Cardiometabolic Disease Staging Predicts Effectiveness of Weight-Loss Therapy to Prevent Type 2 Diabetes: Pooled Results From Phase III Clinical Trials Assessing Phentermine/Topiramate Extended Release

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Diabetes Care 2017;40:856–862 | https://doi.org/10.2337/dc17-0088

OBJECTIVE

To assess the ability of medication-assisted weight loss to prevent diabetes as a function of the baseline weighted Cardiometabolic Disease Staging (CMDS) score.

RESEARCH DESIGN AND METHODS

We pooled data from 3,040 overweight and obese participants in three randomized controlled trials—CONQUER, EQUIP, and SEQUEL—assessing efficacy and safety of phentermine/topiramate extended release (ER) for weight loss. In these double-blind phase III trials, overweight/obese adult patients were treated with a lifestyle intervention and randomly assigned to placebo versus once-daily oral phentermine/topiramate ER. The weighted CMDS score was calculated using baseline quantitative clinical data including waist circumference, blood glucose, blood pressure, and blood lipids. Incident diabetes was defined based on serial measures of fasting glucose, 2-h oral glucose tolerance test glucose, and/or HbA_{1c}.

RESULTS

The absolute decrease in 1-year diabetes incidence rates in subjects treated with medication versus placebo was greatest in those with high-risk CMDS scores at baseline (10.43–6.29%), intermediate in those with moderate CMDS risk (4.67–2.37%), and small in the low-risk category (1.51–0.67%). The number of participants needed to treat to prevent one new case of diabetes over a 56-week period was 24, 43, and 120 in those with baseline CMDS scores of ≥60, 30–59, and 0–29, respectively.

CONCLUSIONS

Numbers needed to treat to prevent one case of type 2 diabetes are markedly lower in patients with high-risk scores. CMDS can be used to quantify risk of diabetes in overweight/obese individuals and predict the effectiveness of weight-loss therapy to prevent diabetes.

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Received 12 January 2017 and accepted 28 March 2017.

Clinical trial reg. nos. NCT00553787, NCT00554216, and NCT00796367, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0088/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

The majority of adults in many societies are overweight or obese, and many are at increased risk of type 2 diabetes mellitus (T2DM) (1). In the U.S., 70% of adults are overweight or obese (2). It is not feasible or safe to treat all overweight/obese individuals with weight-loss therapies sufficient to prevent diabetes. Risk stratification strategies will need to be developed for purposes of targeting aggressive weight-loss interventions to high-risk patients, designed to optimize outcomes, the benefit/risk ratio, and cost-effectiveness of care.

The recent approval of multiple weight-loss medications (3–6) has enabled more robust approaches to obesity management and necessitated the development of guidelines for the use of these new treatment options in a manner that optimizes the benefit/risk ratio and cost-effectiveness. The patients who will benefit most from treatment with medications or surgery have obesity-related comorbidities that can be categorized into two general classes: insulin resistance with cardiometabolic disease, and the mechanical consequences of excess body weight (7). Although an average weight loss of ~10% will not often suffice to meet the cosmetic goals of patients or even bring many patients below the BMI threshold for obesity, it is sufficient to exert powerful benefits regarding weight-related complications (7–10).

To better categorize the risk levels of people with excess body weight, we have established five stages of cardiometabolic disease risk, the Cardiometabolic Disease Staging (CMDS) system (11), based on Adult Treatment Panel III (ATP III) metabolic syndrome risk factors (12,13), to guide decision-making for selection of treatment modality and intensity in the management of obesity. We have validated the CMDS system for the prediction of cardiovascular disease mortality and overall mortality using data from the National Health and Nutrition Examination Survey (NHANES) III–linked mortality file. Metabolic syndrome traits are all important risk factors for T2DM (14); however, each trait may have different prediction power for future diabetes (8,15,16). To enhance the application of the CMDS system in clinical settings for the prediction of T2DM, we have developed a weighted scoring system (17) based on risk factor components in the CMDS system for the prediction of future diabetes by separate identification and weighting of those risk components. The CMDS score system has been validated in two large national cohorts, the Coronary Artery Risk Development in Young Adults (CARDIA) Study (18) and the Atherosclerosis Risk in Communities (ARIC) Study (19), for the prediction of future T2DM risks. However, it remains unknown whether risk stratification for diabetes also predicts efficacy for T2DM prevention following weight-loss therapy.

In this study, we pooled data from three clinical trials—CONQUER (20), EQUIP (4), and SEQUEL (21)—on the efficacy of phentermine/topiramate extended release (ER), introduced in 2012 for the treatment of obesity, to assess the ability of medication-assisted weight loss to prevent T2DM as a function of the baseline CMDS score.

RESEARCH DESIGN AND METHODS

Study Population

We pooled data from overweight or obese participants enrolled in three randomized controlled trials: CONQUER, EQUIP, and SEQUEL. Detailed descriptions of these three trials can be found elsewhere (4,20,21). The CONQUER and EQUIP trials are randomized, double-blinded, placebo-controlled, phase III trials assessing efficacy and safety of the phentermine/topiramate ER combination with weight loss as a primary outcome. In all trials, the enrollees were placed on a lifestyle intervention and then randomized to placebo or drug. The SEQUEL trial is a placebo-controlled, double-blind, 52-week extension of the CONQUER study evaluating 2-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate ER in obese and overweight adults. There were 676 SEQUEL participants who were also on the CONQUER trial. We used the follow-up information from the SEQUEL trial for those participants, because the follow-up is longer. Thus, we included 3,678 unique participants from these three trials and used the longest follow-up available for each participant. After excluding participants randomized to the low dose of 3.75 mg phentermine/23 mg topiramate (n = 234), participants with diabetes at baseline (n = 390), participants with missing information needed to calculate CMDS score (n = 9), and participants with no valid follow-up information (n = 5), we retained 3,040 (82.7%) participants in the analyses. This study was exempt from full board review by the Institutional Review Boards at the University of Alabama at Birmingham, Birmingham, AL, and the University of Texas Medical Branch, Galveston, TX.

CMDS Score

The weighted CMDS score (17) was calculated based on blood pressure, blood lipids, blood glucose, and waist circumferences (Supplementary Table 1). We grouped CMDS scores into three categories of diabetes risk: low risk 0–29, moderate risk 30–59, and high risk ≥60.

New-Onset Diabetes

The glycemic status of study subjects was assessed at defined intervals during the trials in an identical manner across trials. T2DM was defined as fasting glucose ≥126 mg/dL (7.0 mmol/L), 2-h glucose from oral glucose tolerance test ≥200 mg/dL (11.1 mmol/L), or HbA_{1c} ≥6.5% (48 mmol/mol). Patients without diabetes at baseline were judged to have progressed to T2DM if two or more consecutive glycemic measurements confirmed T2DM diagnosis (20).

Statistical Analysis

In these studies, all efficacy analyses were conducted on the intent-to-treat population, which includes all subjects who took one or more doses of the study drug or placebo and had undergone one or more posttreatment measurements. Baseline characteristics of participants were assessed. Kaplan-Meier survival curves were plotted to compare diabetes rates across groups by fitting Cox proportional hazard models. Hazard ratios were derived from the Cox models and adjusted for age, sex, and race/ethnicity. The proportional hazards assumption for Cox models was assessed using Schoenfeld residuals. Number needed to treat to prevent one case of diabetes was calculated for each CMDS score category. Distribution of CMDS scores among U.S. adults (aged ≥20 years) with BMI ≥25 kg/m^2 was estimated using data from NHANES 2013 to 2014. Statistical analyses were carried out using SAS for Windows version 9.4 (SAS Institute, Cary, NC). A two-sided $P < 0.05$ was determined to be statistically significant.

RESULTS

Study Population

Baseline characteristics of the study subjects are presented in Table 1. The

Table 1—Characteristics of the participants by CMDS score group and treatment arm

	Prevalence percentage or mean (95% CI)					
	0–29/Treatment	0–29/Placebo	30–59/Treatment	30–59/Placebo	60+/Treatment	60+/Placebo
n	558	495	644	450	526	367
Sex						
Male	16.1 (13.1–19.2)	15.2 (12.0–18.3)	26.7 (23.3–30.1)	28.2 (24.1–32.4)	34.6 (30.5–38.7)	34.3 (29.5–39.2)
Female	83.9 (80.8–86.9)	84.8 (81.7–88.0)	73.3 (69.9–76.7)	71.8 (67.6–75.9)	65.4 (61.3–69.5)	65.7 (60.8–70.5)
Race/ethnicity						
Non-Hispanic white	63.4 (59.4–67.4)	67.1 (62.9–71.2)	72.8 (69.4–76.3)	76.7 (72.8–80.6)	84.2 (81.1–87.3)	80.4 (76.3–84.4)
Non-Hispanic black	19.5 (16.2–22.8)	17.6 (14.2–20.9)	13.5 (10.9–16.2)	12.7 (9.6–15.7)	5.3 (3.4–7.2)	6.0 (3.6–8.4)
Hispanic	14.7 (11.8–17.6)	12.9 (10.0–15.9)	11.2 (8.7–13.6)	9.3 (6.6–12.0)	8.4 (6.0–10.7)	12.0 (8.7–15.3)
Other	2.3 (1.1–3.6)	2.4 (1.1–3.8)	2.5 (1.3–3.7)	1.3 (0.3–2.4)	2.1 (0.9–3.3)	1.6 (0.3–2.9)
Baseline						
Age (years)	43.2 (42.2–44.3)	43.8 (42.8–44.8)	49.2 (48.3–50.1)	49.8 (48.7–50.8)	52.6 (51.7–53.4)	51.5 (50.5–52.5)
Weight (kg)	112.7 (111.1–114.3)	113.3 (111.5–115.0)	108.0 (106.5–109.5)	110.0 (108.2–111.9)	98.6 (97.1–100.0)	99.9 (98.0–101.8)
BMI (kg/m^2)	41.0 (40.5–41.4)	41.2 (40.7–41.7)	38.4 (38.0–38.8)	38.9 (38.4–39.4)	34.5 (34.2–34.9)	35.2 (34.7–35.7)
WC (cm)	118.4 (117.2–119.6)	118.7 (117.6–119.9)	116.3 (115.3–117.3)	117.3 (116.1–118.6)	109.8 (108.8–110.8)	111.3 (110.1–112.5)
SBP (mmHg)	123.2 (122.2–124.3)	122.9 (121.8–124.0)	127.0 (126.0–128.0)	128.5 (127.4–129.7)	129.6 (128.4–130.8)	129.4 (128.0–130.8)
DBP (mmHg)	78.5 (77.9–79.2)	78.0 (77.3–78.8)	79.8 (79.1–80.5)	80.4 (79.6–81.2)	81.0 (80.3–81.7)	81.8 (80.8–82.7)
HDL-C (mg/dL)	51.1 (50.0–52.3)	50.7 (49.5–52.0)	50.3 (49.3–51.2)	49.8 (48.5–51.1)	46.8 (45.7–48.0)	46.0 (44.7–47.3)
Triglycerides (mg/dL)	118.1 (113.8–122.3)	116.0 (111.8–120.2)	145.3 (140.0–150.5)	149.5 (143.2–155.8)	184.2 (178.2–190.1)	184.4 (177.4–191.4)
FBG (mg/dL)	89.8 (89.2–90.4)	89.9 (89.3–90.5)	100.2 (99.3–101.1)	100.1 (99.0–101.1)	106.2 (105.0–107.4)	106.0 (104.7–107.3)
Percent weight loss*	10.20 (9.46–10.93)	1.22 (0.74–1.70)	9.89 (9.20–10.57)	1.80 (1.27–2.34)	9.38 (8.70–10.07)	1.86 (1.33–2.38)

0–29/Treatment: participants who had a CMDS score in the range of 0–29 and received weight-loss medication (7.5 mg phentermine/46 mg topiramate or 15 mg phentermine/92 mg topiramate). DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, HDL cholesterol; SBP, systolic blood pressure; WC, waist circumference. *Percent weight loss at the end of follow-up.

majority of the participants were non-Hispanic whites (73.6%) and women (74.6%). Mean age at screening visit was 48 years. Characteristics were similar between treatment and placebo arms in each CMDS score category. In both the treatment arm and placebo arm, percent weight loss was similar across CMDS score categories, although percent weight loss in the treatment arm was much higher than that in the placebo arm (9.83 vs. 1.60%; $P < 0.001$).

Diabetes Prevention

Table 2 shows the number of cases of incident diabetes and the total number of subjects in the placebo and treatment arms, as well as 1-year risks of diabetes and hazard ratios, as a function of CMDS score group. During a median 56-week follow-up period, there were 107 new cases of T2DM: 49 cases in the treatment arm and 58 cases in the placebo arm. The CMDS score was able to differentiate 1-year risk for future diabetes by >15-fold with the highest risk in those with CMDS score ≥60 randomized to placebo and the lowest in those with CMDS 0–29 randomized to phentermine/topiramate ER. Among high-risk individuals with CMDS score ≥60, the 1-year risk of diabetes in the placebo plus lifestyle group was 10.43%, and this was reduced to 6.29% in those treated with phentermine/topiramate ER plus lifestyle. In other words, active treatment with phentermine/topiramate ER plus lifestyle reduced the 1-year risk of diabetes in high-risk individuals by ~40%. Compared with placebo, active treatment reduced diabetes risk from 4.67 to 2.37% in the moderate-risk group with CMDS score 30–59 and from 1.51 to 0.67% in the low-risk group with CMDS 0–29. Cumulative diabetes incidence rates were plotted by Kaplan-Meier survival curves to show differences in diabetes risks among the CMDS score categories and treatment arms (Fig. 1).

Adjusted hazard ratios also demonstrated the ability of CMDS to quantify diabetes risk among subjects with overweight and obesity, as well as the differential effects of the weight-loss medication to reduce these risks as a function of baseline risk score category (Table 1). With high-risk subjects (CMDS ≥60) randomized to placebo serving as the referent group, treatment with phentermine/topiramate ER reduced the hazard ratio by 41% to 0.59 in the high-risk category. In those with moderate risk, weight-loss therapy reduced the hazard ratio from 0.43 in those randomized to placebo to 0.19, a reduction of 56%. Weight loss in low-risk subjects led to a 50% reduction in the hazard ratio from 0.10 to 0.05.

Number Needed to Treat

We calculated the number of people needed to treat with phentermine/topiramate ER to prevent one case of T2DM over 56 weeks in all three CMDS risk categories. In people with a CMDS score ≥60, treatment of only 24 people was needed to prevent one case of T2DM (Fig. 2), whereas 43 people with moderate CMDS scores 30–59 and 120 people with low-risk scores 0–29 were needed to treat to prevent one case of T2DM.

CMDS Score Distribution

We estimated the distribution of CMDS scores using data from overweight or obese participants without diabetes in NHANES 2013 to 2014. There were 46.6 million adults who had CMDS scores

Table 2—One-year risk and hazard ratio for incident diabetes by CMDS score group and treatment arm

	n	Diabetes* (number of cases)	One-year risk,† % (95% CI)	Adjusted hazard ratio‡ (95% CI)
0–29/Treatment§	558	3	0.67 (0–1.44)	0.05 (0.02–0.16)
30–59/Treatment	644	13	2.37 (1.08–3.64)	0.19 (0.10–0.36)
60+/Treatment	526	33	6.29 (4.11–8.43)	0.59 (0.36–0.95)
0–29/Placebo	495	5	1.51 (0.16–2.83)	0.10 (0.04–0.27)
30–59/Placebo	450	19	4.67 (2.43–6.86)	0.43 (0.25–0.76)
60+/Placebo	367	34	10.43 (6.88–13.85)	Reference¶

*Number of cases of new-onset diabetes. †One-year (56-week) risk for incident diabetes was calculated from Kaplan-Meier survival curves. ‡Adjusted for age, sex, and race/ethnicity. §0–29/Treatment: participants who had a CMDS score in the range of 0–29 and received weight-loss medication (7.5 mg phentermine/46 mg topiramate or 15 mg phentermine/92 mg topiramate). ¶When the 30–59/Placebo group served as the reference group, hazard ratio for incident diabetes in the 30–59/Treatment group was 0.44 (95% CI 0.22–0.89). When the 0–29/Placebo group served as the reference group, hazard ratio for incident diabetes in the 0–29/Treatment group was 0.48 (95% CI 0.12–2.01).

of ≥60, 53.2 million with CMDS scores of 30–59, and 29.3 million with scores of 0–29 (Supplementary Table 2). Based on the 1-year risk data in Table 2, weight-loss therapy could reduce progression to diabetes at 1 year in 1.93 million patients with CMDS ≥60, 1.22 million with moderate-risk CMDS 30–59, and 250,000 in the low-risk category (CMDS 0–29).

CONCLUSIONS

We developed CMDS to assist clinicians in assessing risk for future diabetes and cardiovascular disease among overweight or obese patients and in targeting higher-risk individuals for more intensive weight-loss therapy. Both a categorical approach involving number of metabolic syndrome traits and/or the presence of prediabetes (11) and a quantitative CMDS approach that weights the various traits based on their differential contribution to diabetes risk (17) have been validated to provide robust risk prediction for diabetes in national cohorts, such as CARDIA and ARIC. In the current study, using combined data from three clinical trials assessing efficacy and safety of phentermine/topiramate ER, we have again shown that weighted CMDS scores can discriminate a wide range of diabetes risk among overweight and obese patients. Moreover, we have now shown for the first time that risk quantification using CMDS can also ascertain the differential effectiveness of weight loss to prevent diabetes in overweight or obese patients. Thus, the application of CMDS can be used to enhance the benefit/risk ratio of obesity interventions and perhaps

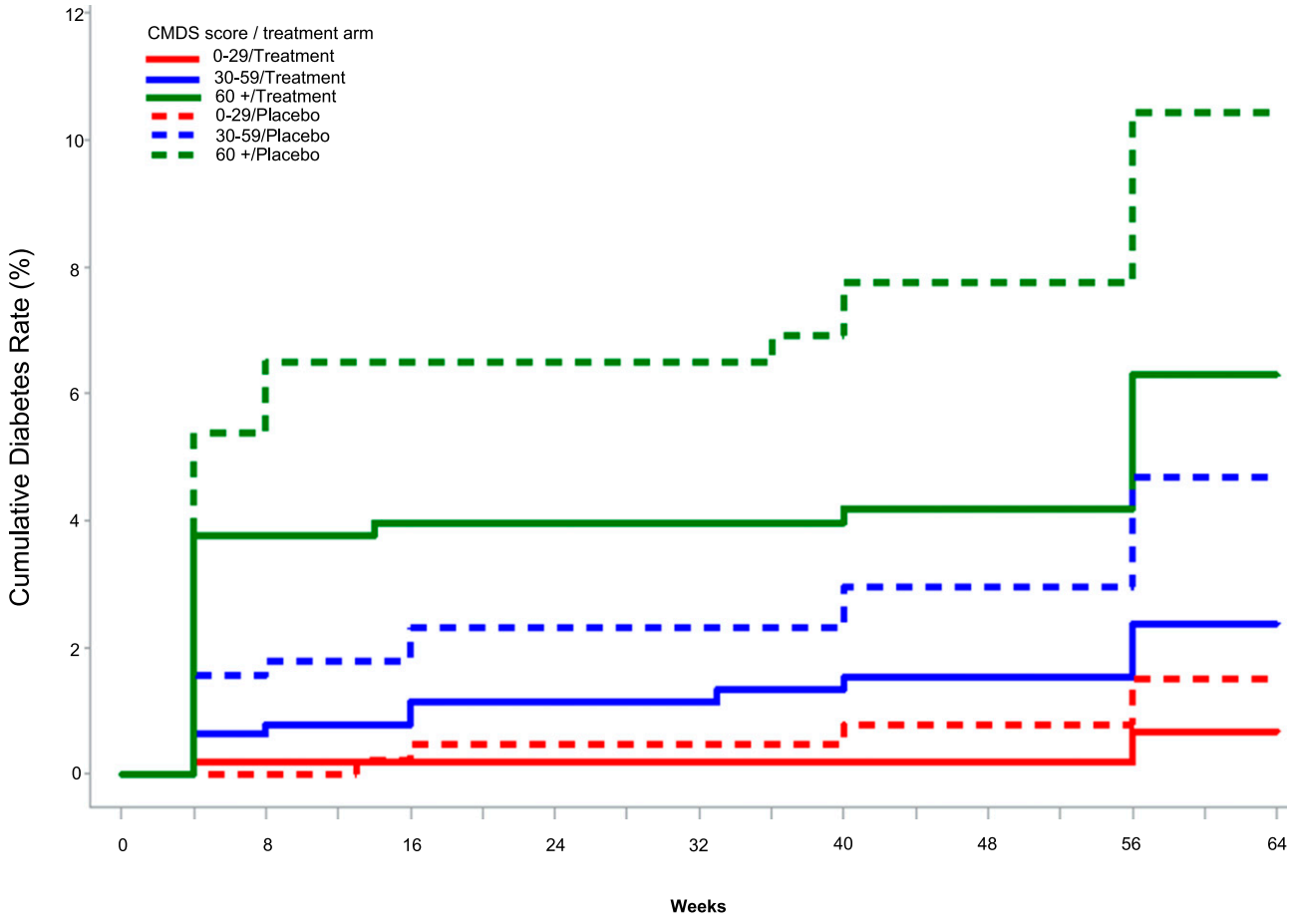

Figure 1—Risk for incident diabetes by CMDS score group and treatment arm.

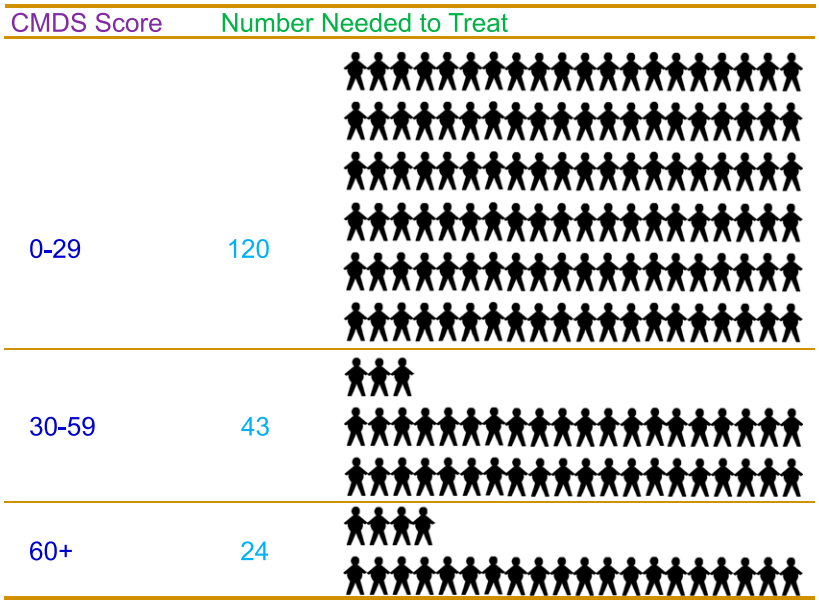

Figure 2—Number needed to treat to prevent one case of diabetes over 56 weeks.

the cost-effectiveness of weight-loss therapy to prevent future T2DM.

T2DM risk increased proportionally across the CMDS score spectrum in patients whether randomized to placebo or to phentermine/topiramate ER, and the weight-loss medication markedly reduced absolute incidence rates of T2DM. In comparing groups randomized to placebo versus medication, the reduction in the 1-year risk of T2DM was greatest in patients with the highest CMDS risk scores (≥60) at baseline, which was reduced from 10.43 to 6.29% (absolute difference 4.14%). The absolute decline in diabetes rates was intermediate for patients with moderate CMDS risk scores (30–59), in whom 1-year risk was reduced from 4.67 to 2.37% (difference 2.30%). Diabetes rates were smallest in patients with low CMDS scores (0–29), as was the absolute reduction with weight-loss therapy from 1.51 to 0.67% (difference 0.84%). These data were reflected in number of people needed to treat to prevent one case of T2DM, which was lowest in the high-risk CMDS subgroup (24 patients) and quite large in the low-risk subgroup (120 patients), with an intermediate number in the moderate-risk group. In the SEQUEL study in which patients were randomized to placebo versus phentermine/topiramate ER, placebo-treated patients progressively experienced incident diabetes at a greater rate than patients receiving active drug over a duration of 2 years (22). For this reason, the differences in the number needed to treat to prevent one case of diabetes would widen further in comparing low versus high CMDS risk with sustained weight loss beyond the 56-week follow-up. Therefore, CMDS is a powerful and useful approach for both stratifying diabetes risk and assessing the relative efficacy of a weight-loss intervention to prevent T2DM in patients with overweight or obesity.

In placebo versus medication-treated patients, it should be noted that the relative risk for T2DM was decreased to a lesser extent within the high-risk CMDS category compared with moderate- and low-risk categories. In previous studies of high-risk patients with prediabetes and/or metabolic syndrome, there appears to be a threshold for the degree of weight loss above which there is no additional benefit regarding T2DM prevention. In both the Diabetes Prevention Program using lifestyle intervention (23) and a study using phentermine/topiramate ER (22), maximal prevention of diabetes was observed at ~10% weight loss, which reduced incident diabetes by ~80%. The percent reduction at 1 year in this study is lower than in the previous report on the reduction in 2 years (22) because the cumulative incidence of diabetes continued to rise in the placebo group, whereas incidence rates remained relatively flat in the medication treatment group, thus increasing the percent reduction with more extended periods of treatment. Any further weight loss (i.e., to ≥15%) did not lead to additional prevention. Bariatric surgery can produce greater degrees of weight loss; however, in two studies, the maximum reduction in diabetes rates was still 76–80% (24,25). The combined data suggest that 10% weight loss is maximally effective and will reduce risk of future T2DM by ~80%. Thus, residual diabetes risk may exist that cannot be eliminated by weight loss such that ~20% of subjects progress inexorably to T2DM. We propose that greater numbers of these patients predestined to develop diabetes regardless of weight loss exist in the highest-risk CMDS category and that this explains the diminished effect of phentermine/topiramate ER in reducing the relative risk of diabetes within the CMDS ≥60 risk category compared with patients in the moderate- and low-risk categories. Even so, from a population perspective, weight-loss therapy was more effective in reducing absolute rates of incident T2DM in the high-risk subgroup of overweight or obese patients.

The CMDS scoring system is developed for the prediction of future T2DM over the subsequent 15 years (17). In the current study, we confirmed that CMDS could also differentiate T2DM risks over a short time period of 56 weeks. We estimated the distribution of CMDS scores in U.S. adult overweight or obese people and found that 36% (46.6 million) of adults had a CMDS score of ≥60, and 41% (53.2 million) had a CMDS score of 30–59. During 1988–2014 after eliminating patients with diabetes, the prevalence of people free of all three cardiometabolic disease risk factors (i.e., normal blood pressure, lipids, and glucose) remained stable at ~15% in the adult obese population, whereas prevalence of presence of all three risk factors (i.e., metabolic syndrome) was increased from 16.4 to 22.4% (26). Metabolic health is declining among people with obesity in the U.S., and this was primarily attributable to worsening blood glucose health (26), which calls for lifestyle interventions (diet and exercise) on a national scale (27–29). To increase physical activity and diet quality in the general population, community-based public health intervention programs may help to alleviate the problem (30,31). Continuing efforts are needed to

target at-risk people with weight-loss therapy to improve cardiometabolic health (32,33) and to prevent progression to diabetes. Given the evidence that weight loss of 10% is highly effective in reducing progression to diabetes among high-risk individuals (20,22), obese adults at high risk for diabetes may require more intense approaches to achieve this degree of weight loss using lifestyle interventions in combination with weight-loss medications (3,20,22,34). Thus, the current data are relevant to a strategic approach for decreasing diabetes prevalence and indicate that weight-loss interventions are most effective in those overweight and obese individuals with high CMDS scores.

The American Association of Clinical Endocrinologists has developed clinical practice guidelines for care of patients with obesity based on 123 evidence-based recommendations and an associated treatment algorithm (35). These guidelines advocate a complications-centric approach to obesity management (36) that targets more aggressive therapy to those patients who will most benefit from the intervention based on risk and severity of weight-related complications (37). The weighted CMDS score uses a simple integer point value and can be easily calculated in clinical settings using basic information readily available to health care professionals. Other risk-stratification systems have also been designed using information from the history and physical examination (38) or using clinical laboratory assays (39) to stage risks in insulin-resistant patients, but may not be as easily calculated in clinical settings. The Edmonton Obesity Staging System (40) is not quantitative and lacks granularity for risk staging because almost all of the participants from this study will fall into stage 1 in the Edmonton system. The CMDS scoring system can be used in clinical settings and health care systems to identify patients with obesity at high risk for diabetes, so that treatment modality and intensity can be chosen accordingly to improve risk benefit-risk ratios and enhance patient outcomes.

Strengths and Limitations

The main strength of this study is the use of pooled data from three clinical trains on the efficacy of weight-loss medication. A diverse population of various ages, both sexes, and different racial/ethnic groups has enabled the generalization of the conclusions of this study. The CMDS scoring system can be used in the general population for the identification of individuals who are likely to benefit most from weight-loss medications. Additionally, incident diabetes was based on repeated glycemic measures of fasting glucose, 2-h oral glucose tolerance test glucose, and HbA_{1c}, such that the ascertained diabetes cases provide a solid basis for assessing the ability of CMDS scoring system to predict effectiveness of weight-loss therapy.

A limitation in this study was that we only assessed the outcome of diabetes prevention for weight-loss medications. People may require weight-loss treatments for other purposes, such as improvements in biomechanical complications such as obstructive sleep apnea and osteoarthritis or other metabolic complications such as management of diabetes or nonalcoholic fatty liver disease (35,36). In addition, the median follow-up period of 56 weeks is relatively short, and additional data will be needed to evaluate outcomes with longer-term medical treatment using phentermine/topiramate ER or other antiobesity medications. Furthermore, those three clinical trials used in this study all used phentermine/topiramate for weight loss, and our findings may not be applicable to weight loss by other means (such as bariatric surgery, other weight-loss medications, or intensive lifestyle intervention). The majority of the participants in this study were non-Hispanic whites and women, and our findings may not be generalizable to other populations.

Conclusion

In this study, we have demonstrated that a validated risk stratification approach can be used to assess the differential efficacy of a weight-loss intervention to prevent the development of diabetes. Specifically, high CMDS scores can identify those overweight or obese patients who are most likely to benefit from weight loss regarding diabetes prevention. The physiological basis of weighted CMDS involves the number and types of metabolic syndrome traits that can readily be identified in individual patients in routine clinical practice. Thus, CMDS is an effective and practical tool for stratifying diabetes risk to enhance and inform clinical decisions regarding the intensity and modality of obesity treatment. The targeting of higher-risk patients for more intensive weight-loss therapy will optimize the benefit/risk ratio of these interventions and help promote rational patterns of medical therapy and health care policy for obesity. Future studies are needed to quantify the ability of CMDS to enhance the cost-effectiveness of weight-loss interventions to prevent diabetes.

Acknowledgments. The authors would like to thank the patient volunteers and staff participating in the clinical trials, and VIVUS, Inc., for providing data from those clinical trials (CONQUER, EQUIP, and SEQUEL) for analyses.

Funding. This study was partly supported by the Merit Review program of the U.S. Department of Veterans Affairs, National Institutes of Health (NIH) (DK-038765), and the University of Alabama at Birmingham Diabetes Research Center (P30-DK-079626). F.G. is currently supported by a research career development award (K12-HD-052023: Building Interdisciplinary Research Careers in Women's Health Program) from the Office of Research on Women's Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the NIH and was previously supported by an institutional training grant (National Research Service Award T32HD055163) from the NICHD of the NIH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NICHD or the NIH.

Duality of Interest. W.T.G. is an advisor for AstraZeneca, Eisai, Janssen Pharmaceuticals, Novo Nordisk, Takeda, Alexion, Merck, and VIVUS, Inc.; is a stockholder for Bristol-Myers Squibb Company, Eli Lilly and Company, Isis/Genzyme, Merck, Novartis, and Pfizer; and has received research support from AstraZeneca, Eisai, Lexicon, Merck, Pfizer, Sanofi, Elcelyx, Novo Nordisk, and Weight Watchers International. No other potential conflicts of interest relevant to this article were reported.

The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author Contributions. F.G. contributed to study design, data analysis and interpretation, and writing of the manuscript. W.T.G. designed the study, researched the data, and reviewed and edited the manuscript. W.T.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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