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FASTTRACK - CLINICAL RESEARCH
Hypertension

Semaglutide and blood pressure: an individual patient data meta-analysis

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Abstract

Background and Aims Randomized clinical trials (RCTs) assessing semaglutide reported reductions of systolic blood pressure (SBP) in trial populations with baseline blood pressure in the normotensive range. This study aimed to determine whether this SBP reduction is greater in hypertensive groups.

Methods Individual patient data (IPD) from three RCTs examining the effect of semaglutide 2.4 mg on body weight over 68 weeks were included. Trial participants were categorized according to a hypertension diagnosis, treatment or baseline measurement (HTN), baseline SBP > 130 mmHg (HTN130) or >140 mmHg (HTN140), and those with apparent resistant hypertension (RH). The primary analysis compared the in-trial change in SBP in the semaglutide and placebo arms. Alterations of anti-hypertensive medications were quantified by treatment intensity score and compared between arms. These analyses were performed using analysis of covariance.

Results Overall, 3136 participants were included. The difference in SBP change between the treatment ($n = 2109$) and placebo ($n = 1027$) groups was −4.95 mmHg [95% confidence interval (CI) −5.86 to −4.05] overall. This difference was −4.78 mmHg (95% CI −5.97 to −3.59) for HTN, −4.93 mmHg (95% CI −6.75 to −3.11) for HTN130, −4.09 mmHg (95% CI −7.12 to −1.06) for HTN140, and −3.16 mmHg (95% CI −8.69–2.37) for RH. Reduction in SBP was mediated substantially by weight loss. The anti-hypertensive treatment intensity score decreased for those on semaglutide compared to placebo (−0.51; 95% CI −0.71 to −0.32).

Conclusions This IPD analysis of three large RCTs found blood pressure reductions with semaglutide in participants with hypertension that were similar to those seen in all trial participants. This finding may in part be due to concurrent reductions to anti-hypertensive medications. These results suggest that semaglutide is a useful adjunctive treatment for patients with hypertension and obesity.

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Structured Graphical Abstract

Key Question

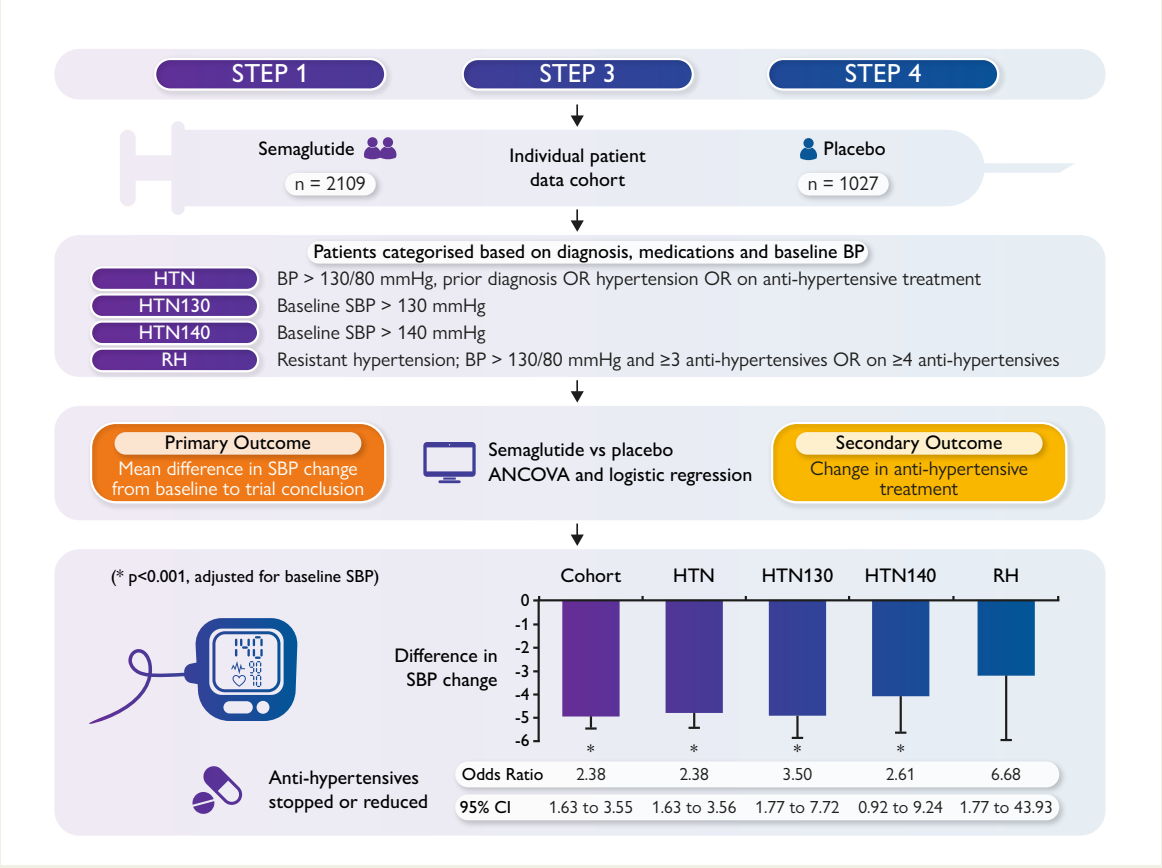
Semaglutide treatment results in a systolic blood pressure (SBP) reduction of 5 mmHg in trial cohorts who are normotensive at baseline. Is this effect on SBP greater for patients with hypertension?

Key Finding

This individual patient data meta-analysis of three randomized controlled trials found the effect on SBP in patients with hypertension was comparable to normotensive cohorts and mediated by weight loss.

Take Home Message

These results suggest semaglutide is a useful adjunctive treatment for patients with hypertension and obesity. A larger treatment effect for patients with hypertension may be masked by alterations to their anti-hypertensive regimens during the trial.



Difference in systolic blood pressure (SBP) change and alterations of anti-hypertensive medications for semaglutide and placebo arms using individual participant data (IPD) from three randomized controlled trials examining the effect of semaglutide 2.4 mg on body weight over 68 weeks. ANCOVA, analysis of covariance; BP, blood pressure; CI, confidence interval.

Keywords Semaglutide • Blood pressure • Hypertension • Weight loss • Obesity • Pharmacotherapy

Introduction

The management of hypertension, particularly in patients with difficult to control blood pressure (BP), requires new treatment strategies.[1] Despite the availability of effective treatments, the achievement of BP targets is challenging and presents a significant global health issue.[2] International consensus to lower BP targets has increased the prevalence of hypertension and the numbers of patients with uncontrolled BP, further necessitating more effective treatment strategies to bridge the gap to optimal levels of BP control.[3] Obesity is also increasing in prevalence; this observation is often referred to as the obesity epidemic.[4]

The interaction of obesity with hypertension is multifaceted. The mechanisms likely involve alterations to salt-handling, an inflammatory milieu, and sympathetic nervous system stimulation.[5–8] Current hypertension treatments target pathways that intersect with those that are affected by excess body weight. However, targeting the disease of obesity may be an effective strategy to control BP particularly for patients suffering from resistant hypertension (RH).[9]

Patients with RH comprise 15%–20% of the general hypertension population and are at greater risk of cardiovascular disease. The attainment of BP targets in this group is particularly challenging.[10,11] The role of excess adipose tissue in RH is highlighted by the significant co-occurrence of obesity and hypertension.[12,13] With the arrival of glucagon-like peptide-1 receptor agonist (GLP-1 RA) as effective treatments for the disease of obesity resulting in >10% weight loss, their role in hypertension treatment needs further consideration. This importance has been further highlighted by SELECT, the first randomized controlled trial (RCT) for obesity to have shown a reduction in major cardiovascular adverse events with semaglutide.[14]

We have previously performed a systematic review and meta-analysis of the BP-lowering effect of semaglutide in patients without diabetes in randomized clinical trials (RCTs).[15] The mean reduction in systolic BP (SBP) was 5 mmHg, which is considered clinically significant. However, this analysis determined the BP reduction for study populations with a mean SBP in the normal range. Thus, the effect of semaglutide on BP in patients with hypertension has yet to be determined.

The aims of this study included determining the effect of semaglutide treatment on SBP in patients with hypertension, SBP in patients with RH, SBP when baseline body mass index (BMI) is considered, and alterations to anti-hypertensive medications.

Methods

A study protocol pre-specified the analysis plan, and this is available at https://osf.io/2n7je. This protocol was submitted and approved by the Independent Review Board (IRB) of the trials' sponsor, Novo Nordisk, to facilitate access to de-identified individual patient data (IPD) via a secure portal (SAS Clinical Trial Data Transparency system, SAS Institute Inc., Cary, NC, USA). Informed consent was sought by the trial sponsor and provided by all study participants.

Study selection

This study follows a systematic review and meta-analysis examining the effect of semaglutide on BP in RCTs which recruited patients with obesity but without diabetes.[15] That systematic review identified six RCTs which met its study selection criteria. These were a dose ranging study and five larger phase III RCTs. Three of these studies were excluded due to treatment with a lower dose of semaglutide,[16] a longer study duration,[17] and the inclusion of an active comparator.[18] Therefore, three large RCTs (STEP 1, 3, and 4) were included in this analysis.

Contributing studies

The details of the included RCTs have been published previously.[15] The selected studies were broadly homogeneous in terms of study design. All RCTs compared semaglutide 2.4 mg to placebo and the treatment period was 68 weeks. The exception was an active run-in period in the STEP 4 trial.[19] In terms of eligibility criteria, all included trials recruited adult participants without diabetes and with a BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 with at least one obesity-related complication. Change from baseline SBP (at randomization) to that at trial conclusion was collected in these RCTs. Ethical approval and written informed consent from participants were obtained in all three trials.[19–21]

Of note, the STEP 4 trial investigated the effect of withdrawing semaglutide treatment on weight loss maintenance.[19] To do so, it included a 20-week period during which both study arms were treated with semaglutide. Randomization occurred at Week 20, and the data at this timepoint were the baseline measure used in this analysis. To determine whether this difference in study design altered our analysis, a pre-specified sensitivity analysis was performed excluding STEP 4.

Measures of blood pressure, hypertension history, anti-hypertensive use, and covariates

The trial processes including endpoint measurements are detailed in the published RCT protocols.[19–21] All outcomes and patient details required for this analysis were routinely collected during the studies.

Systolic blood pressure was measured at baseline (randomization) and the end of each study at the trial sites. The participants were in a sitting position and the measurement was taken with an automated device after the participant had rested for 5 min after avoiding caffeine and smoking for 30 min beforehand. A complete medical history was taken at the screening visit, at which point hypertension was identified as a pre-existing diagnosis. All medications that the participants received were recorded including name, indication, and dates of administration. The latter allowed stop and start dates to be identified. Changes in medication were recorded at each study visit, which were either biweekly or every four weeks.

Body weight was measured without shoes, in light clothing, with an empty bladder on a digital weighing scale which was calibrated at least yearly. Height was measured without shoes. Body mass index was calculated using the standard procedure. Body mass index was classified as follows: Class I (BMI 30–35 kg/m^2), Class II (BMI 35–40 kg/m^2), and Class III (BMI > 40 kg/m^2).

Data preparation

Following approval by the sponsor's IRB, de-identified datasets were prepared for data processing and analysis. For outcome measurements, data at randomization and final follow-up visit were retrieved for each participant. Participants without a measurement at the final visit (Week 68) were excluded ($n = 239$).

We categorized trial participants using their BP information. The first category was a hypertension group (HTN) which included all participants with a BP > 130/80 mmHg, a diagnosis of hypertension, or being on anti-hypertensive medications at the time of randomization. The second group included participants with a SBP > 130 mmHg at randomization (HTN130), irrespective of anti-hypertensive medications. The third group included participants with a SBP > 140 mmHg at randomization (HTN140). Finally, participants with RH were defined as those on three anti-hypertensive medications including a diuretic with a BP > 130/80 mmHg, or those on four or more anti-hypertensive medications including a diuretic regardless of BP. Because a measure of adherence and a 24 h ambulatory BP monitor were not included in the trials, this group is better described as having apparent RH.

Changes in anti-hypertensive medications during the trial were determined. If a new anti-hypertensive was started or a dose increased of a current anti-hypertensive treatment, this was considered as an escalation in treatment. If participants had a treatment stopped or a dose of a current anti-hypertensive treatment decreased, this was considered as treatment de-escalation. To quantify the in-trial adjustments to medications further, a treatment intensity score (TIS) was calculated for the changes in anti-hypertensives. This was based on previously described methods to quantify anti-hypertensive treatment intensity as a proportion of the maximum dose and modified to quantify the treatment change.[22,23]

Statistical analysis

Participants were analysed according to their treatment allocation, thus adhering to the intention-to-treat principle. All analyses were performed for the complete IPD cohort and the pre-specified categories; HTN, HTN130, HTN140, and RH. The primary outcome of interest in this analysis was the change in SBP from baseline to trial conclusion. Differences in SBP change and two-sided 95% confidence intervals (CIs) were estimated for the comparisons of semaglutide vs. placebo. Analysis of covariance (ANCOVA) was used for BP outcomes with randomized treatment as the independent exposure variable. Baseline SBP was a covariate in the primary analysis model. A secondary analysis was performed comparing the change in SBP in the

randomized treatment arms with both baseline SBP and change in body weight as covariates.

The changes in anti-hypertensive medications were compared for the semaglutide and placebo groups using a logistical regression model adjusted for baseline SBP. The between arm difference in TIS change was analysed with ANCOVA adjusted for baseline SBP. Beta adrenoreceptor receptor blocker treatment at baseline was included in a *post hoc* analysis (ANCOVA) to determine its influence on the semaglutide treatment effect in consideration of its metabolic side-effects.[24]

Sensitivity analyses, repeating the above primary and secondary analyses, were performed excluding participants from STEP 4 due to its active run-in phase prior to randomization. In STEP 4, all participants were pre-treated at their randomization measurement and so their anthropometric measurements were not their true baseline. Therefore, as a component of the sensitivity analysis, the change in SBP for STEP 1 and 3 participants was analysed with baseline SBP and baseline BMI as covariates in an ANCOVA model. In addition, the pooled data were analysed with a specific term (trial identifier) for each trial as a covariate.

Mediation analysis, using the 'mediation' package in R, was performed to determine the effect of body weight as a mediator for the change in SBP with semaglutide treatment compared to placebo. A number of additional analyses were performed to examine the relationship between BP change and body weight change on semaglutide. The correlation between change in body weight and BP response was examined as well as the BP response for categories defined by their percentage body weight change. This analysis excluded patients from STEP 4 as these were treated with semaglutide during the run-in phase.

Missing data were addressed by multiple imputation using the predictive mean matching technique for SBP at randomization, and the mean difference of SBP from randomization to the final trial visit assuming data was missing at random. Twenty imputed datasets were created using the 'mice' package in R and a pooled analysis performed.

As standard, a two-sided $P < .05$ was considered statistically significant. Analyses were performed using R Software version 4.3.1 (R Core team, 2023).

Results

Characteristics and blood pressure profile of study participants

A total of 3136 participants without diabetes from three RCTs were included in this study, 2109 in the treated group and 1027 in the placebo group. The characteristics of the cohort and hypertensive groups are displayed in *Table 1*. Systolic blood pressure and diastolic BP (DBP) were 124.8 and 79.8 mmHg, respectively, for patients allocated to semaglutide compared to 124.9 and 79.9 mmHg for those allocated to placebo. A diagnosis of hypertension was recorded for 36.6% and 36% of patients in the semaglutide and placebo groups, respectively, while 43.4% and 44.4% were on treatment for hypertension. Of the overall study cohort, 65% met the criteria for the HTN group, 32% for the HTN130, and 13% for the HTN140 groups (Supplementary data online, *Table S1*). Only 3.5% were classified as having RH.

Blood pressure lowering effect of semaglutide

For the primary analysis (*Figure 1*), the difference in SBP change between semaglutide and placebo (whole cohort) was −4.89 mmHg unadjusted (95% CI −5.92 to −3.87), and −4.95 mmHg when adjusted for baseline BP (95% CI −5.86 to −4.05 mmHg, $P < .001$). The analysis of the hypertension groups provided similar results for change in SBP: HTN group had a difference of −4.62 mmHg (95% CI −5.99 to −3.25), adjusted to −4.78 mmHg (95% CI −5.97 to −3.59, $P < .001$), the HTN130 group had a difference of −5.05 mmHg (95% CI −7.01 to −3.08) and adjusted to −4.93 mmHg (95% CI −6.75 to −3.11, $P < .001$), and the HTN140 group −4.84 mmHg (95% CI −8.12 to −1.59) and adjusted to −4.09 mmHg (95% CI −7.12 to −1.06, $P = .005$). The same comparison for the RH was not significant. The between group difference was −4.93 mmHg (95% CI −11.09–1.23) but reduced to −3.16 mmHg (95% CI −8.69–2.37, $P = .257$) when adjusted for baseline BP.

Figure 2 displays the measured change in SBP across the groups. While the difference between semaglutide treatment and placebo is ∼5 mmHg for each, the absolute change in SBP showed considerable variation. The HTN group had a −6.24 mmHg change for semaglutide and a −1.62 mmHg for placebo, while this was more pronounced for the HTN130 group (−12.07 mmHg for semaglutide and −7.02 mmHg for placebo) and greater yet again for the HTN140 group (−17.41 mmHg for semaglutide and −12.57 mmHg for placebo). There was no evidence of statistical interaction on the BP-lowering effect of semaglutide according to baseline BP category ($P = .628$).

For the secondary analyses, change in body weight was included as a covariate. This attenuated the difference for the cohort such that none were statistically significant (−1.01 mmHg; 95% CI −2.02–0.01, $P = .051$) and its groups; HTN −0.44 mmHg (95% CI −1.77–0.89, $P = .516$), HTN130 −0.34 mmHg (95% CI −2.41–1.73, $P = .748$), HTN140 had an increase of 0.18 mmHg (95% CI −3.34–3.69, $P = .921$), and RH −2.33 mmHg (95% CI −8.68–4.01, $P = .468$).

Changes in anti-hypertensive treatment

For those on treatment, the mean number of anti-hypertensive medications used by those allocated to semaglutide and placebo was 1.8 and 1.7, respectively (*Table 1*). The percentage on diuretics was 13.3% for the semaglutide group and 11.9% for the placebo group. The most frequently prescribed anti-hypertensives were angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (see Supplementary data online, *Table S5*).

Anti-hypertensive treatment was escalated in 3.9% of those on semaglutide and 5.1% of those on placebo (OR 0.75; 95% CI 0.51–1.10, $P = .132$). Changes in anti-hypertensive medications were more pronounced for the hypertension groups (*Figure 3A* and Supplementary data online, *Figure S2*). Comparing semaglutide to placebo, escalation of anti-hypertensive treatment occurred in 5.7% vs. 7.6% for the HTN group (OR 0.73; 95% CI 0.50–1.08, $P = .112$), 8.4% vs. 11.5% for the HTN130 group (OR 0.68; 95% CI 0.43–1.09, $P = .105$), 11.3% vs. 14.3% for the HTN140 group (OR 0.76; 95% CI 0.39–1.49, $P = .420$), and 6.4% vs. 12.1% for the RH group (OR 0.32; 95% CI 0.07–1.30, $P = .109$).

De-escalation of anti-hypertension treatment was more frequently seen in patients allocated to semaglutide (*Figure 3B* and Supplementary data online, *Figure S3*). This effect was consistently observed across all groups. De-escalation occurred more often with semaglutide treatment in the overall study cohort (semaglutide 7.1% vs. placebo 3.5%; OR 2.38; 95% CI 1.63–3.55, $P < .001$), HTN group (10.9% vs. 5.2%; OR 2.38; 95% CI 1.63–3.56, $P < .001$), HTN130 group (8.1% vs. 2.6%; OR 3.50; 95% CI 1.77–7.72, $P < .001$), and the HTN140 group (6.6% v 2.9%; OR 2.61; 95% CI 0.92–9.24, $P = .094$). The effect was most pronounced in patients with RH, as 26.9% of those treated with semaglutide had their anti-hypertensives de-escalated compared to 3% of those on placebo (OR 6.68; 95% CI 1.77–43.93, $P = .015$). For the RH group, 36% of those treated with semaglutide did not meet the RH criteria at the end of the study, compared to 21% for placebo.

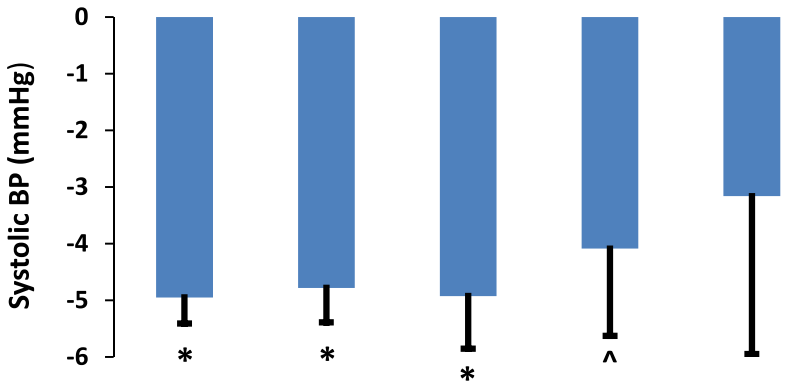
Table 1 Comparison of the baseline characteristics of the study arms

	Cohort		HTN		HTN130		HTN140		RH	
	Semaglutide	Placebo	Semaglutide	Placebo	Semaglutide	Placebo	Semaglutide	Placebo	Semaglutide	Placebo
n	2109	1027	1376	674	656	340	257	140	78	33
Age (years)	46.5 ± 12.5	47 ± 12.3	49.2 ± 12.1	49.4 ± 11.8	51.2 ± 12.1	50.6 ± 12.0	52.9 ± 11.5	52.5 ± 12.3	58 ± 9.2	57.2 ± 8.3
Female sex	75.7%	77.4%	71.4%	73.6%	70.0%	68.8%	68.1%	72.1%	64.1%	63.6%
BMI (kg/m^2)	36.9 ± 6.8	37.0 ± 7.0	37.5 ± 7.0	37.7 ± 7.2	38.2 ± 7.3	38.5 ± 6.9	38.7 ± 8.1	39.1 ± 7.6	39.5 ± 6.8	39.3 ± 9.5
Body weight (kg)	103.1 ± 22.4	102.5 ± 22.8	105.4 ± 23.3	105.2 ± 23.1	107.9 ± 24.1	108.5 ± 22.3	109.7 ± 26.5	109.2 ± 24.3	112.4 ± 22.1	112.8 ± 32.3
SBP (mmHg)	124.8 ± 14.3	124.9 ± 1 4.4	130.3 ± 13.5	130.6 ± 13.4	141.2 ± 9.5	141 ± 8.7	150.2 ± 9.3	149.2 ± 7.7	136.2 ± 16.4	133.5 ± 8.9
DBP (mmHg)	79.8 ± 9.6	79.9 ± 9.6	83.8 ± 8.7	83.9 ± 8.7	86.4 ± 9.1	86.8 ± 8.7	89.9 ± 9.1	90.5 ± 8.7	83.9 ± 11.8	82.0 ± 10.2
Anti-hypertensives (mean)	1.8 ± 0.9	1.7 ± 0.9	1.8 ± 0.9	1.7 ± 0.9	1.8 ± 0.9	1.7 ± 0.9	1.9 ± 0.9	1.6 ± 0.8	3.4 ± 0.7	3.7 ± 0.7
HbA1c (mmol/mol)	38.1 ± 3.8	38.2 ± 3.9	38.6 ± 3.7	38.5 ± 3.8	39.0 ± 3.6	39.0 ± 3.7	39.0 ± 3.5	39.4 ± 4.0	39.5 ± 3.6	40.0 ± 3.5
Lipids[a] (mmol/L)										
LDL	2.9 ± 0.9	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 1.0	2.9 ± 0.9	3.1 ± 1.0	2.7 ± 0.8	2.9 ± 0.8
HDL	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.3
Triglycerides	1.5 ± 0.8	1.4 ± 0.9	1.5 ± 0.8	1.5 ± 0.8	1.5 ± 0.8	1.6 ± 1.0	1.5 ± 0.7	1.6 ± 0.7	1.6 ± 0.9	1.5 ± 0.5
eGFR (mL/min/1.73 m^2)	96.5 ± 17.8	97.1 ± 17.2	94.3 ± 17.8	93.8 ± 17.0	93.7 ± 17.0	92.5 ± 16.6	93.2 ± 16.6	91.7 ± 17.2	84.8 ± 19.6	86.3 ± 16.5
Comorbidities (%)										
Dyslipidaemia	35.9	33.7	41.1	37.7	42.2	35.4	43.2	36.4	62.8	54.5
Obstructive sleep apnoea	13.1	11.1	15.0	13.5	15.4	13.5	17.1	10.0	24.4	27.3
Cardiovascular disease	5.1	5.2	6.6	6.4	6.4	6.8	5.1	7.1	19.2	15.2
Comorbidities[b] (mean)	1.7	1.6	2.1	2.0	2.1	1.9	2.2	2.0	3.7	2.8

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, group with a diagnosis of hypertension, BP > 130 mmHg, or on an anti-hypertensive treatment; HTN130, group with systolic BP > 130 mmHg; HTN140, group with systolic BP > 140 mmHg; RH, group with resistant hypertension. Numbers are means ± standard deviation or percentage of the group (%).

[a]Total cholesterol was not available in the standard dataset of blood results.

[b]Comorbidities at screening: dyslipidaemia, hypertension, coronary artery disease, cerebrovascular disease, obstructive sleep apnoea, impaired glucose metabolism, liver disease, kidney disease, osteoarthritis, gout, or asthma or chronic obstructive pulmonary disease.



	Cohort	HTN	HTN130	HTN140	RH
Effect (mmHg)	-4.9	-4.6	-5.1	-4.8	-4.9
95% CI	-5.9 to -3.9	-6.0 to -3.3	-7.0 to -3.1	-8.1 to -1.6	-11.1 to 1.2
Effect adjusted	-5.0	-4.8	-4.9	-4.1	-3.2
95% CI	-5.9 to -4.1	-6.0 to -3.6	-6.8 to -3.1	-7.1 to -1.1	-8.7 to 2.4

Figure 1 Difference in mean systolic blood pressure change between semaglutide and placebo treated groups in STEP 1, 3, and 4 trials. *$P < .001$, ^$P < .01$ adjusted for baseline blood pressure using ANCOVA. BP, blood pressure; HTN, group with a diagnosis of hypertension, BP > 130 mmHg, or on an anti-hypertensive treatment; HTN130, group with systolic BP > 130 mmHg; HTN140, group with systolic BP > 140 mmHg; RH, group with apparent resistant hypertension

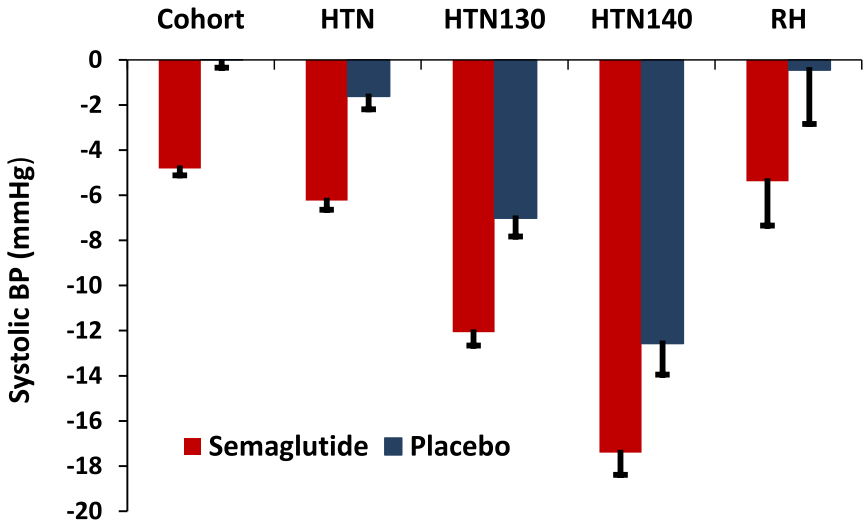


Figure 2 Mean systolic blood pressure change between semaglutide treatment (red) and placebo (blue) in STEP 1, 3, and 4 trials ($n = 3136$). Bars are standard errors. BP, blood pressure; HTN, group with a diagnosis of hypertension, BP > 130 mmHg, or on an anti-hypertensive treatment; HTN130, group with systolic BP > 130 mmHg; HTN140, group with systolic BP > 140 mmHg; RH, group with apparent resistant hypertension

Analysis of change in TIS resulted in a mean difference of −0.51 (95% CI −0.71 to −0.32, $P < .001$) for semaglutide compared to placebo (*Figure 3*). This represented a de-escalation of half a standard anti-hypertensive dose due to semaglutide. This de-escalation or reduction in anti-hypertensive treatment was consistent across the groups; HTN −0.54 (95% CI −0.74 to −0.33, $P < .001$), HTN 130 −0.63 (95% CI −0.97 to −0.29, $P < .001$), HTN140 −0.46 (95% CI −1.09–0.17, $P = .150$), and RHTN −0.58 (95% CI −1.55–0.38, $P = .226$).

A total of 7.6% of the study cohort were on a beta blocker at baseline (see Supplementary data online, *Table S5*), with an equal distribution across the study arms (semaglutide 7.4%, placebo 8.0%). A total of 11% of these patients had their beta blocker discontinued, again there was minimal difference between study arms (11% vs. 12%). The inclusion of baseline BB treatment as a covariate in the ANCOVA model did not alter the finding for mean difference is SBP change (−4.93 mmHg; 95% CI −5.84 to −4.03).

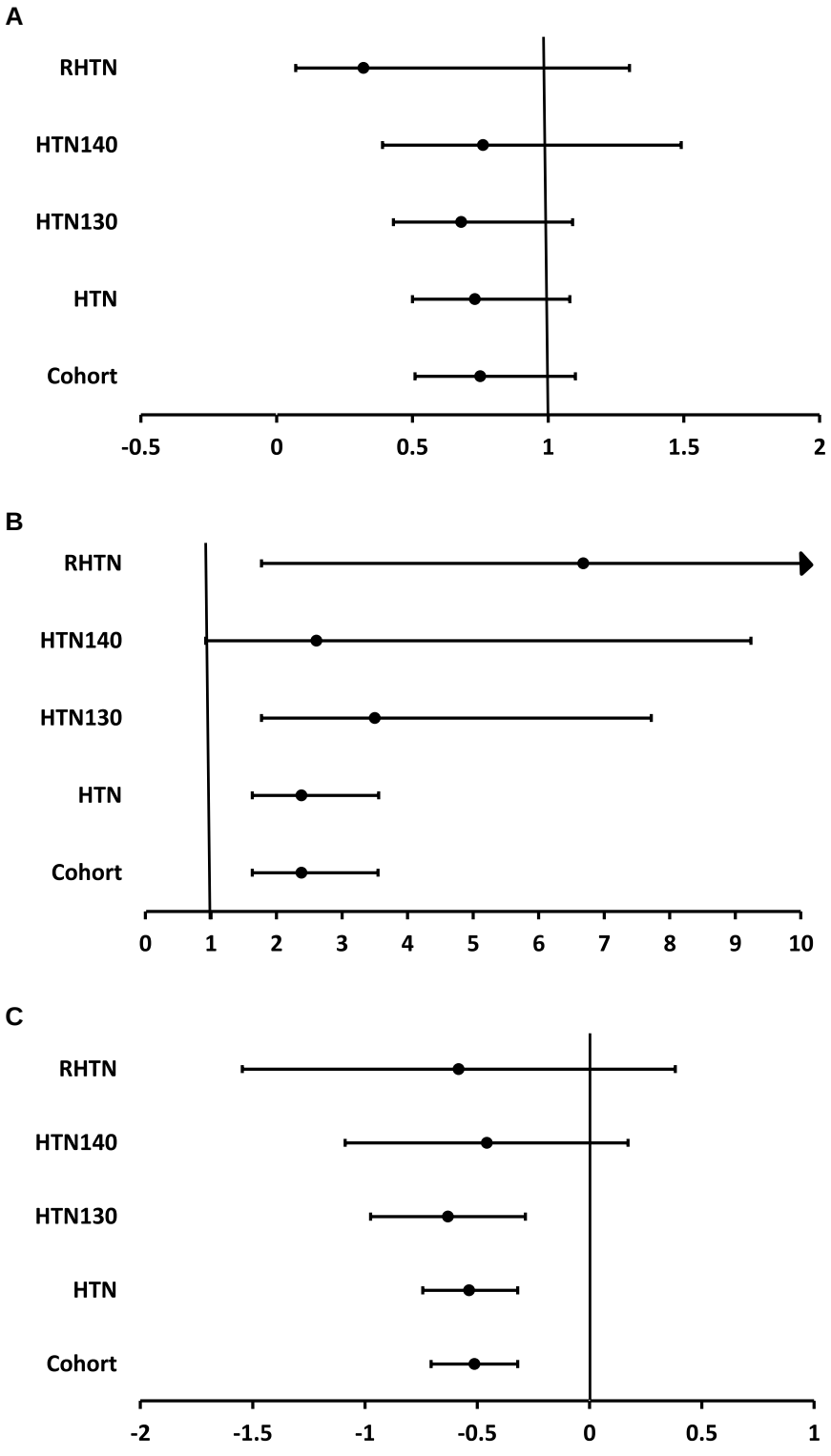
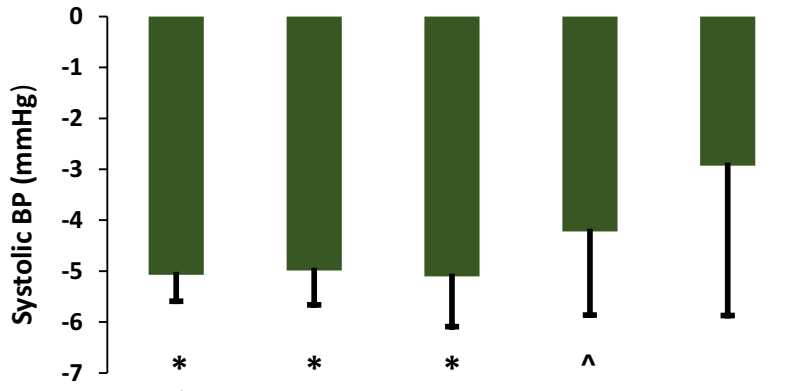


Figure 3 (*A*) Odds ratios for anti-hypertensive escalation, (*B*) odds ratios for anti-hypertensive de-escalation, (*C*) mean difference for change in treatment intensity score. All estimates were adjusted for baseline systolic blood pressure and compare the semaglutide and placebo in the STEP 1, 3, and 4 trials ($n = 3136$). HTN, group with a diagnosis of hypertension, BP > 130 mmHg, or on an anti-hypertensive treatment; HTN130, group with systolic BP > 130 mmHg; HTN140, group with systolic BP > 140 mmHg; RH, group with apparent resistant hypertension

A *post hoc* analysis subdivided the RH group into those at baseline with SBP above or below 130 mmHg. For those with RH with a baseline SBP ≥ 130 mmHg and treated with semaglutide, the SBP change from baseline to trial completion was −10.94 mmHg compared to placebo. The effect on SBP was an increase in SBP of 4.54 mmHg in those with RH and a SBP < 130 mmHg. The percentages of patients who had anti-



	Cohort	HTN	HTN130	HTN140	RH
Effect (mmHg)	-4.9	-4.8	-5.2	-5.3	-5.9
95% CI	-6.1 to -3.8	-6.4 to -3.3	-7.3 to -3.1	-8.8 to -1.7	-12.5 to 0.7
Effect adjusted	-5.1	-5.0	-5.1	-4.2	-2.9
95% CI	-6.1 to -4.1	-6.3 to -3.7	-7.0 to -3.2	-7.5 to -0.1	-9.1 to 3.3

Figure 4 Difference in mean systolic blood pressure change between semaglutide treatment and placebo in STEP 1 and 3 trials ($n = 2365$). STEP 4 was excluded due to its active run-in phase. Bars are standard errors. *$P < .001$, ^$P < .05$ adjusted for baseline blood pressure. HTN, group with a diagnosis of hypertension, BP > 130 mmHg, or on an anti-hypertensive treatment; HTN130, group with systolic BP > 130 mmHg; HTN140, group with systolic BP > 140 mmHg; RH, group with apparent resistant hypertension

hypertension medications de-escalated in these RH subgroups were similar at 26% for those with SBP ≥ 130 mmHg, and 28.6% in those with a SBP < 130 mmHg, while the percentage with anti-hypertensives escalated was 10% and 0%, respectively.

Sensitivity analysis

When data from STEP 4 were omitted, compared to the study cohort (STEP 1, 3, and 4), the baseline SBP was higher at 126.1 mmHg, and a greater percentage of participants presented with SBP above both 130 and 140 mmHg (see Supplementary data online, *Table S2*).

The difference in SBP change for this sensitivity analysis was comparable to the change seen in the primary analysis (*Figure 4*). The difference in mean SBP change between semaglutide and placebo after adjusting for baseline SBP was −5.07 mmHg (95% CI −6.09 to −4.05, $P < .001$) with similar results for the HTN group (−4.99 mmHg; 95% CI −6.31 to −3.66, $P < .001$) and HTN130 group (−5.10 mmHg; 95% CI −7.04 to −3.17, $P < .001$). The difference remained significant for the HTN140 group (−4.22 mmHg; 95% CI −7.45 to −0.10, $P < .011$) but not for the RH group (−2.89 mmHg; 95% CI −9.07–3.29, $P = .355$) after adjustment.

For the analysis of the study cohort (STEP 1, 3, 4), after the inclusion of a trial identifier as a covariate in the analysis, the primary outcome remained unchanged (−4.94 mmHg; 95% CI −5.84 to −4.04) and the variation in the model was comparable (multiple R squared 0.269 with the trial identifier, 0.256 without).

Mediation analysis estimated the mediation effect of change in body weight to be significant and estimated this to be 89.0% of the change in SBP (95% CI 70.1–116.0, $P < .001$). For participants on semaglutide, their change in SBP significantly correlated with their change in body weight (see Supplementary data online, *Figure S1*; correlation coefficient 0.197, $P < .001$). When analysed according to category of body weight response, there was a strong correlation with change in SBP (see Supplementary data online, *Table S4*; correlation coefficient for SBP change 0.9824, $P < .001$; and for DBP change 0.9925, $P < .001$). Those who did not lose body weight (5.3% of those on treatment) also did not have a reduction in their blood pressure (mean SBP change 0.6 mmHg).

Multiple imputation addressed missing data for 239 participants. The adjusted (for SBP at baseline) difference in SBP between semaglutide and placebo was −4.63 (95% CI −5.54 to −3.72, $P < .001$). This imputed estimate is comparable to the estimate derived from observed values.

Blood pressure lowering effect considering baseline body mass index

A pre-specified secondary analysis included baseline BMI as a covariate. However, STEP 4 participants were excluded as their baseline BMI was calculated after the active run-in period. When the difference in SBP change between the semaglutide and placebo was adjusted for both baseline SBP and baseline BMI, the results were equivalent to that in the sensitivity analysis above. For example, the difference for the HTN group was −4.97 mmHg (95% CI −6.30 to −3.65, $P < .001$) and that for the RH group was −3.09 mmHg (95% CI −8.94–2.77, $P = .298$). Again, consistent with the sensitivity analysis, all differences were statistically significant except that for the RH group.

The consistent results across groups suggest that the evident SBP change did not depend on baseline BMI. Stratifying the BP changes by BMI classification corroborated this conclusion (see Supplementary data online, *Table S3*).[25] The differences in mean SBP change for Class I, Class II, and Class III obesity were −4.80, −6.55, and −3.26 mmHg, respectively. Therefore, a notable trend in SBP change as BMI classification increased was not evident. All BMI classifications demonstrated significant reductions in SBP with baseline SBP as a covariate; Class I obesity −4.07 mmHg (95% CI −5.80 to −2.33, $P < .001$), Class II obesity −7.15 mmHg (95% CI −8.95 to −5.36, $P < .001$) and Class III obesity −3.92 mmHg (95% CI −5.83 to −2.01, $P < .001$). Lastly, the weight loss effect of semaglutide was not greater for those with a higher baseline BMI (see Supplementary data online, *Table S3*).

Discussion

This study examined IPD from three RCTs to determine the effect of semaglutide on SBP in patients with hypertension. It succeeded a meta-analysis of BP outcomes from RCTs assessing the weight loss effect of semaglutide, which estimated the reduction of SBP to be 5 mmHg in a population with a baseline mean SBP in the normal range.[15] Interestingly, the reduction in SBP from randomization to trial completion was consistently 5 mmHg with semaglutide, irrespective of the presence of hypertension or whether hypertension was defined by diagnosis, treatment, or baseline SBP (*Structured Graphical Abstract*). The effect of semaglutide on SBP was also comparable for the group with RH, though this effect was not statistically significant due the small sample size and lack of statistical power. The results remained consistent when one trial, STEP 4, was excluded due to its active run-in period.

Besides showing a consistent reduction in SBP with semaglutide, the current analysis demonstrated that anti-hypertensive treatments were more frequently de-escalated with semaglutide compared to placebo (*Structured Graphical Abstract*). This effect was evident across all groups but was most pronounced in patients with higher baseline SBP and RH. There was also a trend that those with a higher baseline SBP, both on semaglutide and placebo, had their anti-hypertensive treatment escalated more often. The change in TIS, a composite score to measure the change in anti-hypertensive treatment, corroborated these results. It suggests that the change in anti-hypertensive treatment due to semaglutide is approximately equivalent to a reduction of half a dose of a standard anti-hypertensive medication.

Including the change in body weight in the analysis negated the blood pressure effect of semaglutide, suggesting that the effect is at least partly mediated by weight loss. Further investigation using mediation analysis suggested that the SBP reduction was significantly mediated by weight change. This is in keeping with a recent study reporting 24 h BP measurements on tirzepatide, a dual GLP-1 RA and glucose-dependent insulinotropic polypeptide (GIP) analogue, which suggested that 70% its BP effect was mediated by body weight reduction.[26] This finding is supported by the significant correlation found for SBP and body weight change when on semaglutide. Our results did not indicate that those with a greater BMI had a greater reduction in SBP or a proportionally greater lowering of body weight.

Reviewing the evidence for BP change with weight loss raises the question whether the effect on BP should be higher than the one observed in our meta-analysis, in which a 13.9% reduction in body weight translated into a 5 mmHg SBP reduction.[15] A meta-analysis of RCTs involving non-pharmacological interventions to reduce body weight, including 25 trials and 4874 participants, reported each kilogram of weight loss may result in at least 1 mmHg reduction in SBP.[27] The mean reduction in SBP was −4.4 mmHg with a mean reduction in weight of 5.1 kg. Interestingly, this same meta-analysis suggested a greater BP reduction in those on anti-hypertensive medication compared with untreated populations (7.0 mmHg vs. 3.8 mmHg). A recently updated Cochrane review of weight loss diets in populations with hypertension identified eight trials including 2100 participants.[28] The authors concluded that these diets were associated with a reduction in BP, a mean difference of −4.5 mmHg. The associated weight loss was ∼4 kg. Importantly, the reviewers noted that two of the included trials used withdrawal of anti-hypertensive medications as a primary outcome.

If a reduction in SBP of 1 mmHg is expected for every 1 kg of weight loss, the STEP trial cohorts might expect a SBP reduction of the magnitude of 13 mmHg, rather than the 5 mmHg observed. An important factor to consider and highlighted by the current study is the change in anti-hypertensive treatments during clinical trials. Allocation to semaglutide was consistently associated with greater de-escalation of anti-hypertensive drugs compared to patients on placebo, accompanied by a reduced requirement for additional anti-hypertensive drugs. These changes in anti-hypertensive treatment may very well contribute to masking larger BP reductions associated with semaglutide treatment. Encompassing the change in medications to quantify the totality of the BP-lowering effect of semaglutide is beyond the scope of this work but a possible area of future research. Similarly, whether the reduction in BP with weight loss interventions is a direct result of weight loss *per se*, or due to other effects of these interventions, is uncertain as is the underlying mechanisms involved. For example, dietary approaches to weight loss are likely to reduce salt intake, which in turn is associated with BP reduction.

GLP-1 RAs, and similar drugs which also affect GIP and glucagon-receptors, are targeting obesity at a time when excess body weight is reaching epidemic proportions. Their effect on BP is likely an important aspect of their cardiovascular benefit. It is apparent that the effect on BP may be modest for older GLP-1 RAs such as dulaglutide (−2.6 mmHg).[29] Newer agents impacting on incretin pathways are entering the treatment paradigm for diabetes and obesity. Tirzepatide, as an example, resulted a 16.4% reduction in body weight in a cohort of 2539 participants for the 15 mg weekly dose of tirzepatide compared with placebo in its flagship RCT for obesity SURMOUNT-1.[30] The reduction in SBP, compared to placebo, was −6.2 mmHg for SBP and −4.0 mmHg for DBP.

The difference in SBP between the semaglutide and placebo cohorts was consistent across the HTN, HTN130, HTN140, and RH groups. However, the measured change in absolute SBP was strikingly different. For example, the SBP change on semaglutide for the HTN group was −6.41 mmHg while that for the HTN140 group was −17.41 mmHg. Notably, the pattern of change in SBP on placebo across the groups aligned with that for semaglutide, −1.79 mmHg for the HTN group and −12.57 mmHg for the HTN140 group. This is at least partly explained by alterations to anti-hypertensive treatment, with more treatment escalated and less de-escalation as the baseline BP of the group increased. Therefore, the effect of enrolling in a trial, an environment in which patients' medical conditions are carefully assessed and managed, is evident. Increased adherence in a trial environment may play an important role, as part of an evident Hawthorne effect.[31,32] Interestingly, two recently published trials of treatments for RH report a large reduction in BP in the placebo arms. A phase II trial of the angiotensinogen synthase inhibitor baxdrostat reported a change in SBP of −9.4 mmHg for its placebo arm.[33] Similarly, a phase III trial testing the endothelin antagonist aprocitentan, a SBP change of −11.5 mmHg was reported for the placebo group after 4 weeks.[34] This is despite both studies having placebo run-in periods. Patients with RH have high rates of non-adherence and might expect greater 'in trial' changes in BP when blinded to treatment allocation.

RH is associated with high cardiovascular disease risk. While newer treatments are in development, the application of an obesity centric strategy to control BP in patients with RH warrants examination. In the current study, <4% of the cohort met the definition for RH. The measured difference in SBP for the RH group was consistent with that for the other hypertension groups and the study cohort as a whole. While adjustment for contributory factors or covariates attenuated the difference in the RH group, the small sample size limited the power of the analysis and conclusions that may be drawn are therefore limited. There was a smaller than expected effect of SBP reduction in patients

with RH, irrespective of semaglutide or placebo treatment. The smaller than expected effect may reflect the greater difficulty intensifying anti-hypertensive medications as physicians must familiarize themselves with anti-hypertensive treatments not used in routine clinical practice. For the RH group with a SBP ≥ 130 mmHg only 10% had their anti-hypertensives escalated while percentages for de-escalations were similar for those above and below 130 mmHg baseline SBP. However, it may also be that the inclusion of patients with controlled SBP, but on more than three anti-hypertensive medications in the RH group, results in an understated effect. Supporting this assertion is the change in SBP during the study, which was −10.94 mmHg for those with RH and a baseline SBP ≥ 130 mmHg on semaglutide compared to placebo.

Limitations

Firstly, the study excludes patients with diabetes thus narrowing its generalizability. Diabetes is a prevalent co-morbidity in those with RH. Secondly, the BP outcomes were based on single measurements with automated devices. This may have led to inaccurate measurements. However, due to randomization, this measurement was the same for both study arms. Thirdly, a pre-specified secondary analysis of the effect on SBP when adjusted for baseline BMI was not valid due to the active run-in period in STEP 4. However, the SBP outcomes for the primary analysis were largely equivalent irrespective of the inclusion of STEP 4. Fourthly, the analysis was completed after the weight loss phase in the trials. The impact of the effect on BP during the weight loss maintenance phase could not be evaluated. Next, the analysis focused on SBP change as the outcome, rather than changes in other measures of BP such as diastolic BP or pulse pressure. It is likely that SBP is most predictive of cardiovascular outcomes, however, DBP may be analysed in future work.[35] Lastly, the small sample of patients with apparent RH did not allow an adequate analysis of the BP outcomes in this group.

Conclusion

This analysis of IPD from three large RCTs assessing semaglutide treatment demonstrated a significant reduction in SBP that is comparable in normotensive and hypertensive participants. The reduction in SBP was mediated by semaglutide's weight loss effect. Both SBP and weight reduction were consistent across hypertension categories, irrespective of the definition of hypertension or its magnitude, as well as across BMI categories. De-escalation of anti-hypertensive drugs was more frequently observed in patients treated with semaglutide and likely masks a larger treatment effect. These results have widespread implications for clinical practice. The evident blood pressure lowering effect of semaglutide allows the recalibration of anti-hypertensive medications and is a useful adjunct for patients with hypertension and obesity.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

C.K., P.H., S.D., J.W.M., L.Z., M.H.: no conflicts of interest. A.F.G.C.: consulting fees/honoraria—Servier, Mylan, and Sharper. C.W.I.R.: consulting fees/honoria/support for meetings—NovoNordisk, Eli Lilly, Johnson & Johnson, Boehringer Ingelheim, GI Dynamics, Roche, Astra Zeneca, and Herbalife. Leadership/fiduciary role in board—Irish Society for Nutrition and Metabolism (unpaid). Stock options—Keyron Previous Chief medical officer and Director of the Medical Device Division of Keyron in 2011. Both of these were unremunerated positions. Previous investor in Keyron, which develops endoscopically implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy and gastric bypass. He continues to provide scientific advice to Keyron for no remuneration.

Data Availability

The data that supports this study are controlled by the sponsor of the trials, Novo Nordisk. Restrictions apply to the availability of these data, which were used under agreement for this study.

Funding

No funding was associated with this research.

Ethical Approval

Ethical approval and written informed consent from participants were obtained in all included trials. This study was approved by Novo Nordisk's Independent Review Board.

Pre-registered Clinical Trial Number

The pre-registered clinical trial numbers for the included trials are ClinicalTrials.gov numbers NCT03548935 (STEP1), NCT03611582 (STEP3), and NCT03548987 (STEP4).

References

1. Dzau VJ, Balatbat CA. Future of hypertension. *Hypertension* 2019;**74**:450–7. https://doi.org/10.1161/HYPERTENSIONAHA.119.13437
2. Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, *et al.* Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* 2021;**398**:957–80. https://doi.org/10.1016/S0140-6736(21)01330-1
3. Tocci G, Presta V, Ferri C, Redon J, Volpe M. Blood pressure targets achievement according to 2018 ESC/ESH guidelines in three European excellence centers for hypertension. *High Blood Press Cardiovasc Prev* 2020;**27**:51–9. https://doi.org/10.1007/s40292-020-00359-0
4. Shams E, Kamalumpundi V, Peterson J, Gismondi RA, Oigman W, de Gusmao Correia ML. Highlights of mechanisms and treatment of obesity-related hypertension. *J Hum Hypertens* 2022;**36**:785–93. https://doi.org/10.1038/s41371-021-00644-y
5. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. *Circ Res* 2015;**116**:991–1006. https://doi.org/10.1161/CIRCRESAHA.116.305697
6. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med* 2017;**376**:254–66. https://doi.org/10.1056/NEJMra1514009
7. Lakkis JI, Weir MR. Obesity and kidney disease. *Prog Cardiovasc Dis* 2018;**61**:157–67. https://doi.org/10.1016/j.pcad.2018.07.005
8. Hall ME, Cohen JB, Ard JD, Egan BM, Hall JE, Lavie CJ, *et al.* Weight-loss strategies for prevention and treatment of hypertension: a scientific statement from the American Heart Association. *Hypertension* 2021;**78:**e38–50. https://doi.org/10.1161/HYP.0000000000000202
9. Kennedy C, Ali O, Farnan R, Hall M, Stinson J, O'Connor P, *et al.* Is it time to reconsider the treatment paradigm for obese patients with hypertension? *J Hum Hypertens* 2021;**36**:482–4. https://doi.org/10.1038/s41371-021-00630-4
10. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, *et al.* Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension* 2018;**72**:e53–90. https://doi.org/10.1161/HYP.0000000000000084
11. Kennedy C, Ali O, Farnan R, Stinson J, Hall M, Gabr A, *et al.* Clinical characteristics of two groups commonly referred to an Irish hypertension service—patients with resistant hypertension and young adults with hypertension. *Ir J Med Sci* 2022;**191**:2549–57. https://doi.org/10.1007/s11845-021-02870-2
12. de la SA, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, *et al.* Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood

pressure monitoring. *Hypertension* 2011;**57**:898–902. https://doi.org/10.1161/HYPERTENSIONAHA.110.168948
13. Kennedy C, Farnan R, Stinson J, Hall M, Hemeryck L, O'Connor P, *et al.* Referrals to, and characteristics of patients attending a specialist hypertension clinic. *J Hum Hypertens* 2021;**36**:315–24. https://doi.org/10.1038/s41371-021-00514-7
14. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, *et al.* Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;**389**:2221–32. https://doi.org/10.1056/NEJMoa2307563
15. Kennedy C, Hayes P, Salama S, Hennessy M, Fogacci F. The effect of semaglutide on blood pressure in patients without diabetes: a systematic review and meta-analysis. *J Clin Med* 2023;**12**:772. https://doi.org/10.3390/jcm12030772
16. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, *et al.* Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018;**392**:637–49. https://doi.org/10.1016/S0140-6736(18)31773-2
17. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, *et al.* Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med* 2022;**28**:2083–91. https://doi.org/10.1038/s41591-022-02026-4
18. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sorrig R, *et al.* Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA* 2022;**327**:138–50. https://doi.org/10.1001/jama.2021.23619
19. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, *et al.* Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA* 2021;**325**:1414–25. https://doi.org/10.1001/jama.2021.3224
20. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, *et al.* Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;**384**:989–1002. https://doi.org/10.1056/NEJMoa2032183
21. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, *et al.* Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA* 2021;**325**:1403–13. https://doi.org/10.1001/jama.2021.1831
22. Levy PD, Willock RJ, Burla M, Brody A, Mahn J, Marinica A, *et al.* Total antihypertensive therapeutic intensity score and its relationship to blood pressure reduction. *J Am Soc Hypertens* 2016;**10**:906–16. https://doi.org/10.1016/j.jash.2016.10.005
23. Min L, Ha J-K, Aubert CE, Hofer TP, Sussman JB, Langa KM, *et al.* A method to quantify mean hypertension treatment daily dose intensity using health care system data. *JAMA Netw Open* 2021;**4**:e2034059. https://doi.org/10.1001/jamanetworkopen.2020.34059
24. Sharma AM, Pischon T, Hardt S, Kunz I, Luft FC. Hypothesis: β-adrenergic receptor blockers and weight gain: a systematic analysis. *Hypertension* 2001;**37**:250–4. https://doi.org/10.1161/01.HYP.37.2.250
25. World Health Organisation. A healthy lifestyle—WHO recommendations. https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle—who-recommendations (03/11/2023, date last accessed).
26. De Lemos JA, Linetzky B, Le Roux CW, Laffin LJ, Vongpatanasin W, Fan L, *et al.* Tirzepatide reduces 24-hour ambulatory blood pressure in adults with body mass index $\geq$ 27 kg/m^2: SURMOUNT-1 ambulatory blood pressure monitoring substudy. *Hypertension* 2024;**81**:e41–3. https://doi.org/10.1161/HYPERTENSIONAHA.123.22022
27. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 2003;**42**:878–84. https://doi.org/10.1161/01.HYP.0000094221.86888.AE
28. Semlitsch T, Krenn C, Jeitler K, Berghold A, Horvath K, Siebenhofer A. Long-term effects of weight-reducing diets in people with hypertension. *Cochrane Database Syst Rev* 2021;**2**:CD008274. https://doi.org/10.1002/14651858.CD008274.pub4
29. Ferdinand KC, Dunn J, Nicolay C, Sam F, Blue EK, Wang H. Weight-dependent and weight-independent effects of dulaglutide on blood pressure in patients with type 2 diabetes. *Cardiovasc Diabetol* 2023;**22**:49. https://doi.org/10.1186/s12933-023-01775-x
30. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, *et al.* Tirzepatide once weekly for the treatment of obesity. *N Engl J Mede* 2022;**387**:205–16. https://doi.org/10.1056/NEJMoa2206038
31. Franke RH, Kaul JD. The Hawthorne experiments: first statistical interpretation. *Am Sociol Rev* 1978;**43**:623–43. https://doi.org/10.2307/2094540
32. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epidemiol* 2001;**54**:217–24. https://doi.org/10.1016/S0895-4356(00)00305-X
33. Freeman MW, Halvorsen Y-D, Marshall W, Pater M, Isaacsohn J, Pearce C, *et al.* Phase 2 trial of baxdrostat for treatment-resistant hypertension. *N Engl J Med* 2023;**388**:395–405. https://doi.org/10.1056/NEJMoa2213169
34. Schlaich MP, Bellet M, Weber MA, Danaietash P, Bakris GL, Flack JM, *et al.* Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. *Lancet* 2022;**400**:1927–37. https://doi.org/10.1016/S0140-6736(22)02034-7
35. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, *et al.* Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med* 2019;**381**:243–51. https://doi.org/10.1056/NEJMoa1803180