Impact of Blood Pressure Lowering on Cardiovascular Outcomes in Normal Weight, Overweight, and Obese Individuals

The Perindopril Protection Against Recurrent Stroke Study Trial

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Abstract—There is considerable uncertainty regarding the efficacy of blood pressure–lowering therapy in reducing cardiovascular risk in obese people. In this report we examine the effects of blood pressure lowering according to baseline body mass index (kilograms per meter squared) in the Perindopril Protection Against Recurrent Stroke Study. A total of 6105 participants with cerebrovascular disease were randomized to perindopril-based blood pressure–lowering therapy or placebo. The overall mean difference in systolic/diastolic blood pressure between participants assigned active therapy or placebo was 9/4 mm Hg (SE: 0.5/0.3 mm Hg), with no difference by body mass index quarters (<23.1, 23.1 to 25.3, 25.4 to 27.8, and ≥27.9 kg/m²). A consistent treatment benefit was demonstrated for protection against major vascular events across quarters with the following hazard ratios (95% CIs): 0.80 (0.62 to 1.02), 0.78 (0.61 to 1.01), 0.67 (0.53 to 0.86), 0.69 (0.54 to 0.88), and 0.74 (0.66 to 0.84; P for heterogeneity = 0.16). Similar results were apparent for stroke and stroke subtypes (all P for heterogeneity < 0.07) or with the standard definitions of overweight and obesity (<25, 25 to 29, and ≥30 kg/m²; all P for heterogeneity ≥ 0.28). The absolute effects of treatment were, however, more than twice that in the highest compared with the lowest body mass index quartile. Across increasing quarters of body mass index over 5 years, active therapy prevented 1 major vascular event among every 28, 23, 13, and 13 patients treated. In conclusion, blood pressure–lowering therapy produced comparable risk reductions in vascular disease across the whole range of body mass indices in participants with a history of stroke. However, the greater baseline level of cardiovascular risk in those with higher body mass index meant that these patients obtained the greatest benefit. (Hypertension. 2010;55:1193-1198.)

Key Words: obesity • blood pressure • perindopril • cardiovascular disease • stroke

Overweight and obesity are common, affecting >1.1 billion individuals worldwide.1 In several industrialized countries, approximately two thirds of the adult population are classified as overweight or obese on the basis of having a body mass index (BMI) in excess of 25 kg/m².2 In addition to reducing life expectancy, excess weight is an independent risk factor for a wide spectrum of chronic disorders, in particular, type-2 diabetes mellitus, cardiovascular disease, and some site-specific cancers.3

Studies have shown that a gain in BMI of 2.1/2.7 kg/m² (men/women) is associated with a 2.2-mm Hg increment in systolic blood pressure (BP)4 and likewise that a weight loss of 1 kg results in a 1-mm Hg reduction in systolic BP.5 There is some indication that the magnitude of the association between BP and subsequent cardiovascular disease or stroke is stronger in obese compared with lean individuals.6 Furthermore, as indicated in North American and European current guidelines for the management of hypertension, because available trials in hypertensive obese are scarce, there are no specific recommendations for high BP management in patients with excess weight.7–15

In this report, we describe the results of new analyses from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), a large, placebo-controlled trial of a perindopril-based BP-lowering regimen in people with previous cerebrovascular disease. The primary aim of this
The analysis was to assess the effects of BP lowering on major cardiovascular events according to BMI at baseline. A secondary aim was to address the same question for the outcomes of stroke and its subtypes, ischemic and hemorrhagic.

**Materials and Methods**

**Main Study**

The design of the PROGRESS has been described in detail previously. In summary, 6105 individuals with a history of cerebrovascular disease (ischemic, hemorrhagic, or transient ischemic attack but not subarachnoid hemorrhage) within the previous 5 years and no clear indication for, or contraindication to, treatment with an angiotensin-converting enzyme inhibitor, were recruited to the study from 172 centers in 10 countries.

Eligible participants received perindopril (2 mg for 2 weeks, followed by 4 mg for 2 weeks) during a 4-week open label active run-in period. Participants who tolerated and adhered to this treatment were subsequently randomly allocated to active therapy or matching placebo. Active treatment was composed of a flexible treatment regimen on the basis of perindopril (4 mg daily) in all of the participants, with the addition of indapamide (2.5 mg daily or 2.0 mg daily in Japan) in those for whom the responsible study physician felt that there was no specific indication for, nor contraindication to, the use of a diuretic. Those participants assigned placebo received 1 or 2 tablets identical in appearance to the active agent(s). “Combination therapy” (perindopril and indapamide or double placebo), rather than “single drug therapy” (perindopril or single placebo), was used wherever possible to maximize the reduction in BP. However, because many investigators had concerns about the safety of BP lowering in patients with stroke (particularly in those with average or below average levels of BP), it was necessary to provide some flexibility with respect to the intensity of treatment. All of the other aspects of medical care of the patients were left to the discretion of the responsible physician.

**Body Mass Index**

Height and weight were measured during the run-in period. BMI (weight in kilograms/height in meters squared) was categorized into quarters of the BMI distribution (<23.1, 23.1 to 25.3, 25.4 to 27.8, and ≥27.9 kg/m²). Supplementary analyses were also performed according to World Health Organization cut points used to define normal, overweight, and obese status (<25, 25 to 29, and ≥30 kg/m²).
Outcomes
The predefined primary outcome for this analysis was “major cardiovascular events,” defined as the composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. Secondary outcomes were total stroke, ischemic stroke, and hemorrhagic stroke.18 Stroke was defined as a neurological deficit lasting ≥24 hours and thought to be attributable to cerebral ischemia or hemorrhage.

Data Analysis
The incidence of events was calculated using the person-year method. All of the analyses of treatment effect were performed on an intention-to-treat basis. The level of BP reduction across BMI categories was tested by adding an interaction term to the relevant linear mixed model after adjustment for combination therapy status. A test for trend across these categories was computed. The effects of randomized treatment on events were calculated using the univariate Cox proportional hazards model. Consistency of treatment effect across BMI quarters, and usual World Health Organization cut points, was examined using tests of homogeneity that were performed by adding an interaction term to Cox models. Consistency of treatment was also tested by fitting BMI as a continuous variable and including a “treatment*BMI” interaction term in the model. Mean difference in BP over time between randomized groups was calculated from a linear mixed model for each BMI group by subtracting the values for the placebo group from those of the active group in each BMI category.

Figure 1. Effects of active therapy compared with placebo on the risk of major vascular events, total stroke, and stroke subtypes according to baseline BMI quartiles (< 23.1, 23.1 to 25.3, 25.4 to 27.8, and ≥ 27.9 kg/m²). Treatment effects in subgroups are standardized for the proportions of the study population receiving combination (58%) or single-drug therapy (42%). Mean difference in blood pressure over time between randomized groups was calculated by subtracting the values for the placebo group from those of the active group in each BMI category.
(58%) or single-drug therapy (42%) was prescribed, by taking weighted averages of the estimates obtained for the 2 therapies. The absolute risk reduction (95% CI) over 5 years was calculated as the difference in the incidence of events between the placebo and the active therapy group. Numbers needed to treat were calculated as reciprocals of the absolute risk differences. A P<0.05 was considered statistically significant. All of the analyses were performed using SAS (SAS Institute, Inc).

Results
A total of 6105 participants were recruited from 172 centers in 10 countries. During a mean follow-up of 4 years, there were 1062 major primary and secondary vascular events including 724 strokes (565 ischemic and 111 hemorrhagic). At study entry, 2545 participants (41.9%) were overweight, and 739 (12.2%) were obese. Baseline characteristics of participants according to baseline BMI categories are shown in Table 1. Median BMI across quarters ranged from 21.6 to 23.1 kg/m². Overall, participants in the highest quartile were less likely to be Asian or smokers but more likely to have preexisting coronary disease or diabetes mellitus and to have higher systolic and diastolic BP levels. Baseline calcium antagonist use was similar across BMI quarters (P=0.7149), whereas β-blocker and diuretic use increased across quarters (P<0.0001). Furthermore, the proportion of baseline users of ≥2 BP-lowering agents increased in quarters (8%, 12%, 12%, and 17%, respectively; P<0.0001). The proportion of participants receiving study treatment combination drug therapy also increased across BMI quarters (P for trend <0.001).

Effects of Perindopril-Based Therapy on Cardiovascular Events According to Baseline BMI
During follow-up, the overall mean difference in systolic/diastolic BP between participants assigned active therapy or placebo was 9/4 mm Hg (SE: 0.5/0.3 mm Hg), with no difference between BMI quarters (P for trend=0.98 and 0.57, respectively, for systolic and diastolic BPs). The perindopril-based BP-lowering regimen produced similar reductions in the risk of major vascular events at all levels of BMI (P for homogeneity=0.16; Figure 1). A similar pattern was observed for total stroke (Figure 1), although there was some evidence of a trend toward greater benefit with increasing BMI (P for homogeneity=0.07 for total stroke and P=0.10 for stroke subtypes). There was no difference in treatment effect at all levels of BMI when the population was separated into those receiving the combination active therapy (P for homogeneity=0.44 for major vascular events and P=0.40 for total stroke) or single (Perindopril) therapy (P for homogeneity=0.60 for major vascular events and P=0.26 for total stroke).

Using the usual World Health Organization cut points for normal weight, overweight, and obesity produced the same conclusions (all P for homogeneity ≥0.44; Figure 2). Likewise, fitting BMI as a continuous variable provided no evidence that the effect of treatment varied by baseline level of BMI (all P for homogeneity ≥0.16).

Compared with participants in the lowest BMI quartile, absolute risk reductions for both major cardiovascular events and stroke were more than twice as great in participants in the highest BMI quartile (Table 2). The number needed to treat for 5 years was accordingly smaller in the highest quartile, with 1 major vascular event prevented among every 13

| Table 2. Incidence Rate and Absolute Risk Reduction Over 5 Years for Major Vascular Events and Total Stroke According to BMI Category in PROGRESS |
|------------------|------------------|------------------|
| Events | 5-y Cumulative Incidence, % | Active | Placebo | NNT for 5 y |
|------------------|------------------|------------------|
| Major vascular events, kg/m² | | | | |
| <23.1 | 20.1 | 23.7 | 28 |
| 23.1 to 25.3 | 17.9 | 22.2 | 23 |
| 25.4 to 27.8 | 18.4 | 25.9 | 13 |
| ≥27.9 | 18.8 | 26.7 | 13 |
| Total stroke, kg/m² | | | | |
| <23.1 | 14.6 | 17.0 | 42 |
| 23.1 to 25.3 | 12.2 | 15.8 | 28 |
| 25.4 to 27.8 | 12.7 | 17.4 | 21 |
| ≥27.9 | 11.3 | 19.0 | 13 |

NNT indicates not needed to treat.

*Cumulative incidences were corrected from 3.9 to 5.0 years, assuming constant risk per year.
patients treated over 5 years compared with 28 patients in the lowest quartile. The corresponding figures for total stroke were 13 and 42 patients treated over the same duration, respectively.

Discussion

In this large, randomized trial of participants with a history of cerebrovascular disease, BP-lowering treatment produced similar reductions in the risks of major CV events and stroke in normal weight, overweight, and obese participants. However, the absolute risk reduction was almost twice as great in the obese group with a correspondingly lower number of patients needing to be treated to prevent one event.

The observed greater absolute risk reduction in those with the highest BMI is unsurprising given that they exhibited the highest prevalence of antihypertensive drug use but also the highest BP levels at baseline. For instance, data from the Framingham study and other cohorts showed that, in study members with hypertension, obese participants were more likely to receive antihypertensive treatment than individuals with normal weight but hypertension was not better controlled.

These findings have important implications in the management of hypertension in the obese because they suggest that, for a given BP reduction, the number needed to treat will be smaller in preventing cardiovascular disease in this group. Our results, on the basis of a population recruited in 1995–1997 with a rather low prevalence of obesity (12.2%), also provide further impetus for the allocation of BP-lowering agents on the basis of overall vascular risk, rather than BP level alone, and identify the obese as another population that warrants specific attention.

Current guidelines for the management of hypertension do not provide specific recommendations for the pharmacological treatment of high BP in overweight or obese patients. This reflects the limited data available regarding the effects of treatment in the hypertensive obese and the few previous analyses designed to address this question. Indeed, even if the obvious treatment for the management of obesity-associated hypertension is weight loss, the expected drop in BP for every kilogram of loss is approximately 1 mm Hg2 or even less in studies with a follow-up of 2 years. Data from the Swedish Obese Study also indicated that, after 10 years of follow-up, no difference was observed in the incidence of hypertension between patients who underwent bariatric surgery compared with those enrolled to a conventional nutritional management. Although weight-loss drugs, such as sibutramine, were developed for the management of weight in obese patients, they tend to increase BP by 1 to 2 mm Hg and present an additional challenge to the management of obesity-related hypertension.

Perspectives

Results of our study involving patients with a history of cerebrovascular disease have shown that patients allocated to receive a perindopril-based BP-lowering therapy experienced an overall risk reduction of 26% in major vascular events and of 28% in total stroke, with consistent reductions in risk across the full range of BMIs, in the absence of evidence to support an interaction between BMI and the effect of BP lowering. The greater absolute effect of treatment in those with higher BMI appears to be a consequence of their greater baseline level of risk. These findings support the use of BP lowering in the obese, but there remain outstanding uncertainties. For example, although all of the commonly used BP-lowering drugs have been shown to protect against the risk of major cardiovascular events in the general population, it remains unclear whether the effects of all of the drug classes are the same in the obese and nonobese individuals. A recent statement of the European Society of Hypertension Working Group on Obesity has highlighted the need for more data to address this issue.

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References


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