms, weight trajectory, and changes in food/fluid intake	Closer reassessment may be appropriate during periods of more rapid weight loss

The greater the weight loss achievable with pharmacological therapy, the more important the question of how to adapt the treatment of comorbidities becomes. Hypertension is one of the clearest examples. If part of hypertension is driven by adiposity, effective treatment of obesity could change not only blood pressure, but also the number and dose of drugs needed to control it.

There are still real gaps in the evidence. Most studies of incretin-based therapies have been designed with weight loss, glycemic control, or cardiovascular events as primary endpoints, rather than hypertension control. Patients with severe or resistant hypertension are often underrepresented. Studies are needed where blood pressure, ABPM, changes in the number of antihypertensive drugs, and deprescribing are prespecified endpoints. Equally important is understanding what happens after discontinuation of therapy. In the STEP 1 extension, one year after stopping semaglutide, participants had regained about two-thirds of their lost weight and most cardiometabolic improvements had returned almost to baseline [23]. This reinforces the idea that obesity is a chronic disease and that the strategy for hypertension should also take a long-term perspective.

Conclusions

Incretin-based therapies should not be seen simply as weight loss drugs that also provide a modest reduction in blood pressure. For clinical practice, the message is simple: when treating hypertension in a patient with obesity, weight management should not remain just a recommendation at the end of the consultation. At the same time, when weight loss is significant and blood pressure falls, antihypertensive therapy should be reassessed and not automatically continued at the same doses. This shift from a solely 'BP-centered' approach to a more 'weight-centered' management does not replace standard hypertension treatment; it complements it and better addresses the mechanisms driving the disease. But incretin-based therapies are not primary treatments for arterial hypertension. Further studies are needed to better define their role in blood pressure control, particularly in patients with severe or resistant hypertension.

Authors' contributions

E.N. contributed to conceptualization, writing - original draft, and writing - review & editing. I.K. and K.Xh. contributed to data curation, resources, and validation. M.Gj. contributed to supervision, validation, and writing - review & editing. All authors approved the final version of the manuscript.

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Statement of Ethics

Not applicable because the present study includes neither human nor animal experiments.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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