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# Effect of semaglutide 2.4 mg on use of antihypertensive and lipid-lowering treatment in five randomized controlled STEP trials

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## Abstract

**Objective:** The objective of this study was to assess antihypertensive and lipid-lowering treatment changes in participants receiving semaglutide 2.4 mg versus placebo across pooled populations from five Semaglutide Treatment Effect in People with Obesity (STEP) trials.

**Methods:** Efficacy and safety of semaglutide 2.4 mg were evaluated in the STEP clinical trials. In this post hoc analysis, STEP 1, 3, 6, and 8 (which included people with overweight or obesity) and, separately, STEP 2 and 6 (which included people with overweight or obesity and type 2 diabetes) were pooled for analysis. Changes in antihypertensive or lipid-lowering treatment intensity from randomization to end of treatment were evaluated.

**Results:** In both pooled samples, a higher proportion of participants in the semaglutide 2.4 mg group versus placebo underwent antihypertensive or lipid-lowering treatment intensity reduction by end of treatment. A smaller proportion underwent antihypertensive or lipid-lowering treatment intensification by end of treatment in the semaglutide 2.4 mg group of both samples versus placebo. In participants receiving antihypertensive or lipid-lowering medications in both samples, greater numeric reductions in body weight were observed in the semaglutide 2.4 mg group versus placebo.

**Conclusions:** These results support a relationship between semaglutide 2.4 mg treatment of overweight and obesity and reduced need for antihypertensive and lipid-lowering treatment, facilitating treatment intensity reduction/discontinuation and abating treatment intensification.

## INTRODUCTION

Obesity is a serious, chronic disease affecting 42.8% of adults aged ≥20 years in the United States [1]. According to public health surveillance data, the US prevalence of obesity increased by 10.5% in adults between 2003 and 2018 [1]. According to one projection, the prevalence of obesity in the United States will approach 50% by 2030 [2]. Furthermore, obesity is associated with an increased risk of

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developing long-term obesity-related complications such as hypertension and dyslipidemia [3].

Hypertension and dyslipidemia are among the most common comorbidities in people with obesity, with a prevalence of approximately 45% and 48%, respectively [4]. Antiobesity medications (AOMs) have generally been associated with improvements in blood pressure (BP) and lipid profiles [5, 6]. For example, phentermine/topiramate was associated with a systolic BP reduction of 3.7 mm Hg and a low-density lipoprotein reduction of 4.2 mg/dL [5]. These improvements may appear to be modest because of concomitant adjustments in antihypertensive or lipid-lowering regimens, changes that are not typically reported from clinical trials.

Semaglutide 2.4 mg, a glucagon-like peptide-1 receptor agonist, is an AOM treatment approved to reduce excess body weight and maintain weight reduction in the long term in adolescents aged ≥12 years with obesity (body mass index [BMI] ≥ 30 kg/m$^2$) and adults aged ≥18 years with obesity or overweight (BMI ≥ 27 kg/m$^2$) with at least one obesity-related complication [7]. A recent examination of the effect of semaglutide 2.4 mg on cardiometabolic risk factors revealed greater improvements in metabolic endpoints and reductions in the use of antihypertensive and lipid-lowering medications in participants receiving semaglutide 2.4 mg versus placebo [8]. Notably, this study had limitations, which necessitate a more thorough analysis of changes in antihypertensive and lipid-lowering treatment in people with obesity treated with semaglutide 2.4 mg. The study included data from only Semaglutide Treatment Effect in People with Obesity (STEP) 1 and 48 weeks of follow-up in STEP 4, leading to a relatively limited sample size and semaglutide 2.4 mg treatment duration. Additionally, people with type 2 diabetes (T2D) were not included in the analysis, precluding the need for an assessment of antihypertensive or lipid-lowering drugs among people with T2D. Finally, only participants treated with antihypertensive or lipid-lowering treatment at randomization were included in the analysis. The need for antihypertensive or lipid-lowering treatment during follow-up was not examined in those without treatment for these conditions at randomization.

The objective of this post hoc analysis was to examine changes in antihypertensive and lipid-lowering treatment intensity in participants receiving semaglutide 2.4 mg versus placebo across pooled data from the STEP 1, 3, 6, and 8 clinical trials (which included people with overweight or obesity) and pooled data from STEP 2 and 6 (which included people with overweight or obesity and T2D).

### Study Importance

#### What is already known?

- Weight loss in people with obesity has been associated with improvements in obesity-related complications, including hypertension and dyslipidemia.

#### What does this study add?

- Treatment of overweight/obesity with semaglutide 2.4 mg is associated with a reduced need for antihypertensive and lipid-lowering treatment.

#### How might these results change the direction of research or the focus of clinical practice?

- Results suggest that weight loss achieved with semaglutide 2.4 mg may allow some participants to reduce or discontinue their medications for hypertension and dyslipidemia.

## METHODS

The safety and efficacy of semaglutide 2.4 mg were assessed in adults aged ≥18 years with overweight or obesity and with or without T2D in US- or global-based, blinded, randomized, placebo-controlled, phase 3 STEP clinical trials. This analysis includes data from STEP 1, 2, 3, 6, and 8 (ClinicalTrials.gov registry numbers: STEP 1, NCT03548935; STEP 2, NCT03552757; STEP 3, NCT03611582, STEP 6: NCT03811574; and STEP 8: NCT04074161). Data from STEP 1, 3, 6 (which excluded those with T2D), and 8 were pooled due to similarities in study designs and populations (which included people with overweight or obesity) [9–12]. Data from participants in STEP 2 and 6 (which included people with overweight or obesity and T2D) were pooled and analyzed separately [11, 13]. People treated with semaglutide 1.7 mg in STEP 6 or treated with liraglutide 3.0 mg in STEP 8 were excluded from this analysis. Owing to differences in trial characteristics (i.e., population, design, or duration), other STEP trials were not included in the analysis. All STEP trials were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocols and amendments were approved by an independent ethics committee or institutional review board at each study site. The trials were designed and overseen by a steering group of clinical professionals, including representatives from the trial sponsor.

### STEP 1, 2, 3, 6, and 8 trial design

The STEP 1, 2, 3, 6, and 8 trial designs, including participant eligibility, locations, sample sizes, randomization, blinding, and statistical methods, have been previously published [9–13]. Key details, including cohort descriptions, randomization, dose escalation, behavioral and lifestyle requirements, primary and secondary endpoints, and safety assessments, are summarized for all relevant trials in Table S1. Data on antihypertensive and lipid-lowering medications were collected in all trials. Changes to medications were based on medical judgments by site investigators and reported changes in "treatment intensity" (i.e., increase or decrease in dose or addition or discontinuation of medication).

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## Post hoc analysis: endpoints

Participants who attended the end of treatment visit at week 68 were included. All endpoints were assessed separately for the STEP 1, 3, 6, and 8 pool and the STEP 2 and 6 pool. Each pool was further separated into subgroups based on drug exposure status, i.e., participants on antihypertensive or lipid-lowering medications at randomization and participants not on antihypertensive or lipid-lowering medications at randomization. Endpoints were the changes in antihypertensive or lipid-lowering treatment regimens from randomization (week 0) to week 68 among participants, as assessed and reported by the investigators. Specifically, the endpoints were as follows: 1) "treatment intensity increase," i.e., dose escalation or addition of another medication; 2) "treatment intensity decrease," i.e., dose reduction or discontinuation of a medication; and 3) "stopped," i.e., discontinuation of all antihypertensive lipid-lowering medications.

Systolic and diastolic BP and lipid levels were assessed for all participants who were treated with antihypertensive or lipid-lowering medications at randomization and separately for participants who were treated at randomization but who experienced changes in treatment regimens (i.e., increased treatment intensity, including patients who underwent a treatment intensification or no change in treatment, decreased treatment intensity, or discontinued all antihypertensive or lipid-lowering medications). All results were summarized separately for the semaglutide 2.4 mg and placebo groups. Hypertension remission, defined as BP < 140/90 mm Hg without antihypertensive medications [14, 15], was determined. Finally, changes in body weight from randomization to week 68 in participants with measurements at both randomization and end of treatment were also assessed.

# RESULTS

Demographics and baseline characteristics were collected for participants treated with antihypertensive or lipid-lowering medications (Table 1) and for participants who were not on antihypertensive or lipid-lowering medications (Table S2) at the time of randomization.

For participants who were treated with antihypertensive or lipid-lowering medications, most were White, female, and non-Hispanic/Latino in the STEP 1, 3, 6, and 8 pool. The mean age of participants taking antihypertensives and those taking lipid-lowering medications was 55 and 58 years, respectively. In the STEP 2 and 6 pool, most participants were White and non-Hispanic/Latino, with an approximately even distribution of male and female participants. The mean age was 58 years in those taking antihypertensives and 57 years in those taking lipid-lowering medications.

For participants who were not on antihypertensive or lipid-lowering medications, the mean age was 44 and 45 years, respectively, and most were White, female, and non-Hispanic/Latino in the STEP 1, 3, 6, and 8 pool. The STEP 2 and 6 sample had a roughly 50:50 distribution of male to female participants, and most were White and non-Hispanic/Latino. The mean age of this group was 51 and 52 years for those not on antihypertensive or lipid-lowering medications, respectively.

The most common antihypertensive agents used in the STEP 1, 3, 6, and 8 pool, as well as the STEP 2 and 6 pool, were those acting on the renin-angiotensin system, i.e., 75.2% and 83.5%, respectively (Table S3). In both samples, the proportion of participants prescribed antihypertensives within each medication group was similar between the semaglutide 2.4 mg and placebo groups at randomization.

The most common lipid-lowering agents used in the STEP 1, 3, 6, and 8 pool, as well as the STEP 2 and 6 pool, were statins, i.e., 89.8% and 92.6%, respectively (Table S4). At randomization, the semaglutide 2.4 mg and placebo groups had a similar proportion of participants prescribed lipid-lowering medications within each medication group.

Treatment intensity was monitored from randomization to end of treatment in participants taking antihypertensives at randomization in both the STEP 1, 3, 6, and 8 and the STEP 2 and 6 pools (Figure 1A,B). In the semaglutide 2.4 mg and placebo groups of both pooled samples, a majority of participants continued antihypertensive treatment (STEP 1, 3, 6, and 8: 82.3% and 91.0%, respectively; STEP 2 and 6: 89.8% and 92.4%, respectively) from randomization to week 68. The semaglutide 2.4 mg group had a higher proportion of participants who discontinued all antihypertensive medications (STEP 1, 3, 6, and 8: 17.7% and 9.0%, respectively; STEP 2 and 6: 9.8% and 7.3%, respectively) or had a treatment intensity reduction (STEP 1, 3, 6, and 8: 16.5% and 4.8%, respectively; STEP 2 and 6: 14.7% and 5.7%, respectively) compared with the placebo groups. Additionally, a smaller proportion of participants on semaglutide 2.4 mg had a treatment intensification versus the placebo groups (STEP 1, 3, 6, and 8: 8.3% and 14.2%, respectively; STEP 2 and 6: 7.9% and 11.5%, respectively).

In both the STEP 1, 3, 6, and 8 and STEP 2 and 6 pools, treatment intensity was monitored from randomization to end of treatment in participants treated with lipid-lowering medications at randomization (Figure 1C,D). A majority of participants in the semaglutide 2.4 mg and placebo groups continued lipid-lowering treatment from randomization to week 68 (STEP 1, 3, 6, and 8: 89.9% and 95.5%, respectively; STEP 2 and 6: 89.5% and 94.6%, respectively). The semaglutide 2.4 mg group had a higher proportion of participants who discontinued all lipid-lowering medications compared with the placebo groups (STEP 1, 3, 6, and 8: 10.1% and 4.5%, respectively; STEP 2 and 6: 10.1% and 5.4%, respectively). In the STEP 1, 3, 6, and 8 pool, a similar proportion of participants underwent a treatment intensity reduction (4.0% and 3.9% for semaglutide 2.4 mg and placebo, respectively), and a smaller proportion of participants in the semaglutide 2.4 mg group underwent a lipid-lowering treatment intensification compared with the placebo groups (2.1% and 9.7%, respectively). In the STEP 2 and 6 pool, a larger proportion of participants continuing lipid-lowering medications had a treatment intensity reduction in the semaglutide 2.4 mg group versus the placebo groups (4.6% and 0.9%, respectively); however, treatment intensification was similar between both the semaglutide 2.4 mg and placebo groups (2.9% and 4.5%, respectively) by week 68. Most participants continuing lipid-lowering treatment at week 68 had no change in treatment intensity.

Changes in treatment were also monitored from randomization to end of treatment for participants who were not treated with

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**TABLE 1** Baseline demographics and participant characteristics for participants treated with antihypertensive or lipid-lowering medications at randomization.

| STEP 1, 3, 6, and 8 | Participants treated with antihypertensive medications at randomization | | | Participants treated with lipid-lowering medications at randomization | | |
|---|---|---|---|---|---|---|
| | Semaglutide 2.4 mg | Placebo | Total | Semaglutide 2.4 mg | Placebo | Total |
| *n* | 605 | 289 | 894 | 327 | 154 | 481 |
| Sex, *n* (%) | | | | | | |
| Female | 397 (65.6) | 189 (65.4) | 586 (65.5) | 191 (58.4) | 101 (65.6) | 292 (60.7) |
| Male | 208 (34.4) | 100 (34.6) | 308 (34.5) | 136 (41.6) | 53 (34.4) | 189 (39.3) |
| Race, *n* (%) | | | | | | |
| White | 391 (64.6) | 191 (66.1) | 582 (65.1) | 222 (67.9) | 111 (72.1) | 333 (69.2) |
| Asian | 125 (20.7) | 59 (20.4) | 184 (20.6) | 79 (24.2) | 27 (17.5) | 106 (22.0) |
| Black or African American | 66 (10.9) | 30 (10.4) | 96 (10.7) | 18 (5.5) | 12 (7.8) | 30 (6.2) |
| American Indian or Alaska Native | 4 (0.7) | 3 (1.0) | 7 (0.8) | 1 (0.3) | 3 (1.9) | 4 (0.8) |
| Native Hawaiian or other Pacific Islander | 1 (0.2) | 1 (0.3) | 2 (0.2) | 0 | 0 | 0 |
| Other | 6 (1.0) | 1 (0.3) | 7 (0.8) | 5 (1.5) | 1 (0.6) | 6 (1.2) |
| NA[a] | 12 (2.0) | 4 (1.4) | 16 (1.8) | 2 (0.6) | 0 | 2 (0.4) |
| Ethnicity, *n* (%) | | | | | | |
| Not Hispanic/Latino | 543 (89.8) | 260 (90.0) | 803 (89.8) | 312 (95.4) | 138 (89.6) | 450 (93.6) |
| Hispanic/Latino | 50 (8.3) | 25 (8.7) | 75 (8.4) | 13 (4.0) | 16 (10.4) | 29 (6.0) |
| NA[a] | 12 (2.0) | 4 (1.4) | 16 (1.8) | 2 (0.6) | 0 | 2 (0.4) |
| Age, mean (SD), y | 54 (11) | 55 (10) | 55 (11) | 59 (10) | 58 (9) | 58 (10) |
| Weight, mean (SD), kg | 104.4 (24.0) | 103.9 (23.6) | 104.2 (23.8) | 98.8 (19.8) | 100.3 (20.2) | 99.3 (19.9) |
| BMI, mean (SD), kg/m$^2$ | 37.3 (7.1) | 37.3 (7.2) | 37.3 (7.1) | 35.5 (5.7) | 36.5 (6.3) | 35.8 (5.9) |
| HbA1c, mean (SD), % | 5.8 (0.3) | 5.8 (0.3) | 5.8 (0.3) | 5.8 (0.3) | 5.8 (0.3) | 5.8 (0.3) |
| Systolic BP, mean (SD), mm Hg | 131 (14) | 131 (14) | 131 (14) | | | |
| Diastolic BP, mean (SD), mm Hg | 82 (10) | 82 (10) | 82 (10) | | | |
| Lipid levels, geometric mean (CV), mg/dL | | | | | | |
| Total cholesterol | | | | 175.4 (20.9) | 178.9 (22.8) | 176.5 (21.5) |
| HDL cholesterol | | | | 50.4 (24.7) | 50.1 (25.2) | 50.3 (24.8) |
| LDL cholesterol | | | | 94.2 (33.3) | 97.2 (36.8) | 95.1 (34.5) |
| VLDL cholesterol | | | | 25.5 (46.0) | 25.9 (45.0) | 25.7 (45.7) |
| Triglycerides | | | | 132.3 (48.9) | 132.7 (45.2) | 132.4 (47.7) |

| STEP 2 and 6 | Participants treated with antihypertensive medications at randomization | | | Participants treated with lipid-lowering medications at randomization | | |
|---|---|---|---|---|---|---|
| | Semaglutide 2.4 mg | Placebo | Total | Semaglutide 2.4 mg | Placebo | Total |
| *n* | 265 | 262 | 527 | 238 | 222 | 460 |
| Sex, *n* (%) | | | | | | |
| Female | 147 (55.5) | 115 (43.9) | 262 (49.7) | 127 (53.4) | 85 (38.3) | 212 (46.1) |
| Male | 118 (44.5) | 147 (56.1) | 265 (50.3) | 111 (46.6) | 137 (61.7) | 248 (53.9) |
| Race, *n* (%) | | | | | | |
| White | 150 (56.6) | 159 (60.7) | 309 (58.6) | 130 (54.6) | 135 (60.8) | 265 (57.6) |
| Asian | 77 (29.1) | 63 (24.0) | 140 (26.6) | 73 (30.7) | 56 (25.2) | 129 (28.0) |
| Black or African American | 27 (10.2) | 31 (11.8) | 58 (11.0) | 23 (9.7) | 20 (9.0) | 43 (9.3) |

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**TABLE 1** (Continued)

| STEP 2 and 6 | Participants treated with antihypertensive medications at randomization | | | Participants treated with lipid-lowering medications at randomization | | |
|---|---|---|---|---|---|---|
| | Semaglutide 2.4 mg | Placebo | Total | Semaglutide 2.4 mg | Placebo | Total |
| American Indian or Alaska Native | 3 (1.1) | 1 (0.4) | 4 (0.8) | 1 (0.4) | 0 | 1 (0.2) |
| Native Hawaiian or other Pacific Islander | 0 | 1 (0.4) | 1 (0.2) | 0 | 1 (0.5) | 1 (0.2) |
| Other | 8 (3.0) | 7 (2.7) | 15 (2.8) | 11 (4.6) | 10 (4.5) | 21 (4.6) |
| NA[a] | 0 | 0 | 0 | 0 | 0 | 0 |
| Ethnicity, *n* (%) | | | | | | |
| Not Hispanic/Latino | 240 (90.6) | 225 (85.9) | 465 (88.2) | 219 (92.0) | 190 (85.6) | 409 (88.9) |
| Hispanic/Latino | 25 (9.4) | 37 (14.1) | 62 (11.8) | 19 (8.0) | 32 (14.4) | 51 (11.1) |
| Age, mean (SD), y | 58 (9) | 57 (10) | 58 (10) | 58 (10) | 57 (10) | 57 (10) |
| Weight, mean (SD), kg | 100.3 (23.2) | 101.6 (20.6) | 100.9 (21.9) | 97.5 (22.2) | 99.0 (19.2) | 98.2 (20.8) |
| BMI, mean (SD), kg/m$^2$ | 36.3 (6.8) | 36.1 (6.5) | 36.2 (6.7) | 35.1 (6.1) | 35.0 (6.1) | 35.0 (6.1) |
| HbA1c, mean (SD), % | 8.1 (0.8) | 8.1 (0.8) | 8.1 (0.8) | 8.0 (0.8) | 8.1 (0.8) | 8.1 (0.8) |
| Systolic BP, mean (SD), mm Hg | 132 (13) | 131 (14) | 132 (13) | | | |
| Diastolic BP, mean (SD), mm Hg | 80 (9) | 80 (10) | 80 (9) | | | |
| Lipid levels, geometric mean (CV), mg/dL | | | | | | |
| Total cholesterol | | | | 160.5 (21.5) | 162.4 (21.9) | 161.4 (21.6) |
| HDL cholesterol | | | | 46.0 (24.6) | 44.0 (23.5) | 45.0 (24.1) |
| LDL cholesterol | | | | 81.4 (34.5) | 82.2 (34.0) | 81.7 (34.2) |
| VLDL cholesterol | | | | 27.8 (46.6) | 30.6 (50.5) | 29.1 (48.7) |
| Triglycerides | | | | 144.2 (49.4) | 159.4 (54.5) | 151.3 (52.2) |

Abbreviations: BP, blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; STEP, Semaglutide Treatment Effect in People with Obesity; VLDL, very low-density lipoprotein.

[a]Race and ethnicity were specified by the participant according to fixed selection categories, including the option of answering "other," "NA," or "unknown," in accordance with regulatory requirements [16].

antihypertensive or lipid-lowering medications at randomization (Figure S1). In both pooled samples, a smaller proportion of participants in the semaglutide 2.4 mg group versus the placebo groups started antihypertensive (STEP 1, 3, 6, and 8: 5.1% and 7.3%, respectively; STEP 2 and 6: 8.0% and 9.7%, respectively) or lipid-lowering treatment (STEP 1, 3, 6, and 8: 4.2% and 5.9%, respectively; STEP 2 and 6: 9.9% and 13.6%, respectively) between week 0 and week 68. Most participants who were not treated with antihypertensive or lipid-lowering medications at randomization did not start these medications between week 0 and week 68.

The mean (standard deviation [SD]) reduction in body weight for the semaglutide 2.4 mg group was numerically greater than that of the placebo groups in both participants treated with antihypertensives (STEP 1, 3, 6, and 8: −14.8% [8.7%] and −3.8% [6.9%], respectively; STEP 2 and 6: −11.0% [8.2%] and −3.2% [5.8%], respectively) and those treated with lipid-lowering medications (STEP 1, 3, 6, and 8: −15.0% [8.8%] and −3.4% [6.8%], respectively; STEP 2 and 6: −10.4% [8.4%] and −2.9% [5.7%], respectively). These changes in body weight were similar to the clinically significant reduction in mean body weight observed in the overall population of the STEP trials [9–13].

As previously reported [9–13], systolic BP significantly improved from randomization to week 68 in participants taking semaglutide 2.4 mg versus placebo (Table 2). For participants who had a reduction in treatment intensity, BP remained normal and was not significantly different from those who underwent a treatment intensification. Changes in pulse in participants from this analysis were consistent with pulse data reported in the original publications (data not shown) [9–13].

In the STEP 1, 3, 6, and 8 pool, hypertension remission was achieved by 13.7% in the semaglutide 2.4 mg group and 6.2% in the placebo groups. In the STEP 2 and 6 pool, 5.7% and 3.4% in semaglutide 2.4 mg and placebo groups, respectively, achieved hypertension remission. The baseline demographics and characteristics of participants taking semaglutide 2.4 mg who achieved hypertension remission by week 68 were consistent with those of the total group (Table S5). The American College of Cardiology/American Heart Association 2017 Guideline for the Prevention, Detection,

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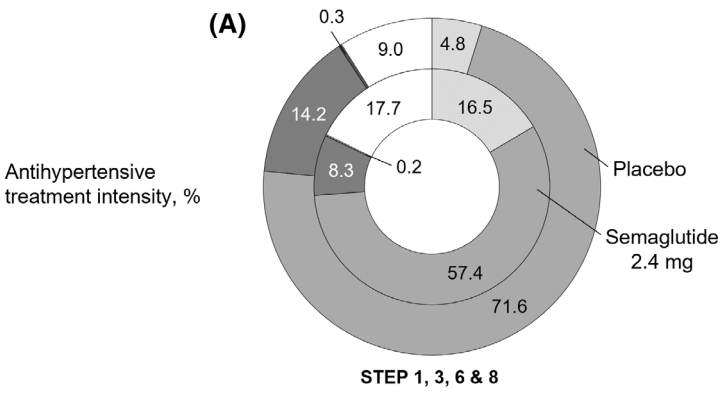
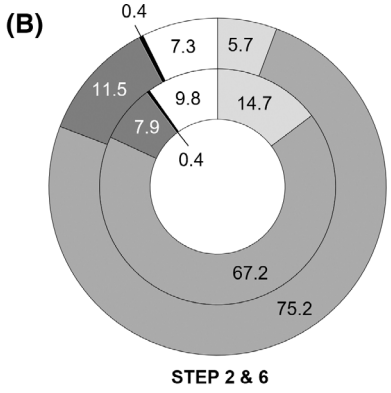
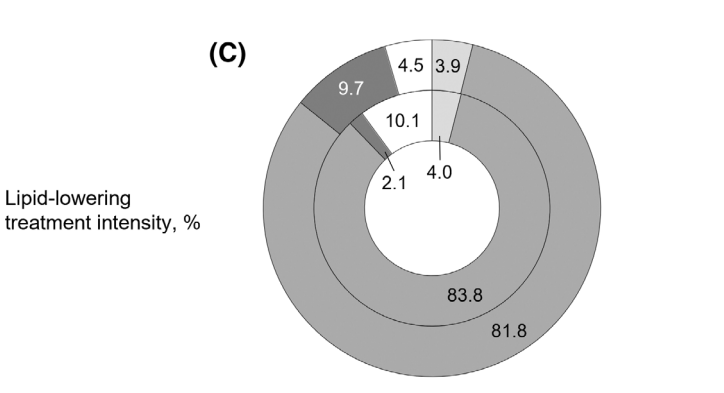
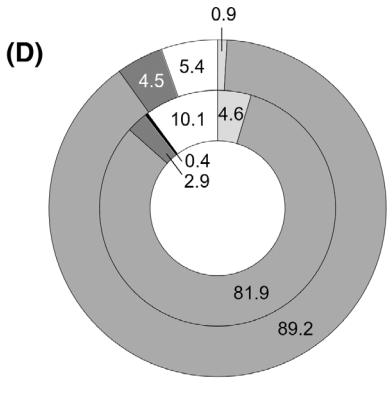



| | Stopped | Continued from week 0 to 68 | | | | Missing status at week 68 | Total |
|---|---|---|---|---|---|---|---|
| | | Decreased | No change | Increased | Missing | | |
| **Semaglutide 2.4 mg, n** | 107 | 100 | 347 | 50 | 1 | 0 | 605 |
| **Placebo, n** | 26 | 14 | 207 | 41 | 1 | 0 | 289 |

| | Stopped | Continued from week 0 to 68 | | | | Missing status at week 68 | Total |
|---|---|---|---|---|---|---|---|
| | | Decreased | No change | Increased | Missing | | |
| **Semaglutide 2.4 mg, n** | 26 | 39 | 178 | 21 | 0 | 1 | 265 |
| **Placebo, n** | 19 | 15 | 197 | 30 | 0 | 1 | 262 |




| | Stopped | Continued from week 0 to 68 | | | | Missing status at week 68 | Total |
|---|---|---|---|---|---|---|---|
| | | Decreased | No change | Increased | Missing | | |
| **Semaglutide 2.4 mg, n** | 33 | 13 | 274 | 7 | 0 | 0 | 327 |
| **Placebo, n** | 7 | 6 | 126 | 15 | 0 | 0 | 154 |

| | Stopped | Continued from week 0 to 68 | | | | Missing status at week 68 | Total |
|---|---|---|---|---|---|---|---|
| | | Decreased | No change | Increased | Missing | | |
| **Semaglutide 2.4 mg, n** | 24 | 11 | 195 | 7 | 0 | 1 | 238 |
| **Placebo, n** | 12 | 2 | 198 | 10 | 0 | 0 | 222 |

**FIGURE 1** Treatment intensity changes from randomization to end of treatment in the Semaglutide Treatment Effect in People with Obesity (STEP) 1, 3, 6, and 8 and STEP 2 and 6 pools in participants treated with (A,B) antihypertensives and (C,D) lipid-lowering medications at randomization.

Evaluation, and Management of High Blood Pressure in Adults does not define "hypertension remission" but does establish cutoffs for normal and elevated BP without diagnosis of hypertension. When analyzing the proportion of participants according to these cutoffs [17], the proportion of participants was as follows in both the semaglutide 2.4 mg and placebo groups: STEP 1, 3, 6, and 8: 6.6% and 1.7%, respectively; and STEP 2 and 6: 1.5% and 1.1%, respectively.

Lipid levels improved from randomization to week 68 in participants taking semaglutide 2.4 mg versus placebo (Table 3), as previously reported [9–13]. Participants who underwent a treatment intensity reduction had normal lipid levels, which did not significantly differ from those who underwent a treatment intensification.

## DISCUSSION

Among individuals with overweight/obesity (STEP 1, 3, 6, and 8) and those with overweight/obesity plus T2D (STEP 2 and 6), more

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**TABLE 2** BP analysis at randomization and end of treatment in participants taking antihypertensives.

| STEP 1, 3, 6, and 8 | | | | |
|---|---|---|---|---|
| | Semaglutide 2.4 mg | | Placebo | |
| | Week 0 | Week 68 | Week 0 | Week 68 |
| All participants treated with antihypertensives at randomization | | | | |
| *n* | 605 | 598 | 289 | 285 |
| BP, mean (SD), mm Hg | | | | |
| Systolic | 131 (14) | 125 (14) | 131 (14) | 129 (14) |
| Diastolic | 82 (10) | 79 (10) | 82 (10) | 81 (9) |
| Participants treated with antihypertensives at randomization who decreased treatment[a] | | | | |
| *n* | 207 | 204 | 40 | 38 |
| BP, mean (SD), mm Hg | | | | |
| Systolic | 128 (15) | 123 (13) | 127 (14) | 128 (14) |
| Diastolic | 80 (10) | 78 (10) | 78 (11) | 81 (10) |
| Participants treated with antihypertensives at randomization who increased treatment[b] | | | | |
| *n* | 397 | 393 | 248 | 246 |
| BP, mean (SD), mm Hg | | | | |
| Systolic | 133 (14) | 126 (14) | 131 (14) | 129 (13) |
| Diastolic | 84 (9) | 80 (10) | 83 (10) | 81 (9) |
| **STEP 2 and 6** | | | | |
| | Semaglutide 2.4 mg | | Placebo | |
| | Week 0 | Week 68 | Week 0 | Week 68 |
| All participants treated with antihypertensives at randomization | | | | |
| *n* | 265 | 263 | 262 | 258 |
| BP, mean (SD), mm Hg | | | | |
| Systolic | 132 (13) | 127 (14) | 131 (14) | 131 (14) |
| Diastolic | 80 (9) | 78 (9) | 80 (10) | 79 (9) |
| Participants treated with antihypertensives at randomization who decreased treatment[a] | | | | |
| *n* | 65 | 64 | 34 | 34 |
| BP, mean (SD), mm Hg | | | | |
| Systolic | 130 (13) | 126 (17) | 132 (17) | 132 (15) |
| Diastolic | 78 (10) | 79 (11) | 82 (11) | 81 (9) |
| Participants treated with antihypertensives at randomization who increased treatment[b] | | | | |
| *n* | 199 | 199 | 227 | 223 |
| BP, mean (SD), mm Hg | | | | |
| Systolic | 133 (13) | 127 (13) | 131 (13) | 131 (14) |
| Diastolic | 80 (9) | 78 (8) | 80 (9) | 78 (9) |

Abbreviations: BP, blood pressure; STEP, Semaglutide Treatment Effect in People with Obesity.
[a]Includes participants who underwent antihypertensive treatment intensity reduction or discontinuation.
[b]Includes patients who underwent treatment intensification or had no change in treatment.

participants experienced antihypertensive and lipid-lowering treatment discontinuation or treatment intensity reduction compared with the placebo groups. Correspondingly, a smaller proportion of participants in the semaglutide 2.4 mg group underwent an antihypertensive and lipid-lowering treatment intensification compared with placebo. Importantly, the goal of this analysis was to evaluate the changes in treatment intensity based on clinical assessment, not the individual changes in medication regimens, which would result in a high level of heterogeneity impractical for exploring clinically useful information.

The majority of participants experienced no change in therapy intensity for hypertension or hyperlipidemia. This observation elicits a few hypotheses, including the following: 1) the degree of weight loss was insufficient to resolve the comorbidity; 2) hypertension or hyperlipidemia was not weight-related; 3) providers are not accustomed to

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**TABLE 3** Lipid levels at randomization and end of treatment in participants taking lipid-lowering medications.

| STEP 1, 3, 6, and 8 | | | | |
|---|---|---|---|---|
| | Semaglutide 2.4 mg | | Placebo | |
| | Week 0 | Week 68 | Week 0 | Week 68 |
| All participants treated with lipid-lowering medications at randomization | | | | |
| *n* | 327 | 325 | 154 | 152 |
| Lipid levels, geometric mean (CV), mg/dL | | | | |
| Total cholesterol | 175.4 (20.9) | 168.4 (22.1) | 178.9 (22.8) | 181.5 (22.0) |
| HDL cholesterol | 50.4 (24.7) | 52.6 (24.6) | 50.1 (25.2) | 51.3 (24.5) |
| LDL cholesterol | 94.2 (33.3) | 91.3 (34.7) | 97.2 (36.8) | 100.1 (32.7) |
| VLDL cholesterol | 25.5 (46.0) | 19.8 (44.8)[a] | 25.9 (45.0) | 24.3 (53.4) |
| Triglycerides | 132.3 (48.9) | 102.5 (47.4) | 132.7 (45.2) | 125.4 (56.4) |
| Participants treated with lipid-lowering medications at randomization who decreased treatment[b] | | | | |
| *n* | 46 | 45 | 13 | 13 |
| Lipid levels, geometric mean (CV), mg/dL | | | | |
| Total cholesterol | 174.6 (23.4) | 183.7 (23.7) | 188.5 (22.5) | 218.9 (21.1) |
| HDL cholesterol | 49.2 (24.7) | 52.2 (24.6) | 53.0 (21.3) | 54.4 (17.0) |
| LDL cholesterol | 92.0 (35.3) | 102.4 (39.3) | 99.4 (42.6) | 131.8 (32.5) |
| VLDL cholesterol | 27.9 (50.8) | 22.2 (52.6) | 27.9 (57.3) | 25.9 (59.7) |
| Triglycerides | 146.3 (56.9) | 113.8 (52.6) | 142.8 (57.6) | 132.8 (59.5) |
| Participants treated with lipid-lowering medications at randomization who increased treatment[c] | | | | |
| *n* | 281 | 280 | 141 | 139 |
| Lipid levels, geometric mean (CV), mg/dL | | | | |
| Total cholesterol | 175.5 (20.5) | 166.1 (21.6) | 178.1 (22.9) | 178.3 (21.3) |
| HDL cholesterol | 50.6 (24.7) | 52.6 (24.6) | 49.8 (25.5) | 51.0 (25.1) |
| LDL cholesterol | 94.5 (33.1) | 89.6 (33.6) | 97.0 (36.4) | 97.6 (31.5) |
| VLDL cholesterol | 25.2 (45.1) | 19.5 (43.3)[d] | 25.7 (43.9) | 24.1 (53.0) |
| Triglycerides | 130.1 (47.4) | 100.8 (46.4) | 131.8 (44.2) | 124.8 (56.3) |
| **STEP 2 and 6** | | | | |
| | Semaglutide 2.4 mg | | Placebo | |
| | Week 0 | Week 68 | Week 0 | Week 68 |
| All participants treated with lipid-lowering medications at randomization | | | | |
| *n* | 238 | 232 | 222 | 216 |
| Lipid levels, geometric mean (CV), mg/dL | | | | |
| Total cholesterol | 160.5 (21.5) | 156.4 (22.6) | 162.4 (21.9) | 163.5 (25.6) |
| HDL cholesterol | 46.0 (24.6) | 49.4 (23.7)[e] | 44.0 (23.5) | 45.4 (24.1)[f] |
| LDL cholesterol | 81.4 (34.5) | 80.2 (36.1) | 82.2 (34.0) | 83.3 (38.3) |
| VLDL cholesterol | 27.8 (46.6) | 21.7 (48.8) | 30.6 (50.5) | 28.5 (58.4) |
| Triglycerides | 144.2 (49.4) | 111.4 (49.1) | 159.4 (54.5) | 148.8 (63.8) |
| Participants treated with lipid-lowering medications at randomization who decreased treatment[b] | | | | |
| *n* | 35 | 35 | 14 | 13 |
| Lipid levels, geometric mean (CV), mg/dL | | | | |
| Total cholesterol | 152.8 (20.9) | 165.7 (27.3) | 160.0 (21.4) | 151.1 (29.0) |
| HDL cholesterol | 46.4 (23.3) | 50.7 (20.4) | 42.2 (23.8) | 39.8 (24.9)[g] |
| LDL cholesterol | 76.6 (30.5) | 88.5 (40.6) | 88.4 (29.8) | 83.2 (43.0) |
| VLDL cholesterol | 25.9 (44.5) | 22.0 (52.0) | 26.2 (43.7) | 22.9 (54.5) |
| Triglycerides | 137.6 (53.2) | 112.5 (51.9) | 134.3 (44.0) | 117.2 (54.6) |

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**TABLE 3** (Continued)

| STEP 2 and 6 | | | | |
|---|---|---|---|---|
| | Semaglutide 2.4 mg | | Placebo | |
| | Week 0 | Week 68 | Week 0 | Week 68 |
| Participants treated with lipid-lowering medications at randomization who increased treatment[c] | | | | |
| *n* | 202 | 197 | 208 | 203 |
| Lipid levels, geometric mean (CV), mg/dL | | | | |
| Total cholesterol | 161.8 (21.5) | 154.8 (21.6) | 162.6 (21.9) | 164.4 (25.4) |
| HDL cholesterol | 45.9 (25.0) | 49.1 (24.3)[h] | 44.1 (23.5) | 45.8 (23.8)[i] |
| LDL cholesterol | 82.1 (35.1) | 78.8 (35.0) | 81.8 (34.3) | 83.3 (38.1) |
| VLDL cholesterol | 28.2 (47.0) | 21.7 (48.4) | 31.0 (50.8) | 28.9 (58.4) |
| Triglycerides | 145.5 (48.9) | 111.2 (48.8) | 161.2 (55.0) | 151.0 (64.1) |

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; STEP, Semaglutide Treatment Effect in People with Obesity; VLDL, very low-density lipoprotein.
[a]$n = 324$.
[b]Includes participants who underwent lipid-lowering treatment intensity reduction or discontinuation.
[c]Includes patients who underwent treatment intensification or had no change in treatment.
[d]$n = 279$.
[e]$n = 230$.
[f]$n = 214$.
[g]$n = 12$.
[h]$n = 195$.
[i]$n = 202$.

de-escalating therapy, especially as there are no guidelines to provide direction in the absence of hypotension or other adverse effect. Clinical experience reinforces that a combination of all three of these hypotheses may be contributors.

Hypertension remission was achieved by more participants on semaglutide 2.4 mg than on placebo (STEP 1, 3, 6, and 8: 13.7% vs. 6.2%, respectively; STEP 2 and 6: 5.7% vs. 3.4%, respectively). In a post hoc analysis of the Diabetes Remission Clinical Trial (DiRECT), in which participants achieved mean weight loss of 14% at 20 weeks, 19 of 78 (24%) individuals remained off antihypertensive medications at 24 months [18]. In the Gastric Bypass to Treat Obese Patients With Steady Hypertension (GATEWAY) randomized trial, hypertension remission was observed in 25 of 49 (51%) patients at 12 months [14]. Our data, with a substantially larger cohort, support a direct relationship between medically controlled obesity and hypertension remission, demonstrating the role of AOMs in individuals who may consider lifestyle therapy or bariatric surgery infeasible.

Among participants who were not on antihypertensive or lipid-lowering regimens at randomization, a smaller proportion of participants in the semaglutide 2.4 mg group were initiated on medications compared with placebo groups in both the STEP 1, 3, 6, and 8 and STEP 2 and 6 pools. These data indicate that semaglutide 2.4 mg may reduce the need for antihypertensive or lipid-lowering medications in people without hypertension or hyperlipidemia at randomization. Although we could only track individuals for 68 weeks, this suggests that semaglutide 2.4 mg and 15% average weight loss may be helpful in the primary prevention of hypertension or hyperlipidemia. In the Trials of Hypertension Prevention, ≥4.5 kg weight loss at 6 months was associated with a 65% risk reduction in incident hypertension [19].

The present study substantially expands our understanding of the impact of semaglutide 2.4 mg on the need for antihypertensive and lipid-lowering drugs in people living with overweight or obesity. A prior analysis of STEP 1 and 4 found a reduction in antihypertensive and lipid-lowering medication use associated with semaglutide 2.4 mg treatment [8]. These findings are consistent with the results presented in this study, which are further strengthened by the increased sample size (including participants from five STEP trials vs. two), inclusion of a cohort with T2D, and inclusion of participants who did not receive antihypertensive or lipid-lowering medications at randomization.

The semaglutide 2.4 mg group had a greater reduction in body weight by week 68 compared with the placebo groups in both pooled samples, supporting a relationship between weight loss with semaglutide 2.4 mg treatment and improvements in BP and lipid levels.

BP and lipid levels were not significantly different in participants who decreased or stopped antihypertensive or lipid-lowering treatment versus participants who experienced increases in treatment intensity. These data indicate an association between improvements in metabolic markers and treatment intensity reduction and precludef the possibility that participants inappropriately discontinued treatment (i.e., without BP or lipid improvements). In treating obesity, providers should aim to reduce the risk or consequence of comorbid diseases, which is reflected in therapy de-escalation among some of the trial participants. However, certain medications are known to have multiple benefits beyond their primary indication (e.g., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are reno-protective antihypertensive agents) [20] and may require continuation for those reasons. Similarly, certain patient populations might require treatment with specific medications for reasons beyond the primary indication (e.g., patients with T2D and atherosclerotic cardiovascular disease may require treatment with a statin regardless of lipid levels). Discontinuation may, in fact, be detrimental in such

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circumstances, and, as such, any decisions on changes in antihypertensive and lipid-lowering treatment intensity should be individualized to the specific needs of the patient, completed under the advisement of the treating health care professional, and followed by appropriate monitoring of BP and lipid levels.

Several limitations intrinsic to a post hoc analysis are notable. Deliberate selection of pools limits generalizability to those with overweight or obesity (STEP 1, 3, 6, and 8) and to those with overweight or obesity plus T2D (STEP 2 and 6). A comparison of outcomes and medication changes between participants with versus without diabetes was not conducted because the treatment recommendations and goals related to BP and lipids differ for patients with diabetes, but this relationship would be of interest for future investigations. Demographics in both cohorts were largely characterized by a non-Hispanic, White, female population, further precluding application to male individuals and individuals of other ethnicities and races. Granularity with respect to specific medication changes (e.g., dose, medication class, number of medications) was not analyzed due to a high level of heterogeneity among antihypertensive and lipid-lowering regimens. The heterogeneity of the medication regimens precludes the ability to elicit relationships between specific medication changes and clinical outcomes (e.g., discontinuation of β-blockers and weight loss). Additionally, this analysis could not disentangle the relationship between the degree of weight loss and changes in treatment intensity because information related to treatment changes was only collected at baseline and end of treatment, precluding the possibility of assessing whether treatment changes occurred before or after weight loss. Trial limitations for STEP 1, 3, 6, and 8 have been previously discussed [9–12].

## CONCLUSION

The present study adds to the well-supported relationship between obesity treatment and hypertension and dyslipidemia changes, finding that medically managed obesity with semaglutide 2.4 mg was associated with a reduced need for antihypertensive and lipid-lowering treatment. This association could facilitate dose reduction or discontinuation and abate dose intensification of antihypertensive or lipid-lowering treatment in people with overweight or obesity with or without T2D. These results highlight the benefit of semaglutide 2.4 mg treatment beyond chronic weight management.O

### AUTHOR CONTRIBUTIONS

Beverly G. Tchang, Michael G. Knight, Jennifer N. Clements, Kasper Adelborg, and Andrea Traina were involved in study design, data analysis, and interpretation. Aske Thorn Iversen was involved in data analysis and interpretation. All authors revised the manuscript content and approved the final version.

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### CONFLICT OF INTEREST STATEMENT

Michael G. Knight has participated in advisory boards and received payment for consulting from Novo Nordisk Inc.; has received support from Novo Nordisk for medical writing; has received payment for educational event participation from Gilead Sciences, Inc.; and is a member of the National Medical Association Board of Trustees (unpaid). Kasper Adelborg is an employee and shareholder of Novo Nordisk A/S and has received support from Novo Nordisk for research, medical writing, fees associated with article publication and travel, and registration fees for conferences/meetings. Jennifer N. Clements is a member and has received payment from the Novo Nordisk Cardiometabolic Speakers Bureau and the Eli Lilly Speakers Bureau. Aske Thorn Iversen is an employee and shareholder of Novo Nordisk A/S and has received support from Novo Nordisk for travel and registration fees for conferences/meetings. Beverly G. Tchang is a shareholder of Novo Nordisk Inc. and an advisor to Novo Nordisk and Palatin Technologies, Inc. Andrea Traina is an employee and shareholder of Novo Nordisk Inc. and has received support from Novo Nordisk for research, medical writing, fees associated with article publication and travel, and registration fees for conferences/meetings.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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