A clinical score to predict dose reductions of antidiabetes medications with intentional weight loss: A retrospective cohort study

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ABSTRACT

Background: We assessed the predictive accuracy of an empirically-derived score (weight loss, insulin resistance, and glycemic control: “WIG”) to predict patients who will be successful in reducing diabetes mellitus (DM) medication use with weight loss.

Methods: Case records of 121 overweight and obese patients with DM at two outpatient weight management centers were analyzed.

Results: Mean period of follow-up was 12.5 ± 3.5 months. To derive the “WIG” scoring algorithm, one point each was assigned to “W” (loss of 5% of initial body weight within the first 3 months of attempting weight loss), “I” (triglyceride [TGL]/high-density lipoprotein ratio >3 [marker of insulin resistance] at baseline), and “G” (glycosylated hemoglobin [A1c %] >8.5 at baseline). WIG score showed moderate accuracy in discriminating anti-DM dose reductions at baseline, and after 3 months of weight loss efforts (likelihood ratios [LR] + >1, LR− <1, and area under the curve >0.7), and demonstrated good reproducibility.

Conclusions: WIG score shows promise as a tool to predict success with dose reductions of antidiabetes medications.
Nearly 35% of American adults are obese (body mass index [BMI] ≥ 30 kg/m²) [1]. American adults who are overweight (BMI: 25–29.9), obese (BMI: 30–39.9), and morbidly obese (BMI: >40) have 1.59, 3.44, and 7.37 times higher odds, respectively, of having diabetes mellitus (DM) [2]. Obesity and DM create enormous healthcare costs, and the cost and adverse effects of pharmacotherapy is a major contributor to the burden of these conditions [3].

Intentional weight loss is associated with a decrease in the need for antidiabetic (DM) medications [4–9]. However, not everyone who loses weight is successful in reducing use of these medications. Clinical trials assessing weight loss as an intervention have used reduction in the need for medication use as an important end point denoting success of the intervention [7]. For a patient who is attempting weight loss, the ability to dose reduce or stop using medications can be objective evidence of success and a potential motivating factor. Weight loss trials have shown that motivation and counseling are important factors associated with success and adherence to attempts at weight loss [10,11]. We hypothesized that developing a simple scoring system, using commonly available clinical and biochemical parameters that can predict an obese patient’s probability of success with dose reductions of antidiabetes medications when attempting weight loss, would have clinical applicability in assisting practitioners in patient counseling and individualizing the intensity of weight loss intervention. Use of risk scores is common practice in the care of patients with diabetes [12,13] and is known to improve outcomes. Though clinically applicable scoring systems assessing surgical weight loss efforts are available [13], a clinically applicable score assessing nonsurgical weight loss efforts is lacking.

This retrospective cohort study, involving overweight and obese patients from two university-based weight management programs, was used to develop a predictive score: The weight loss, insulin resistance, glycemic control (“WIG”) score and its components are weight loss of 5% achieved within the first 3 months of attempting weight loss, triglyceride (TGL)/high-density lipoprotein (HDL) ratio ≤ 3 (a marker of insulin resistance) [12–15] at the time of initiating weight loss, and glycosylated hemoglobin (HbA1c%) ≤ 8.5 at the time of initiating weight loss. We studied its utility for predicting success with at least one dose reduction of any anti-DM medication.

Materials and methods

Study setting and design

The study was conducted in two university-based specialty outpatient weight management clinics, the Johns Hopkins Weight Management Center in Baltimore, MD, and the George Washington Weight Management program in Washington, DC. A retrospective cohort design was chosen, and approval was obtained from the Johns Hopkins Bloomberg School of Public Health Institutional Review Board. Informed consent waiver was granted by the Institutional Review Board.

Case records of patients with a BMI >25 kg/m² at the time of enrollment into the two weight management programs during the period March 2008 to January 2012 were assessed for eligibility (total cohort). The study cohort consisted of patients with a diagnosis of DM at the time of enrollment who reported taking at least one antidiabetes medication. Patients were excluded (excluded cohort) if they did not have a diagnosis of DM at the time of enrollment into the weight management programs.

Baseline data collection

Demographic data (age, gender, and race/ethnicity), cardiovascular risk factors (smoking, diabetes, and hypertension), medication history (antidiabetes medications, anti-hypertension medications, and lipid-lowering drugs), clinical parameters (height, weight, systolic blood pressure, diastolic blood pressure), and laboratory parameters (fasting glucose, HbA1c, total cholesterol, low-density lipoprotein cholesterol (LDL), HDL cholesterol, and TGL) were collected from the study cohort at the time of entry into the weight management program. BMI was calculated as per standard guidelines [16]. DM was identified by physician diagnosis and medication usage.

Cohort description, patient follow-up, and weight management intervention

Our cohort was an open cohort with regards to entry and exit. Participants entered the cohort upon enrollment into our two weight management centers if they already had a diagnosis of DM at the time of enrollment or upon physician reported a diagnosis of incident DM during follow-up. Patients exited the cohort if they achieved at least one dose reduction of any of their anti-DM medications or were administratively censored upon study conclusion in January of 2012.

The weight loss intervention protocols followed at the two participating clinics were similar, and consisted of team-based, comprehensive evaluation and treatment for weight loss. The study participants had physician visits for follow-up twice a month on average. The baseline visit consisted of a physician-conducted medical history and physical...
examination, blood tests (as described above), and detailed dietary, behavioral, and exercise evaluations. Treatment was individualized but typically consisted of an approximately 1000 kcal/day energy deficit diet, often utilizing meal replacements, a behavior modification plan, and a plan for increasing physical activity utilizing both aerobic exercise and strength training. These interventions with diet, physical activity, and behavior modification were similar in both participating institutions. Depending on treatment response, the intervention was tailored to address individual patient needs. The decision to alter the dose of or discontinue anti-diabetic medications was based on the clinical judgment of the treating physicians. During the follow-up period of the study, if there was a documented reduction of ≥25% of daily insulin dose (short acting and/or long acting insulin), it was coded as one dose reduction for insulin. Factors considered in deciding on dose reductions included the magnitude of weight loss, glycemic control, hypoglycemic symptoms, and the patient's compliance with the weight management protocol.

### Statistical analysis and “weight loss, insulin resistance, glycemic control” score development

Continuous and categorical variables were expressed as mean ± standard deviation and number (%), respectively. The study cohort was categorized into those who achieved at least one dose reduction of any anti-DM medication and those who did not; these two groups were compared using Student's t-test or Chi-square test, as appropriate, with regard to baseline demographic, clinical, and laboratory variables. From our prior analyses using the same study population, we knew that magnitude of weight loss, TGL/HDL ratio, and glycemic control (HbA1c) were associated with dose reductions of anti-diabetes medications in our study cohort [5,6,15]. We arbitrarily assigned numerical values to these three variables, namely: 5% weight loss at 3 months after entry into our study cohort (W) (coded as a categorical variable, yes/no), TGL/HDL ratio ≤3 (a marker of insulin resistance; coded as a categorical variable, yes/no) at the time of entry into the study cohort (l) and HbA1c ≤8.5% (G) (coded yes/no) at the time of entry into the study cohort, together forming the “WIG” score. The rationale for using HbA1C cut-off of ≤8.5% was because this showed the best predictive accuracy among other cut-offs considered (<9.5%, ≤9%, ≤8%, and ≤7.5%) in identifying patients who achieved successful dose reductions of antidiabetic medications with weight loss (Supplemental Table 1). Using univariate logistic regression analysis, we assessed the association between these three variables, age (in years), gender (male/female), smoking (yes/no), hypertension diagnosis (yes/no), baseline BMI (continuous variable), and the dependent variable: At least one dose reduction of any antidiabetes medication (coded as yes/no). Variables that were significantly associated (p < 0.05) with at least one dose reduction of any antidiabetes medication in the univariate analysis were then assessed for their association with at least one dose reduction using multivariate logistic regression analysis to gauge their strength of association (odds ratios). Goodness-of-fit of the model was determined by means of Hosmer and Lemeshow’s goodness-of-fit test [17]. Based on the log-odds ratios (beta coefficient) from the multivariate logistic regression analysis, a three-point scoring system named “WIG” score was developed, as these were the only variables that remained significant in the multivariate logistic regression analysis. The accuracy of the scoring system for predicting success with achieving at least one dose reduction of any antidiabetes medication was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value, likelihood ratio (LR+), LR−, and area under receiver operator characteristics (ROC) curve [17]. In the “WIG” score, variables “I” and “G” are baseline variables as they can be assessed in a patient at baseline. Variable “W” must be assessed at 3 months after an effort to lose weight has begun.

### Simultaneous and sequential testing of the scoring system

We considered three clinical scenarios: (1) when a care provider is seeing a patient for the first time at the time of enrollment into a weight management program, (2) when the care provider is seeing the patient again after 3 months of the patient's participation in a weight management program, and (3) when the care provider is seeing the patient for the first time, but the patient has already been actively involved for the preceding 3 months in a weight management program. For all three scenarios, we wanted to assess the predictive accuracy of the “WIG” score in predicting success with antidiabetes medication dose reductions. For scenario 1, we assessed if our participants were positive for baseline variables of the scoring system and accordingly assessed the discrimination potential of these variables for antidiabetes medication dose reductions. For scenario 2, we assessed the predictive accuracy, by taking only those participants who were positive for one or both baseline variables, and assessed if they were also positive for the 3-month variable “W” of our scoring system, i.e.,; “I” and “W” positive, “G” and “W” positive and “I” and “G” and “W” positive. This method, sequential testing, is used in diagnostic test research to improve the specificity of the research tool [17]. For scenario 3, we assessed simultaneously the baseline and – month variables of the scoring system on all study cohort participants, i.e.,; “W” or “I” or “G” positive. This method, simultaneous testing of variables, is used in diagnostic test research, in this case to improve sensitivity of the tool [17]. The ROC curves were compared with one another using the method described by DeLong et al. [18] A p ≤ 0.05 was considered statistically significant. All analyses were performed using STATA 8.2, Illinois, USA [19].

### Testing reproducibility of “weight loss, insulin resistance, glycemic control” score

Two of the authors, one an internist and another an MD, were involved in this experiment. One of them was an internist, with 5 years’ postmedical school experience; the other was also a physician with 3 years’ postmedical school experience. Both authors received a brief 20 min training regarding calculation of “WIG” score: Baseline variables, sequential testing, and simultaneous testing. A computer generated random sample (n = 60) from the study cohort was selected. First, the internist calculated “WIG” score for this random study cohort patients, blinded with regard to patient and
medication history. To test intra-observer agreement, the internist recalculated “WIG” score, for the same random sample of study cohort participants after 2 days, blinded with regard to earlier “WIG” score results, patient and medication history. Agreement was calculated comparing the present and previous findings of the internist. Then, the physician calculated “WIG” score for the same random sample used by the internist, blinded with regard to patient, and medication details. Agreement was calculated comparing the “WIG” score of the internist with that of the physician. Kappa statistics was used to assess intra- and inter-observer agreement in interpreting “WIG” score.

Results

In total, 179 patient records (107 from Johns Hopkins and 72 from George Washington) were identified and reviewed. Of these, 58 (32%) were excluded because they did not have a diagnosis of DM at the time of enrollment into the programs. The remaining 121 (68%) with a diagnosis of DM formed the study cohort. By study exit, 81 (67%) in the study cohort failed to achieve even one dose reduction of any antidiabetes medication (nondose reduction group). The remaining 40 (33%) achieved at least one dose reduction of any antidiabetes medications (dose reduction group). Baseline comparison between the dose reduction group and the nondose reduction group is detailed in Table 1. Mean period of follow-up in the dose reduction group was 13 ± 2.5 months and that in the nondose reduction group was 12.5 ± 2.5 months (p = 0.511). Weight loss (16.9 ± 4.7 kg vs. 9.2 ± 3.1 kg, p = 0.029) and HbA1c% reduction (0.7 ± 0.3 vs. 0.2 ± 0.1, p = 0.035) in the dose reduction group was significantly greater than those in the nondose reduction group. By the end of follow-up, TGL/HDL ratio in the dose-reduction group and the nondose reduction group were 2.8 ± 0.6 and 2.5 ± 0.3, respectively. Though both groups achieved reductions in TGL/HDL ratio by the end of follow-up (difference from baseline: −0.3 ± 0.5 in the dose reduction group and −0.3 ± 0.4 in the nondose reduction group), this was not significantly different when the two groups were compared (p = 0.114). The mean insulin dose at the end of follow-up was 35 ± 10 and 55 ± 7 units in the dose reduction group and the nondose reduction group, respectively (p = 0.029). The reduction from baseline dose of insulin to the insulin dose at the end of follow-up was significantly better in the dose reduction group (−30 ± 10 units) compared to the nondose reduction group (−15 ± 12 units) (p = 0.037). When followed after the incident diabetes medication dose reduction, 36% of participants reported weight gain during the follow-up period of the study (4 ± 2 kg), 40% maintained the weight loss and remained at the same body weight, whereas the remaining 24% lost further body weight (−3 ± 1 kg). None of the study participants had to be dose-increased until study completion, even those who regained weight.

In the univariate logistic regression analysis, smoking, hypertension diagnosis, baseline BMI, weight loss (W) of 5% by 3 months after study entry, TGL/HDL ratio ≤3 (l) and HbA1c <8.5% (G) were significantly associated with at least one dose reduction of any antidiabetes medication [Table 2]. In multivariate logistic regression analysis, only weight loss of 5% by 3 months after study entry (3-month variable), TGL/HDL ratio ≤3 (baseline variable) and HbA1c <8.5% (baseline variable) remained significantly associated with dose reductions of antidiabetes medications, with log-odds ratios of association of 2.41, 2.31, and 2.56, respectively [Table 2]. Hence, in the proposed “WIG” score, each of these variables were assigned one point each, forming the three-point scoring system.

### Table 1 – Baseline characteristics of the study cohort.

| Variables                        | Study cohort (n = 121) | Dose reduction group (n = 81) | Nondose reduction group (n = 40) | p     |
|----------------------------------|-----------------------|-----------------------------|----------------------------------|-------|
| Age (years)                     | 51.8 ± 8.9            | 52.7 ± 9.1                  | 53.7 ± 9.3                       | 0.133 |
| Males – n (%)                   | 67 (55)               | 45 (56)                     | 22 (55)                          | 0.681 |
| Caucasians – n (%)              | 90 (74)               | 63 (78)                     | 27 (68)                          | 0.042 |
| African Americans – n (%)       | 31 (26)               | 18 (22)                     | 13 (32)                          | 0.044 |
| Current smoking – n (%)         | 24 (20)               | 16 (20)                     | 8 (20)                           | 0.996 |
| Duration of diabetes (years)    | 7.5 ± 2.5             | 8.0 ± 2.0                   | 7.5 ± 2.0                        | 0.371 |
| Mean baseline weight (kg)       | 126.5 ± 18.2          | 127.1 ± 16.4                | 126.9 ± 19.3                     | 0.417 |
| Mean BMI (kg/m²)                | 36.1 ± 6.2            | 36.1 ± 5.5                  | 35.6 ± 4.7                       | 0.226 |
| HbA1c%                          | 8.2 ± 1.6             | 8.1 ± 2.3                   | 8.0 ± 1.7                        | 0.179 |
| Mean TGL/HDL ratio              | 2.9 ± 1.2             | 3.1 ± 0.8                   | 2.8 ± 1.1                        | 0.051 |
| HTN diagnosis - n (%)           | 102 (84)              | 69 (85)                     | 33 (83)                          | 0.067 |
| MS – n (%)                      | 68 (56)               | 45 (56)                     | 23 (58)                          | 0.116 |
| Anti-HTN drugs – n (%)          | 102 (84)              | 69 (85)                     | 33 (83)                          | 0.067 |
| Metformin - n (dose/day)         | 71 (1.7 g)            | 51 (1.7 g)                  | 20 (1.7 g)                       | 0.044 |
| Sulfonylureas – n (%)           | 59 (49)               | 40 (49)                     | 19 (48)                          | 0.133 |
| Glyburide – n (dose/day)        | 24 (10 mg)            | 16 (10 mg)                  | 8 (10 mg)                        | 0.091 |
| Glipizide – n (dose/day)        | 21 (10 mg)            | 12 (10 mg)                  | 9 (10 mg)                        | 0.046 |
| Glimepride – n (dose/day)       | 14 (2–4 mg)           | 9 (2–4 mg)                  | 5 (2–4 mg)                       | 0.117 |
| Sitagliptin – n (dose/day)      | 19 (100 mg)           | 11 (100 mg)                 | 8 (100 mg)                       | 0.061 |
| Insulin – n (dose/day)          | 59 (60 + 10 U)        | 45 (65 + 7 U)               | 14 (60 U)                        | 0.155 |

Abbreviations: BMI: Body mass index; HbA1c: Glycosylated hemoglobin; TC: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TGL: Triglycerides; HTN: Hypertension; MS: Metabolic syndrome.
Scenario 1: predictive accuracy of baseline variables

Of the 121 study cohort participants, 94 (78%), 96 (79%), and 66 (54%) were positive for “I,” “G,” and “I and G,” respectively [Table 3]. Area under the curve (AUC) was significantly better in participants with both “I” and “G” compared to those with only “I” positive (p = 0.031) and only “G” positive (p = 0.031).

Scenario 2: sequential testing analysis

Of the 94 participants with “I” positive at baseline, 65 (69%) were positive for both “I and W” [Table 3]. Of the 96 participants with “G” positive at baseline, 60 (63%) were positive for both “G and W.” Of the 66 participants with both “I” and “G” positive at baseline, 39 (59%) were positive for all three – “W,” “I” and “G” variables. AUCs were similar in participants with “I” and “W” positive, “G” and “W” positive, and all three positive (all p > 0.05).

Scenario 3: simultaneous testing analysis

Of the 121 study cohort participants, 97 (80%) had either “W” or “I” or “G” positive [Table 3]. Sensitivity was 95%, with AUC of 0.70, which was significantly lower than the AUC with baseline variables (both I and G, AUC = 0.79) (p = 0.041), and sequential testing (all three variables positive, AUC = 0.77) (p = 0.048). Fig. 1 details the difference in ROC curves between simultaneous and sequential testing.

Reproducibility of “weight loss, insulin resistance, glycemic control” score

The intra- and inter-observer agreements in the calculation of “WIG” score for baseline variables, sequential testing, and simultaneous testing were 0.99–1.00.

Discussion

Our retrospective cohort study involving overweight and obese participants from two tertiary care weight management programs has shown “WIG” score to have moderately good accuracy and reliability for discriminating patients who will be successful in achieving at least one dose reduction of anti-DM medication when attempting weight loss. The components of the “WIG” score worked well in all three clinical scenarios [Table 3] (scenario 1: I and G components, scenario 2: I and G for baseline and WIG for sequential testing at 3 months and scenario 3: All three components such as W, I, and G for simultaneous testing). Mechanistically, “WIG” score with its component variables “I,” “G” and “W” ties together weight loss and its associated reduction in insulin resistance with success at achieving anti-DM medication dose reductions. Weight loss lowers insulin resistance by changing fat mass and modifying the release of adipokines such as leptin, adiponectin, and resistin [20,21]. Reduction in insulin resistance results in better glycemic control and thus decreases the need for anti-DM medications [7]. Prior work on scores for assessing the effect of medical management of obesity on DM are very limited. The DiaRem score, used for pre-operative prediction of diabetes remission following bariatric surgery, relies on insulin use, age, HbA1c%, and type of anti-DM medication used to predict remission of diabetes postoperatively [11]. Mechanistically, the component variables of DiaRem score strongly weighs on anti-DM medication use, which reflect a patient’s baseline preoperative insulin resistance and glycemic control to predict postoperative diabetes remission, similar to the concept underlying the “WIG” score.

In the assessment of the predictive accuracy of the “WIG” score in the three clinical scenarios, there was a wide range of sensitivities and specificities [Table 3]. Baseline variables, though sensitive, lacked specificity [Table 3]. Sequential testing improved specificity, as expected [Table 3]. Although simultaneous testing improved sensitivity (95%), it lacked specificity (50%). Sequential testing showed good PPV (>90%) [Table 3]. With sequential and simultaneous testing, “WIG” score showed LR+1, LR−, and AUC values >1, <1 and >0.7, respectively, which should be interpreted as denoting moderate predictive accuracy [15], though baseline variables “I” alone or “G” alone showed poor AUC (0.60) whereas “I” and “G” at baseline had an AUC of 0.79 [Table 3].

The high incidence of dose reductions observed in our study cohort may have been due to surveillance bias, the intensity of weight loss interventions offered, and the decision to dose reduce being subjective and at the discretion of the treating physicians. However, this may not affect the validity.

Table 2 – Associations with antidiabetes medication dose reductions and relative weights of each variable.

| Variables | Univariate analysis | Multivariate analysis | Relative weights |
|-----------|---------------------|-----------------------|------------------|
|           | Log-OR (95% CI) | p | Log-OR (95% CI) | p |                |
| Age | 1.05 (0.81–2.98) | 0.211 | 1.01 (0.77–2.32) | 0.216 |                |
| Gender | 1.45 (0.84–3.01) | 0.179 | 1.15 (0.67–2.37) | 0.210 |                |
| Hypertension | 1.21 (1.01–2.03) | 0.033 | 0.96 (0.82–1.93) | 0.132 |                |
| Smoking | 1.18 (1.15–1.99) | 0.039 | 1.07 (0.66–2.11) | 0.286 |                |
| Baseline BMI | 1.13 (1.04–2.66) | 0.030 | 1.07 (0.81–2.35) | 0.131 |                |
| Weight loss (%) (W) | 2.47 (2.25–3.00) | 0.021 | 2.41 (2.19–2.76) | 0.031 | 1 |
| TGL/HDL ratio ≤3 (I) | 2.46 (2.10–3.86) | 0.018 | 2.31 (2.03–3.41) | 0.022 | 1 |
| HbA1c ≤8.5% (G) | 2.49 (2.18–3.17) | 0.028 | 2.56 (2.12–2.93) | 0.030 | 1 |

Abbreviations: ‘Logistic regression analysis; BMI: Body mass index; OR: Odds ratio; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein; TGL: Triglycerides.'
of the “WIG” score, as we are not attempting to assess a cause and effect relationship in our study, in which case surveillance bias may be a significant internal validity issue. Rather, we are developing a risk score for use in the population of overweight and obese patients who attempted weight loss through a structured effort.

The utility of the “WIG” score may potentially extend to discriminating patients who may fail medical management and may be better candidates for bariatric surgery. This is because “WIG” score works well in those patients who have at baseline low insulin resistance (TGL/HDL ratio <3) and better glycemic control (HbA1c% <8.5) and thus will potentially benefit from medical management whereas those with poor baseline glycemic control (HbA1c% >8.5) and high baseline insulin resistance (TGL/HDL >3) may fail by “WIG” score and be better candidates for bariatric surgery. The “WIG” score could also be of value in the setting of bariatric surgery, like the “DiaRem” score [13], as bariatric surgery is a better tool to improve insulin resistance than medical management with its potential to work with incretin gut hormones in addition to the adipocytes [22,23].

**Limitations**

Because of the small sample size of our study population, we could not internally validate our score, nor perform subgroup analyses by BMI class and racial differences nor study the score’s validity in predicting reductions in the dose of specific, individual antidiabetes medications. Validation and potentially subgroup analyses could be accomplished using data from large medical weight loss trials [4,7]. In addition, the “WIG” score may not be generalizable to primary care-based weight loss efforts. This can be studied using data from weight loss trials which were primary care based [10,11]. We observed significantly greater magnitudes of weight loss (15.4 kg by 15 months of follow-up) compared to typical weight loss trials (weight loss: 4–6 kg within 12–15 months of follow-up) [10,11]. It is thus possible that confounding due to unknown factors may have played a role. Finally, the retrospective cohort design limited us to what was consistently recorded in patient charts; for example, we did not have data on waist circumference, which might also have relevance as a predictor. In the same note, the reasons for dose reductions of antidiabetic medications were not consistently documented in the case records. However, since these dose-reductions accompanied a significant reduction in HbA1c% by the end of follow-up, we may infer that dose reductions possibly happened due to the beneficial glucose-lowering effects of weight loss.

**Conclusions**

“WIG” score shows promise as a tool to predict success with dose reduction of at least one antidiabetes medication in overweight and obese DM patients who attend structured
weight management programs. In addition, “WIG” score may potentially have wider applicability in assessing interventions such as bariatric surgery, where insulin resistance reduction is the central mechanism of action. Before advocating widespread clinical use, this tool should be prospectively validated in large weight loss trials [4,7,10,11]. Use of “WIG” score in a primary care setting should also be studied.

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Conflicts of interest
There are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j bj.2016.06.002.

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