Multivariate Prediction Equations for HbA$_{1c}$ Lowering, Weight Change, and Hypoglycemic Events Associated with Insulin Rescue Medication in Type 2 Diabetes Mellitus: Informing Economic Modeling

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A B S T R A C T

Background: Type 2 diabetes mellitus (T2DM) is chronic and progressive disease characterized by overweight, insulin resistance, a reduced ability to secrete insulin over time, and corresponding chronic hyperglycemia, with demonstrated links to debilitating microvascular complications [1]. These outcomes are serious and costly and T2DM is a major cause of premature mortality.

Although at present there is no cure for T2DM, tight glycemic control has been shown to improve long-term patient outcomes [2], and influential guidelines issued by the American Diabetes Association and the European Association for the Study of Diabetes recommend treatment intensification to maintain good glycemic control and minimize the risk of long-term complications [3]. As T2DM progresses over time, treatment intensification with multiple drug combinations and ultimately insulin rescue medication is routinely needed to achieve goals.

The benefits and costs of T2DM treatment interventions are often fully realized only over long time horizons and so economic decisions on which interventions to fund are ideally based on long-term cost-effectiveness data [4]. Because T2DM treatments have limited durability, economic evaluations compare treatment strategies and not just individual agents in a vacuum. Given the long time horizons involved, simulated time on rescue medication can be as important as the initial comparator agents [5,6]. Assumptions about the nature of rescue medication can have a large impact on estimated incremental cost-effectiveness ratios [5]. For example, simulations involving an efficacious, inexpensive, and well-tolerated rescue medication will (in relative terms) punish a more durable agent for withholding this ‘wonder’ rescue medication, whereas simulating an

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inefficacious, expensive, and poorly tolerated rescue medication, in contrast, rewards good durability.

Trials that take sufficiently long to inform the safety and efficacy of relevant therapy sequences in T2DM are usually infeasible, and this has led to widespread adoption of economic modeling [7,8]. In most economic simulation models, short-term randomized controlled trial changes in surrogate biomarkers (in particular, glycated hemoglobin $A_1c$ [HbA$_{1c}$]) are converted into long-term microvascular and macrovascular complication and mortality risks, often using the risk equations of the UK Prospective Diabetes Study [9,10]. In this modeling, insulin rescue therapy is often applied at different time points for different hypothetical patients (leading to a heterogeneity not typical of clinical trials). For example, because HbA$_{1c}$ lowering is correlated with baseline HbA$_{1c}$ [11,12], applying a single HbA$_{1c}$ lowering to this heterogeneous set of patients will tend to overstate the HbA$_{1c}$ lowering for well-controlled patients and underestimate the HbA$_{1c}$ lowering for poorly controlled patients. Similarly, insulin-related weight gain is dose-dependent and so differing insulin needs leads to differing weight gain. Despite its importance, insulin rescue medication is typically modeled crudely, often with invariable treatment effects and hypoglycemic event rates, ignoring key characteristics such as HbA$_{1c}$ level and insulin dose. Even the ability to titrate doses flexibly to individual characteristics is rarely included in health economic modeling.

Using prediction equations that tailor simulated treatment effects and adverse events (such as hypoglycemia) to individual patients on the basis of their characteristics provides a way to address these concerns. Although we are unaware of any such equations for simulating insulin-related changes in HbA$_{1c}$ and weight, McEwan et al. [13] used this approach to develop prediction equations for nonsevere and severe hypoglycemic event rates, finding that baseline HbA$_{1c}$, HbA$_{1c}$ lowering, age, and duration of diabetes were important determinants. Although the inclusion of HbA$_{1c}$ as a predictor is a good start, the equations did not include insulin dose, which has been shown in multivariate regression with patient-level data to explain hypoglycemia rates for T1DM [14].

The objective of this study was to use meta-regression to estimate parsimonious multivariate treatment effect and hypoglycemic event risk equations for insulin rescue therapy, which are suitable for use in parameterizing model-based cost-effectiveness analysis.

**Methods**

**Literature Search**

A review of the published literature in PubMed was conducted to identify studies containing evidence on HbA$_{1c}$ change, weight change, and hypoglycemic events associated with insulin therapy in patients treated with T2DM. Any review articles and meta-analyses identified were retrieved and their reference lists reviewed, increasing the degree of coverage. We intentionally adopted an inclusive search strategy, using the following search terms:

- (Diabetes Mellitus, Type 2[MeSH Terms]) and (insulin[MeSH Terms]) and ([clinical trial][Title] OR observational[Title/Abstract] or meta-analysis[Title])

Inclusion required subjects with T2DM; controlled trial or interventional/noninterventional observational study designs; inclusion of at least one study arm with exposure to insulin (either treatment or control); and information on the change in HbA$_{1c}$ or cumulative incidence or the rate of symptomatic, severe, or nocturnal hypoglycemic events. Studies were excluded if publication was before 1990; follow-up was less than 18 weeks; type, frequency of delivery, or dose of insulin was not reported; or if the study was not written in English. Studies that reported changes in the proportion of patients using concomitant antihyperglycemic agents (AHAs) were excluded if it was unclear which agents were affected.

All studies identified from the search (conducted in February 2015) were downloaded and two trained health economists assessed the titles and then the abstracts for relevance (M.W. and C.A.). Qualifying abstracts (including meta-analyses and review articles) were then retrieved in full-length and reviewed for final study qualification (M.W. and C.A.). The reference lists of the meta-analyses and review articles, as well as other relevant studies known to the reviewers, were subjected to the same screening process, and qualifying studies were added to the final analysis data set.

To detect the effects on weight and HbA$_{1c}$ associated with starting a new insulin therapy, and to reduce the risk of confounding, the “treatment effects data set” includes data from interventional studies only and is limited to study arms in which a new insulin regimen was started at baseline. If insulin combination therapy was given in these study arms, study insulin 1 was defined to refer to the experimental insulin component(s) of each study and any other insulin component taken by the study participants was referred to as study insulin 2. Because hypoglycemic event risks are related to the full set of AHAs being taken by the patient and not just to a particular intervention agent, a broader “hypoglycemic events data set” was created for the analyses of hypoglycemia risk, using these study arms as well as information from other study arms that involved insulin medication (including observational studies). Although beyond the scope of the formal search criteria, we also opportunistically included in this second analysis data set even insulin-containing arms of interventional studies of oral agents that were captured in the search.

**Data Capture and Management**

Information was extracted into a standardized data extraction worksheet, separately for each insulin-containing treatment arm and for all subgroups presented in the study. Study arms featuring insulin pumps were excluded because study characteristics differed considerably from those of the other studies. Multiple publications from the same study were indexed to a unique study level; when results for both the overall study population and subgroups were reported, only data from the entire study population were used to prevent double-counting. When results for multiple time points in a study were available, the last time point was used. The extracted data were checked for consistency and double-checked against the original publication.

The following data were extracted from each qualifying study: study design, sample size, duration, baseline patient characteristics, type (basal, bolus, premix, and combination of basal and bolus) and dose of insulin regimen, pretest washout period, concomitant noninsulin AHA treatment, and HbA$_{1c}$ change, weight (kilogram and body mass index [BMI]) change, and hypoglycemic events (both event rates and proportions of patients experiencing events). Full details can be found in Appendix Table 1 in Supplemental Materials 1 found at http://dx.doi.org/10.1016/j.jval.2016.10.004.

Two measures of the type of insulin regimen were constructed, one limited to the intervention insulin agents for use in analyzing initial treatment effects (consisting of study arms in which a new insulin was started at study start, and requiring a washout in patients with previous insulin use) and a second one covering all insulin agents being taken for use in analyzing
hypoglycemic events (including the aforementioned arms and all other identified insulin treatment arms).

For hypoglycemic events, reporting formats differed considerably across studies, and every effort was made to standardize measurements (symptomatic, severe, and nocturnal). In addition to differences in definitions, some studies reported event rates and others the proportions of patients experiencing an event during the study follow-up; a small number of studies reported both. Cumulative incidences and event rates were analyzed separately.

For the analysis of hypoglycemic events, arithmetic mean HbA1c, weight, BMI, insulin dose, and proportion of noninsulin AHA use were created. To reduce the number of observations lost because of missing information, we imputed values (explained in Supplemental Materials 2 found at http://dx.doi.org/10.1016/j.jval.2016.10.004) for some key variables (see Appendix Table 1 in Supplemental Materials 1, which shows all extracted data and indicates missing values).

Statistical Methods

Descriptive statistics of the study data were generated separately for the treatment effect and the hypoglycemia data sets. The unit of observation is the study arm. Commonly, this type of analysis is weighted by the inverse of the variance, which was not possible given erratic reporting. In line with Esposito et al. [15], we thus weighted the observations by the sample size instead.

Descriptive statistics for HbA1c change, weight change, and frequency of symptomatic, severe, and nocturnal hypoglycemic events were calculated by strata for a number of key covariates. For each outcome, results were stratified by insulin regimen and insulin dose. HbA1c change was also stratified by baseline HbA1c and weight change was stratified by baseline weight. Hypoglycemic events were also stratified by average HbA1c and study duration. Results were generated separately for insulin-naive and insulin-experienced populations. For hypoglycemic events, results were reported for the pooled naive and experienced populations as well. Because of differences in missing values, sample sizes vary.

Multivariate meta-regression techniques were then used to estimate parsimonious prediction equations, which controlled for each of these explanatory factors simultaneously (reducing potential confounding effects and improving the likelihood for correctly specified causal equations). For changes in HbA1c and in weight, linear regression was applied to the treatment effects data set. For hypoglycemic events, when the broader analysis data set was used, generalized linear modeling was applied, with a log-link function and a quasi-Poisson likelihood for event rate and a logit-link function with a quasibinomial likelihood for event rates. Multivariate meta-regression techniques were then used to estimate parsimonious prediction equations, which controlled for each of these explanatory factors simultaneously (reducing potential confounding effects and improving the likelihood for correctly specified causal equations). For changes in HbA1c and in weight, linear regression was applied to the treatment effects data set. For hypoglycemic events, when the broader analysis data set was used, generalized linear modeling was applied, with a log-link function and a quasi-Poisson likelihood for event rate and a logit-link function with a quasibinomial likelihood for event rates.

The explanatory variables were chosen to support economic modeling applications, and so only factors routinely used by an analyst’s control were considered (i.e., factors that are routinely modeled explicitly or that can be used to define and motivate particular subgroups for particular analyses). A core list of covariates that were expected a priori to exhibit strong and causal relationships with the dependent variables and natural implementation in economic modeling was created. Broader sets of variables with potential to confound the estimates, but which were less certain to be causal, were also considered to evaluate the stability of the parsimonious specification, giving rise to the sets of “Core+” and “All” covariates.

1. “Core” specification:
   - HbA1c change: Study insulin intervention dose was included to capture dose-response relationship; baseline HbA1c was included because HbA1c lowering is inversely related to close-ness to goal [16] and because of likely correlation with the choice of insulin dose; and insulin type and study duration were included because they are clear drivers of observed HbA1c change.
   - Weight change: Study insulin intervention dose was included to capture dose-response relationship; baseline weight was included as a potential confounder of the dose-response relationship because it may be correlated with choice of insulin type; and insulin type and study duration were included because they are clear drivers of observed weight change.
   - Hypoglycemic events: Average HbA1c (defined as the mean of baseline and end of follow-up values) was included because patients with T2DM with tighter glycemic control generally face greater risks for hypoglycemic events; insulin type was included because of well-known differences in hypoglycemia profiles; average insulin dose (defined as the mean of baseline and end of follow-up values) was included to capture dose-response relationship; average weight (defined as the mean of baseline and end of follow-up values) was included because of its potential to confound estimation of the dose-response relationship; and study duration was used to capture habituation to insulin.

2. The Core+ specification used stepwise regression to include further covariates on the basis of statistical significance, from among the following candidate covariates chosen because of their potential to confound the estimated core relationships:
   - HbA1c change: Proportion of patients using noninsulin AHAs, separately for metformin (MET), sulfonylurea (SU), metformin and sulfonylurea combination (MET + SU), and glucagon-like peptide-1 receptor agonists; T2DM duration; age; weight; and proportion male.
   - Weight change: Baseline HbA1c, proportion of patients using noninsulin AHAs, T2DM duration, age, and proportion male.
   - Hypoglycemic events: Concomitant use of noninsulin AHAs, HbA1c change, T2DM duration, age, and proportion male.

3. A full set of “All predictors” that forced inclusion of both Core and Core+ covariates.

The set of Core+ predictors included in the final specification was arrived at using backward stepwise regression, using an F test of the residual model variance with cutoff of F less than 0.05. Variables in the Core set were not eligible for removal. F tests of the residual model variances were conducted for the Core and for the All predictors regressions, respectively, to establish whether pooling of insulin-naive and nonnaive studies was appropriate. Heterogeneity in the outcomes and goodness of fit of the linear regressions were evaluated using the R² and adjusted R².

In exploratory analysis, nonlinear transformations were applied to relevant explanatory variables, including logarithmic and quadratic transformations of baseline HbA1c, baseline weight, and insulin dose. Interaction terms between insulin dose and baseline HbA1c and between insulin type and insulin-naivety were also explored. Because these did not improve model fit, nontransformed variables without interactions were used in the final specification.

Results

Literature Search

The search, consistent with the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Fig. 1), took
place in February 2015 and yielded a total of 365 references. A secondary search of reference lists from identified meta-analyses yielded another 131 references. After review of titles, abstracts, and full-text, 109 studies were identified that satisfied the inclusion and exclusion criteria, including 224 study arms with exposure to insulin. Two study arms were excluded because of insulin pump use. Fifty-one study arms reported subpopulation results and were excluded to avoid double-counting, yielding 91 studies and 171 study arms. Sixty-four studies satisfied the requirements for inclusion in the analysis of treatment effects, including 112 study arms and 22,820 patients. Missing data on hypoglycemic events limited sample sizes. Forty-seven studies (159,778 patients) contributed data on hypoglycemic event rates, yielding 95 study arms for symptomatic event rates, 56 study arms for severe event rates, and 58 study arms for nocturnal event rates. Because of small sample sizes (17–28 study arms), we were unable to analyze the proportions of patients experiencing hypoglycemic events. Descriptive statistics are presented in Table 1.

**Statistical Analysis of Treatment Effects**

**Change in HbA1c**

Mean HbA1c lowering stratified by type of insulin intervention, baseline HbA1c value, and insulin intervention dose is presented in Table 2, separately for insulin-naive and insulin-experienced subjects. Mean lowering varied somewhat across insulin types—for example, premix was associated with the largest reduction for insulin-naive subjects and bolus insulin for the insulin-experienced subjects—though differences in mean baseline HbA1c may partly explain this. The expected positive relationship between mean baseline HbA1c and magnitude of HbA1c lowering is clear for both subject groups, though the gradient appears steeper for insulin-naive subjects. The dose-response relationship is also clear, though there are a small number of deviations that correlate with differences in mean baseline HbA1c.

Multivariate meta-regression results are presented in Table 3. For the subgroup of studies with insulin-naive subjects, the coefficient for baseline HbA1c was statistically significant ($P < 0.001$) and negative as expected in the parsimonious Core specification, as was the dose-response coefficient ($P < 0.001$). Coefficients for insulin type (basal as the reference) were not statistically significant. The set of Core covariates explained 84% of the variability in HbA1c change. Only the proportion male was statistically significant and was included in the Core+ specification ($P = 0.004$); the key Core coefficients were robust to this inclusion. The key Core coefficients were also robust to the forced inclusion of T2DM duration, concomitant oral medications, and age (the All specification). A loss of eight studies reduced the $R^2$ to 0.67.

The multivariate regression results were also strong for studies with insulin-experienced subjects. The coefficient for baseline HbA1c in the parsimonious Core specification was modestly smaller in absolute value than for insulin-naive subjects and magnitude of HbA1c lowering is clear for both subject groups, though the gradient appears steeper for insulin-naive subjects. The dose-response relationship is also clear, though there are a small number of deviations that correlate with differences in mean baseline HbA1c.

*Fig. 1 – Literature flow chart. T2DM, type 2 diabetes mellitus.*
Table 1 – Descriptive statistics.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>All studies</th>
<th>Studies for treatment effects (interventional)</th>
<th>Studies for hypoglycemic analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Combined</td>
<td>Interventional</td>
</tr>
<tr>
<td>Number of study arms</td>
<td>171</td>
<td>95</td>
<td>66</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>176,371</td>
<td>159,778</td>
<td>15,656</td>
</tr>
<tr>
<td>Proportion insulin-naïve</td>
<td>0.44</td>
<td>0.47</td>
<td>0.52</td>
</tr>
<tr>
<td>Disease duration (y), mean ± SD</td>
<td>10.5 ± 3.0</td>
<td>10.1 ± 1.8</td>
<td>9.8 ± 1.6</td>
</tr>
<tr>
<td>Study duration (wk), mean ± SD</td>
<td>36.9 ± 19.5</td>
<td>35.5 ± 9.7</td>
<td>35.7 ± 28.1</td>
</tr>
<tr>
<td>Age (y), mean ± SD</td>
<td>57.9 ± 3.3</td>
<td>57.4 ± 3.1</td>
<td>57.8 ± 3.6</td>
</tr>
<tr>
<td>Proportion female</td>
<td>0.46</td>
<td>0.46</td>
<td>0.45</td>
</tr>
<tr>
<td>Type of insulin regimen (proportion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>0.32</td>
<td>0.28</td>
<td>0.38</td>
</tr>
<tr>
<td>Bolus</td>
<td>0.03</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Premix</td>
<td>0.62</td>
<td>0.67</td>
<td>0.45</td>
</tr>
<tr>
<td>Basal and bolus</td>
<td>0.03</td>
<td>0.01</td>
<td>0.13</td>
</tr>
<tr>
<td>Insulin dose, mean ± SD</td>
<td>0.37 ± 0.16</td>
<td>0.32 ± 0.14</td>
<td>0.29 ± 0.20</td>
</tr>
<tr>
<td>Average starting insulin dose (IU/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant use of other AHAs (proportions, assuming 0 if not reported)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET, not SU</td>
<td>0.32</td>
<td>0.39</td>
<td>0.32</td>
</tr>
<tr>
<td>MET and SU</td>
<td>0.17</td>
<td>0.19</td>
<td>0.27</td>
</tr>
<tr>
<td>SU, not MET</td>
<td>0.20</td>
<td>0.20</td>
<td>0.16</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>0.03</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>TZD</td>
<td>0.02</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Covariates, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c</td>
<td>8.8 ± 0.4</td>
<td>8.8 ± 0.3</td>
<td>8.7 ± 0.7</td>
</tr>
<tr>
<td>Δ HbA1c</td>
<td>−1.3 ± 0.5</td>
<td>−1.4 ± 0.4</td>
<td>−1.3 ± 0.7</td>
</tr>
<tr>
<td>Baseline weight (kg)'</td>
<td>85.3 ± 7.9</td>
<td>85.8 ± 7.2</td>
<td>88.0 ± 6.7</td>
</tr>
<tr>
<td>Δ Weight</td>
<td>1.6 ± 1.1</td>
<td>1.7 ± 1.0</td>
<td>2.3 ± 1.4</td>
</tr>
<tr>
<td>Baseline BMI'</td>
<td>30.4 ± 2.5</td>
<td>30.5 ± 2.3</td>
<td>31.1 ± 1.9</td>
</tr>
<tr>
<td>Δ BMI'</td>
<td>0.6 ± 0.4</td>
<td>0.6 ± 0.3</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td>Hypoglycemia event rates per patient-year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic, mean ± SD</td>
<td>6.37 ± 3.24</td>
<td>6.37 ± 3.24</td>
<td>7.49 ± 9.18</td>
</tr>
<tr>
<td>Severe, mean ± SD</td>
<td>0.04 ± 0.02</td>
<td>0.04 ± 0.02</td>
<td>0.06 ± 0.07</td>
</tr>
<tr>
<td>Nocturnal, mean ± SD</td>
<td>1.95 ± 1.13</td>
<td>2.03 ± 1.13</td>
<td>2.80 ± 3.40</td>
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<tr>
<td>Hypoglycemia events: proportions experiencing at least one event</td>
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<tr>
<td>Symptomatic</td>
<td>0.35</td>
<td>0.37</td>
<td>0.38</td>
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<tr>
<td>Severe</td>
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<td>0.05</td>
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<tr>
<td>Nocturnal</td>
<td>0.13</td>
<td>0.06</td>
<td>0.13</td>
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</tbody>
</table>

* Including imputed values.

(P = 0.312). Combination basal and bolus (P < 0.001) and premix (P = 0.042) insulin regimens both had statistically significant HbA1c lowering versus the reference basal insulin category. The coefficient for study duration was double that of insulin-naive subjects and statistically significant (P = 0.014). The parsimonious specification explained 68% of variability in HbA1c change. Age (P = 0.033) and the proportion of patients using SU (P = 0.082) were included in the Core+ specification on the basis of the stepwise elimination algorithm, which attenuated modestly the dose-response coefficients from −1.218 to −0.894 for study insulin 1 and from −0.716 to −0.571 for study insulin 2. Further inclusion of T2DM duration, concomitant oral medications, and baseline subject age (the All specification) resulted in an estimated coefficient of −0.458 for study insulin 1 and of 0.681 for the more fragile study insulin 2. Results (not presented) identified the cause of this weakening relationship as confounding associated with changing use patterns of SU and MET (obvious confounders given their primary use is to lower blood glucose) over time in a number of studies. Unfortunately, non-insulin comediations are often poorly documented in insulin intervention studies and the change may be attributable to measurement error.

For the Core regressions, the F test of the residual variances between the insulin-naive and insulin-experienced regression fits
<table>
<thead>
<tr>
<th>Sub group</th>
<th>Insulin-naive</th>
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<th>Insulin-experienced</th>
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<td></td>
<td>Study arms</td>
<td>No. of patients</td>
<td>HbA1c (%)</td>
<td>Baseline mean ± SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Type of insulin</td>
<td>Basal</td>
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<td>6004</td>
<td>8.70 ± 0.40</td>
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<td></td>
<td>Bolus</td>
<td>4</td>
<td>537</td>
<td>8.61 ± 0.15</td>
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<tr>
<td></td>
<td>Premix</td>
<td>19</td>
<td>6619</td>
<td>9.66 ± 0.52</td>
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<tr>
<td></td>
<td>Basal and</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>bolus</td>
<td>59</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Baseline HbA1c</td>
<td>≤7.5%</td>
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<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td>7.5%–8.0%</td>
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<td>347</td>
<td>7.86 ± 0.17</td>
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<td>12</td>
<td>1360</td>
<td>8.32 ± 0.11</td>
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<td>8.5%–9.0%</td>
<td>22</td>
<td>4311</td>
<td>8.65 ± 0.12</td>
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<td>12</td>
<td>1573</td>
<td>9.12 ± 0.07</td>
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<td>9.5%–10.0%</td>
<td>8</td>
<td>5321</td>
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<td>&gt;10.0%</td>
<td>2</td>
<td>248</td>
<td>10.20 ± 0.10</td>
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<td></td>
<td>59</td>
<td>–</td>
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<td>–</td>
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<td>ΔIU/kg</td>
<td>≤0.0</td>
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<td>–</td>
<td>–</td>
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<td>–</td>
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<td>0.1–0.2</td>
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<td>0.2–0.3</td>
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<td>742</td>
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<td></td>
<td>0.3–0.4</td>
<td>7</td>
<td>980</td>
<td>8.62 ± 0.24</td>
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<td>0.4–0.5</td>
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<td>3138</td>
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<td>0.6–0.7</td>
<td>4</td>
<td>228</td>
<td>8.92 ± 0.26</td>
</tr>
<tr>
<td></td>
<td>0.7–0.8</td>
<td>6</td>
<td>5588</td>
<td>9.74 ± 0.41</td>
</tr>
<tr>
<td></td>
<td>&gt;0.8</td>
<td>6</td>
<td>1020</td>
<td>8.99 ± 0.69</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

HbA1c, glycated hemoglobin A1c.
### Table 3 - Multivariate meta-regression for HbA1c lowering by study subgroups.

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>Core</th>
<th>Core+</th>
<th>All</th>
<th>Core</th>
<th>Core+</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intercept</strong></td>
<td>3.371 (0.659)</td>
<td>&lt;0.001</td>
<td>4.796 (0.800)</td>
<td>&lt;0.001</td>
<td>5.043 (1.988)</td>
<td>0.015</td>
</tr>
<tr>
<td>Baseline HbA1c</td>
<td>−0.515 (0.079)</td>
<td>&lt;0.001</td>
<td>−0.592 (0.080)</td>
<td>&lt;0.001</td>
<td>−0.575 (0.116)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ Insulin dose (IU/kg) (study insulin 1)</td>
<td>−0.993 (0.252)</td>
<td>&lt;0.001</td>
<td>−0.823 (0.243)</td>
<td>0.001</td>
<td>−0.699 (0.273)</td>
<td>0.014</td>
</tr>
<tr>
<td>Δ Insulin dose (IU/kg) (study insulin 2)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Study insulin 1 is bolus</td>
<td>−0.212 (0.171)</td>
<td>0.220</td>
<td>−0.184 (0.161)</td>
<td>0.258</td>
<td>−0.184 (0.177)</td>
<td>0.306</td>
</tr>
<tr>
<td>Study insulin 1 is premix</td>
<td>−0.038 (0.092)</td>
<td>0.683</td>
<td>−0.037 (0.088)</td>
<td>0.677</td>
<td>0.005 (0.108)</td>
<td>0.961</td>
</tr>
<tr>
<td>Study insulin 1 is basal and bolus</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>−0.714 (0.183)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study duration (wk)</td>
<td>0.004 (0.001)</td>
<td>0.003</td>
<td>0.005 (0.001)</td>
<td>&lt;0.001</td>
<td>0.004 (0.002)</td>
<td>0.009</td>
</tr>
<tr>
<td>Δ Proportion using SU</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4.157 (3.549)</td>
<td>0.249</td>
</tr>
<tr>
<td>Δ Proportion using MET + SU</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>−4.828 (4.871)</td>
<td>0.328</td>
</tr>
<tr>
<td>Δ Proportion using MET</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>−5.121 (3.610)</td>
<td>0.164</td>
</tr>
<tr>
<td>Δ Proportion using TZD</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Baseline weight (kg)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>−0.011 (0.008)</td>
<td>0.198</td>
</tr>
<tr>
<td>DM duration (y)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.044 (0.049)</td>
<td>0.373</td>
</tr>
<tr>
<td>Age (y)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>−0.007 (0.024)</td>
<td>0.777</td>
</tr>
<tr>
<td>Proportion male</td>
<td>—</td>
<td>—</td>
<td>1.612 (0.537)</td>
<td>0.004</td>
<td>−0.698 (0.895)</td>
<td>0.440</td>
</tr>
</tbody>
</table>

| Sample size (arms) | 59 | 57 | 51 | 51 | 49 | 47 |
| **R^2** | 0.836 | 0.859 | 0.669 | 0.682 | 0.734 | 0.780 |
| **Adjusted R^2** | 0.820 | 0.843 | 0.565 | 0.631 | 0.673 | 0.694 |

DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c; MET, metformin; SE, standard error; SU, sulfonylurea; TZD, thiazolidinedione.

* Reference category is basal regimen.
was statistically significant ($P = 0.015$), suggesting that the populations should not be pooled.

**Change in weight**

Mean weight change stratified by type of insulin intervention, baseline weight, and insulin intervention dose is presented in Table 4, separately for insulin-naive and nonnaive subjects. Each insulin type was associated with substantial weight increases. Mean change was consistently smaller for insulin-experienced subjects than for insulin-naive subjects. There was no clear relationship between baseline weight and the magnitude of weight gain in either subgroup. The dose-response relationship is apparent in both subpopulations. Mean BMI stratified by type of insulin intervention, BMI, and insulin intervention dose is presented in Appendix Table 1 in Supplemental Materials 2.

Multivariate meta-regression results are presented in Table 5. For insulin-naive subjects, the coefficient for insulin intervention dose in the parsimonious Core specification was statistically significant ($P = 0.001$) and positive as expected. Each increase of 1 IU/kg was associated with a weight gain of 3.26 kg, even after controlling for other factors. The coefficient associated with study duration was also positive and statistically significant ($P = 0.049$), reflecting continued weight gain over time. Baseline weight had a small but statistically insignificant effect ($P = 0.291$). Although not statistically significant, premix and especially the combination of basal and bolus had numerically greater weight gain than basal insulin. The Core covariates together explained 49% of the variation in weight change. Only age was statistically significant and included in the Core+ specification ($P = 0.039$), but the key Core coefficients were robust to this inclusion. The key Core coefficients were also relatively robust to the forced inclusion of T2DM duration, concomitant oral medications, baseline subject age, and proportion male, though there was some attenuation of the dose-response relationship and the impact of baseline weight increased. Nine observations were lost to missing values, however. Meta-regression results for BMI are presented in Appendix Table 2 in Supplemental Materials 2 found at http://dx.doi.org/10.1016/j.jval.2016.10.004.

The multivariate regression results were also strong for insulin-experienced subjects. The coefficient for the primary insulin intervention dose in the Core specification was positive as expected, larger than for insulin-naive subjects, and statistically significant ($P < 0.001$). The coefficient associated with the second dose-response coefficient (estimable for studies with two insulin interventions) was similar in magnitude and nearly statistically significant ($P = 0.060$). The Core covariates together explained 44% of the variation in weight change. No variables were statistically significant and included in the Core+ specification. With the exception of insulin dose, which was attenuated by 50% and statistically insignificant ($P = 0.155$), the key Core coefficients were generally robust to the forced inclusion of the candidate Core+ covariates. Possible confounding due to measurement error regarding comedication with noninsulin AHAs is a likely explanation.

For the Core regressions, the $F$ test of the residual variances between the insulin-naive and the insulin-experienced regression fits was not statistically significant ($P = 0.137$), providing insufficient evidence to conclude that the variance structure of the residuals differs between these two regressions.

### Table 4 – Change in weight, stratified by insulin type, weight, and dose.

<table>
<thead>
<tr>
<th>Sub group</th>
<th>Insulin-naive</th>
<th></th>
<th></th>
<th>Insulin-experienced</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study arms</td>
<td>No. of patients</td>
<td>Mean ± SD</td>
<td>Δ Mean ± SD</td>
<td>Study arms</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Type of insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>33</td>
<td>5285</td>
<td>86.10 ± 7.40</td>
<td>2.47 ± 1.08</td>
<td>17</td>
<td>2661</td>
</tr>
<tr>
<td>Bolus</td>
<td>4</td>
<td>537</td>
<td>85.00 ± 1.30</td>
<td>4.58 ± 1.69</td>
<td>3</td>
<td>307</td>
</tr>
<tr>
<td>Premix</td>
<td>17</td>
<td>6367</td>
<td>95.50 ± 6.40</td>
<td>3.13 ± 0.94</td>
<td>11</td>
<td>1721</td>
</tr>
<tr>
<td>Basal and bolus</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>2676</td>
</tr>
<tr>
<td>Baseline weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>6</td>
<td>461</td>
<td>68.20 ± 1.70</td>
<td>2.50 ± 1.42</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>70-75</td>
<td>3</td>
<td>351</td>
<td>71.30 ± 1.60</td>
<td>2.72 ± 1.18</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>75-80</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>625</td>
</tr>
<tr>
<td>80-85</td>
<td>12</td>
<td>1880</td>
<td>83.40 ± 1.40</td>
<td>2.87 ± 1.72</td>
<td>15</td>
<td>2314</td>
</tr>
<tr>
<td>85-90</td>
<td>15</td>
<td>2474</td>
<td>87.10 ± 1.40</td>
<td>2.89 ± 1.40</td>
<td>13</td>
<td>3073</td>
</tr>
<tr>
<td>90-95</td>
<td>10</td>
<td>1571</td>
<td>91.70 ± 1.70</td>
<td>3.08 ± 1.02</td>
<td>3</td>
<td>524</td>
</tr>
<tr>
<td>95-100</td>
<td>8</td>
<td>5452</td>
<td>98.20 ± 0.60</td>
<td>2.93 ± 0.69</td>
<td>4</td>
<td>552</td>
</tr>
<tr>
<td>≥100</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ IU/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>0.0-0.1</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>1223</td>
</tr>
<tr>
<td>0.1-0.2</td>
<td>1</td>
<td>19</td>
<td>68.10 ± 0</td>
<td>0.40 ± 0</td>
<td>12</td>
<td>2054</td>
</tr>
<tr>
<td>0.2-0.3</td>
<td>4</td>
<td>504</td>
<td>82.80 ± 7.80</td>
<td>1.53 ± 0.48</td>
<td>9</td>
<td>1255</td>
</tr>
<tr>
<td>0.3-0.4</td>
<td>12</td>
<td>728</td>
<td>88.40 ± 8.20</td>
<td>1.49 ± 0.15</td>
<td>6</td>
<td>910</td>
</tr>
<tr>
<td>0.4-0.5</td>
<td>15</td>
<td>2657</td>
<td>84.10 ± 8.40</td>
<td>2.59 ± 1.08</td>
<td>6</td>
<td>1350</td>
</tr>
<tr>
<td>0.5-0.6</td>
<td>13</td>
<td>1445</td>
<td>88.40 ± 5.90</td>
<td>2.52 ± 1.43</td>
<td>2</td>
<td>221</td>
</tr>
<tr>
<td>0.6-0.7</td>
<td>4</td>
<td>228</td>
<td>91.10 ± 4.00</td>
<td>2.73 ± 0.46</td>
<td>1</td>
<td>187</td>
</tr>
<tr>
<td>0.7-0.8</td>
<td>6</td>
<td>5588</td>
<td>96.90 ± 4.00</td>
<td>3.20 ± 0.59</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>&gt;0.8</td>
<td>6</td>
<td>1020</td>
<td>86.20 ± 4.10</td>
<td>4.46 ± 1.40</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5 – Multivariate meta-regression for weight change by study subgroups.

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>Core</th>
<th>Core+</th>
<th>All</th>
<th>Core</th>
<th>Core+</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (SE)</td>
<td>P</td>
<td>Coefficient (SE)</td>
<td>P</td>
<td>Coefficient (SE)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Intercept</strong></td>
<td>2.188 (1.544)</td>
<td>0.163</td>
<td>9.758 (3.865)</td>
<td>0.015</td>
<td>14.328 (7.994)</td>
<td>0.082</td>
</tr>
<tr>
<td><strong>Baseline weight (kg)</strong></td>
<td>−0.020 (0.019)</td>
<td>0.291</td>
<td>−0.030 (0.019)</td>
<td>0.117</td>
<td>−0.060 (0.032)</td>
<td>0.070</td>
</tr>
<tr>
<td><strong>Δ Insulin dose (IU/kg) (study insulin 1)</strong></td>
<td>3.258 (0.960)</td>
<td>0.001</td>
<td>3.057 (0.931)</td>
<td>0.002</td>
<td>2.434 (1.060)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Δ Insulin dose (IU/kg) (study insulin 2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study insulin 1 is bolus</strong></td>
<td>0.812 (0.639)</td>
<td>0.210</td>
<td>0.842 (0.617)</td>
<td>0.179</td>
<td>0.924 (0.679)</td>
<td>0.182</td>
</tr>
<tr>
<td><strong>Study insulin 1 is premix</strong></td>
<td>0.216 (0.331)</td>
<td>0.516</td>
<td>0.004 (0.335)</td>
<td>0.992</td>
<td>0.038 (0.466)</td>
<td>0.935</td>
</tr>
<tr>
<td><strong>Study insulin 1 is basal and bolus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study duration (wk)</strong></td>
<td>0.010 (0.005)</td>
<td>0.049</td>
<td>0.015 (0.005)</td>
<td>0.007</td>
<td>0.018 (0.006)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Δ Proportion using SU</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Δ Proportion using MET + SU</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Δ Proportion using MET</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Δ Proportion using TZD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DM duration (y)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proportion male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sample size (arms)</strong></td>
<td>56</td>
<td>54</td>
<td>47</td>
<td>44</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td><strong>R²</strong></td>
<td>0.490</td>
<td>0.534</td>
<td>0.603</td>
<td>0.438</td>
<td>0.438</td>
<td>0.521</td>
</tr>
<tr>
<td><strong>Adjusted R²</strong></td>
<td>0.437</td>
<td>0.475</td>
<td>0.463</td>
<td>0.328</td>
<td>0.328</td>
<td>0.291</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c; MET, metformin; SE, standard error; SU, sulfonylurea; TZD, thiazolidinedione.

* Reference category is basal regimen.
Nevertheless, for consistency with the HbA1c equations estimated earlier, we recommend using the insulin-naive or insulin-experienced fits.

Statistical Analysis of Hypoglycemic Events

Symptomatic hypoglycemic events
Mean symptomatic hypoglycemic event rates stratified by type of insulin, average HbA1c, insulin dose, and study duration are presented in Table 6. There is strong evidence that hypoglycemic event rates vary by insulin type, with the combination of basal and bolus having higher rates than the other types. The expected negative relationship between average HbA1c and symptomatic hypoglycemic event rates was unclear, though studies with average HbA1c exceeding 9.0% did have consistently lower event rates than those with HbA1c less than 8.5%. Neither was evidence for a dose-response relationship clear, and pooling insulin-naive and insulin-experienced subgroups appears to disguise heterogeneity at the more disaggregated level.

Not surprisingly, thus, the multivariate meta-regression results had a relatively poor fit. The results are presented in Appendix Tables 3 and 4 in Supplemental Materials 2 found at http://dx.doi.org/10.1016/j.jval.2016.10.004. The coefficients associated with the key covariates (in particular, average HbA1c and average insulin dose) were sensitive to subgroup and model specification. For example, in the insulin-naive subset, the coefficient for average HbA1c is $-1.441 (P = 0.004)$ in the Core, $-0.712 (P = 0.059)$ in the Core+, and $-0.942 (P = 0.067)$ in the All covariates specifications, but takes implausible positive values instead for insulin-experienced patients. In the subset of observational studies, this coefficient changes sign depending on which covariates are included. The dose-response relationship is similarly inconsistent. This sensitivity to specifications could not be resolved by transformation of variables or inclusion of interaction terms, and the most likely explanation is inconsistent reporting of hypoglycemic event rates and measurement error related to differing event definitions.

Severe hypoglycemic events
Mean severe hypoglycemic event rates stratified by type of insulin, average HbA1c, insulin dose, and study duration are presented in Table 7. As with symptomatic hypoglycemia, clear differences by type of insulin are seen, and the combination of basal and bolus appears to be associated with the highest rate (0.042 per patient-year). A consistent relationship between average HbA1c and severe hypoglycemic event rate was not detected, nor was a clear dose-response relationship. As with symptomatic hypoglycemia, the meta-regression results (presented in Appendix Table 5 in Supplemental Materials 2 found at http://dx.doi.org/10.1016/j.jval.2016.10.004) were sensitive to assumptions on which covariates to include. The small sample size likely exacerbated the lack of robustness.

Nocturnal hypoglycemic events
Mean nocturnal hypoglycemic event rates stratified by type of insulin, average HbA1c, insulin dose, and study duration are presented in Table 8. As with symptomatic and severe hypoglycemic events, differences in nocturnal event rates were apparent by type of insulin regimen, but no clear relationships to average HbA1c or insulin dose could be identified. Meta-regression results, presented in Appendix Table 6 in Supplemental Materials 2 found at http://dx.doi.org/10.1016/j.jval.2016.10.004, were sensitive to model specification and to small sample size.

Proportion of patients experiencing at least one hypoglycemic event
Small sample sizes limited our ability to analyze cumulative incidence proportion data. For models that are based on this measure, stratified descriptive statistics are presented for symptomatic, severe, and nocturnal hypoglycemic events separately in Appendix Tables 7, 8, and 9, respectively, in Supplemental Materials 2 found at http://dx.doi.org/10.1016/j.jval.2016.10.004.

Discussion

Study results from a large number of clinical trials of subjects with T2DM treated with insulin therapy were used to estimate parsimonious, multivariate treatment effect and hypoglycemic event risk prediction equations to inform insulin-related rescue treatment effects on surrogate biomarkers in model-based cost-effectiveness evaluations. Although inclusion of a broad set of studies covering different treatment settings, patient groups, and lines of therapy is discouraged in traditional meta-analysis, in which study inclusion is set to match closely the intended usage [17], here it enhanced our ability to fit the expected causal relationships in a meta-regression and improved the generalizability of the prediction equations to different treatment settings.

The multivariate prediction equations for changes in HbA1c and weight exhibited good fit and the coefficients associated with the key covariates had expected signs and were statistically significant. Estimates were generally robust to the inclusion of potentially noncausal confounding factors. The insulin dose-response relationship for weight change was attenuated by the inclusion of comedication with SU and MET, though this might be attributable to lesser rigor in study reporting for background noninsulin AHA and the likelihood of measurement error. The $R^2$ values were high, especially for HbA1c change. There was evidence of heterogeneity by previous insulin experience, which is accommodated easily within economic modeling because separate profiles for insulin-naive and insulin-experienced patients are routinely modeled.

The insulin dose and baseline HbA1c are shown in a three-dimensional bar chart in Figure 2, using the set of coefficients from the parsimonious Core specification for the insulin-naive studies. The other covariates were set to basal insulin and 52-week study duration. Predicted HbA1c lowering increases with increasing insulin dose, for example, ranging from 0.12 at a dose of 0.1 IU/kg to 0.52 at a dose of 0.5 IU/kg (for patients with baseline HbA1c of 7.0%). HbA1c lowering also increased with baseline HbA1c, for example, ranging from 0.12 at baseline HbA1c of 7.0% to 1.67 at baseline HbA1c of 10.0% (for patients with an insulin dose of 0.1 IU/kg).

The prediction equations for hypoglycemic events were less successful. Considerable heterogeneity in the event definitions appears to be the most plausible explanation. Unlike HbA1c and weight change in which standardization is naturally high, we encountered more than 100 different definitions of hypoglycemic event types. For example, for symptomatic hypoglycemia, we included the following definitions: “all” (14 studies), “symptomatic” (15 studies), and “minor, confirmed by plasma glucose less than 3.1 mmol/L” (4 studies), together with 44 less frequently used definitions involving alternative thresholds or terminology. Category assignment was conducted pragmatically by a qualified clinician, but without question has led to heterogeneity. As noted by Swinnen et al. [18], the choice of cutoff values has a major impact on reported frequencies. In addition, the methods for collection of hypoglycemia differ a lot between studies, and symptomatic events tend to be under-reported in noninterventional studies because health care visits are seldom required.
Table 6 - Symptomatic hypoglycemia, stratified by insulin type, HbA$_{1c}$, dose, and study duration.

<table>
<thead>
<tr>
<th>Sub group</th>
<th>Insulin-naive and insulin-experienced</th>
<th>Insulin-naive</th>
<th>Insulin-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study arms</td>
<td>No. of patients</td>
<td>Symptomatic hypoglycemic events/patient-year, mean ± SD</td>
</tr>
<tr>
<td>Type of insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>43</td>
<td>46,536</td>
<td>2.08 ± 2.48</td>
</tr>
<tr>
<td>Bolus</td>
<td>9</td>
<td>4,825</td>
<td>2.99 ± 3.52</td>
</tr>
<tr>
<td>Premix</td>
<td>29</td>
<td>106,415</td>
<td>2.32 ± 2.64</td>
</tr>
<tr>
<td>Basal and bolus</td>
<td>14</td>
<td>2,002</td>
<td>10.28 ± 13.70</td>
</tr>
<tr>
<td>Average HbA$_{1c}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7.5%</td>
<td>11</td>
<td>1,521</td>
<td>3.74 ± 3.10</td>
</tr>
<tr>
<td>7.5%–8.0%</td>
<td>29</td>
<td>5,533</td>
<td>9.85 ± 12.52</td>
</tr>
<tr>
<td>8.0%–8.5%</td>
<td>35</td>
<td>124,758</td>
<td>2.15 ± 1.78</td>
</tr>
<tr>
<td>8.5%–9.0%</td>
<td>14</td>
<td>26,712</td>
<td>1.81 ± 1.56</td>
</tr>
<tr>
<td>&gt;9.0%</td>
<td>6</td>
<td>1,254</td>
<td>1.37 ± 1.57</td>
</tr>
<tr>
<td>Average IU/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.3</td>
<td>23</td>
<td>36,385</td>
<td>2.32 ± 3.22</td>
</tr>
<tr>
<td>0.3–0.4</td>
<td>21</td>
<td>61,737</td>
<td>2.71 ± 1.74</td>
</tr>
<tr>
<td>0.4–0.5</td>
<td>13</td>
<td>38,275</td>
<td>1.11 ± 0.88</td>
</tr>
<tr>
<td>0.5–0.6</td>
<td>12</td>
<td>15,149</td>
<td>2.35 ± 0.76</td>
</tr>
<tr>
<td>0.6–0.7</td>
<td>9</td>
<td>2,951</td>
<td>3.94 ± 5.26</td>
</tr>
<tr>
<td>0.7–0.8</td>
<td>7</td>
<td>3,631</td>
<td>2.69 ± 1.56</td>
</tr>
<tr>
<td>0.8–0.9</td>
<td>7</td>
<td>1,044</td>
<td>17.23 ± 16.04</td>
</tr>
<tr>
<td>&gt;0.9</td>
<td>3</td>
<td>606</td>
<td>15.89 ± 22.00</td>
</tr>
<tr>
<td>Study duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 or 24 wk</td>
<td>48</td>
<td>96,322</td>
<td>2.07 ± 3.88</td>
</tr>
<tr>
<td>26 wk</td>
<td>15</td>
<td>58,157</td>
<td>2.54 ± 0.66</td>
</tr>
<tr>
<td>28 or 36 wk</td>
<td>11</td>
<td>1,354</td>
<td>7.23 ± 4.26</td>
</tr>
<tr>
<td>52 wk or longer</td>
<td>21</td>
<td>3,945</td>
<td>5.56 ± 4.90</td>
</tr>
</tbody>
</table>

HbA$_{1c}$, glycated hemoglobin A$_{1c}$.
Table 7 – Severe hypoglycemia, stratified by insulin type, HbA1c, dose, and study duration.

<table>
<thead>
<tr>
<th>Sub group</th>
<th>Insulin-naive and insulin-experienced</th>
<th>Insulin-naive</th>
<th>Insulin-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study arms</td>
<td>No. of patients</td>
<td>Severe hypoglycemic events/patient-year, mean ± SD</td>
</tr>
<tr>
<td>Type of insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>23</td>
<td>41,273</td>
<td>0.008 ± 0.021</td>
</tr>
<tr>
<td>Bolus</td>
<td>6</td>
<td>4,826</td>
<td>0.002 ± 0.006</td>
</tr>
<tr>
<td>Premix</td>
<td>19</td>
<td>104,314</td>
<td>0.012 ± 0.026</td>
</tr>
<tr>
<td>Basal and bolus</td>
<td>8</td>
<td>770</td>
<td>0.042 ± 0.037</td>
</tr>
<tr>
<td>Average HbA1c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7.5%</td>
<td>5</td>
<td>593</td>
<td>0.017 ± 0.015</td>
</tr>
<tr>
<td>7.5%–8.0%</td>
<td>17</td>
<td>3,451</td>
<td>0.039 ± 0.078</td>
</tr>
<tr>
<td>8.0%–8.5%</td>
<td>25</td>
<td>123,230</td>
<td>0.007 ± 0.020</td>
</tr>
<tr>
<td>&gt;8.5%</td>
<td>9</td>
<td>23,909</td>
<td>0.027 ± 0.023</td>
</tr>
<tr>
<td>Average IU/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.3</td>
<td>9</td>
<td>30,870</td>
<td>0.004 ± 0.011</td>
</tr>
<tr>
<td>0.3–0.4</td>
<td>14</td>
<td>60,799</td>
<td>0.010 ± 0.024</td>
</tr>
<tr>
<td>0.4–0.5</td>
<td>12</td>
<td>39,233</td>
<td>0.009 ± 0.023</td>
</tr>
<tr>
<td>0.5–0.6</td>
<td>5</td>
<td>13,727</td>
<td>0.019 ± 0.003</td>
</tr>
<tr>
<td>0.6–0.7</td>
<td>6</td>
<td>2,480</td>
<td>0.010 ± 0.011</td>
</tr>
<tr>
<td>0.7–0.8</td>
<td>2</td>
<td>2,349</td>
<td>0.009 ± 0.003</td>
</tr>
<tr>
<td>0.8–0.9</td>
<td>6</td>
<td>1,007</td>
<td>0.163 ± 0.087</td>
</tr>
<tr>
<td>&gt;0.9</td>
<td>2</td>
<td>718</td>
<td>0.025 ± 0.009</td>
</tr>
<tr>
<td>Study duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 or 24 wk</td>
<td>30</td>
<td>93,704</td>
<td>0.010 ± 0.024</td>
</tr>
<tr>
<td>26 wk</td>
<td>7</td>
<td>53,401</td>
<td>0.008 ± 0.001</td>
</tr>
<tr>
<td>28 or 36 wk</td>
<td>3</td>
<td>375</td>
<td>0.029 ± 0.045</td>
</tr>
<tr>
<td>52 wk or longer</td>
<td>16</td>
<td>3,703</td>
<td>0.059 ± 0.085</td>
</tr>
</tbody>
</table>

HbA1c, glycated hemoglobin A1c.
Table 8 – Nocturnal hypoglycemia, stratified by insulin type, HbA1c, dose, and study duration.

<table>
<thead>
<tr>
<th>Sub group</th>
<th>Insulin-naive and insulin-experienced</th>
<th>Insulin-naive</th>
<th>Insulin-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study arms</td>
<td>No. of patients</td>
<td>Nocturnal hypoglycemic events/patient-year, mean ± SD</td>
</tr>
<tr>
<td>Type of insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>25</td>
<td>41,193</td>
<td>0.60 ± 1.42</td>
</tr>
<tr>
<td>Bolus</td>
<td>6</td>
<td>4,466</td>
<td>0.51 ± 1.32</td>
</tr>
<tr>
<td>Premix</td>
<td>20</td>
<td>105,314</td>
<td>0.97 ± 0.94</td>
</tr>
<tr>
<td>Basal and bolus</td>
<td>7</td>
<td>1,252</td>
<td>1.67 ± 2.00</td>
</tr>
<tr>
<td>Average HbA1c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7.5%</td>
<td>5</td>
<td>717</td>
<td>1.51 ± 1.01</td>
</tr>
<tr>
<td>7.5%–8.0%</td>
<td>20</td>
<td>4,393</td>
<td>2.77 ± 3.37</td>
</tr>
<tr>
<td>8.0%–8.5%</td>
<td>25</td>
<td>123,233</td>
<td>0.87 ± 1.00</td>
</tr>
<tr>
<td>&gt;8.5%</td>
<td>8</td>
<td>23,882</td>
<td>0.45 ± 0.18</td>
</tr>
<tr>
<td>Average IU/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.3</td>
<td>16</td>
<td>33,470</td>
<td>0.64 ± 1.61</td>
</tr>
<tr>
<td>0.3–0.4</td>
<td>15</td>
<td>61,071</td>
<td>0.61 ± 0.90</td>
</tr>
<tr>
<td>0.4–0.5</td>
<td>10</td>
<td>37,869</td>
<td>1.52 ± 0.79</td>
</tr>
<tr>
<td>0.5–0.6</td>
<td>5</td>
<td>13,765</td>
<td>0.58 ± 0.33</td>
</tr>
<tr>
<td>0.6–0.7</td>
<td>3</td>
<td>2,286</td>
<td>0.55 ± 0.59</td>
</tr>
<tr>
<td>0.7–0.8</td>
<td>3</td>
<td>2,886</td>
<td>0.84 ± 0.20</td>
</tr>
<tr>
<td>0.8–0.9</td>
<td>5</td>
<td>691</td>
<td>2.75 ± 1.29</td>
</tr>
<tr>
<td>&gt;0.9</td>
<td>1</td>
<td>187</td>
<td>6.17 ± 0.1</td>
</tr>
<tr>
<td>Study duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 or 24 wk</td>
<td>36</td>
<td>95,204</td>
<td>1.02 ± 1.39</td>
</tr>
<tr>
<td>26 wk</td>
<td>9</td>
<td>55,055</td>
<td>0.57 ± 0.14</td>
</tr>
<tr>
<td>28 or 36 wk</td>
<td>5</td>
<td>752</td>
<td>0.98 ± 0.56</td>
</tr>
<tr>
<td>52 wk or longer</td>
<td>8</td>
<td>1,214</td>
<td>1.29 ± 0.78</td>
</tr>
</tbody>
</table>

HbA1c, glycated hemoglobin A1c.
The use of multivariate meta-regression, fit to a broad evidence base, enhances generalizability to different treatment settings. Moreover, we recommend the choice of a parsimonious Core set of variables, which makes the prediction equations relevant to modeling new interventions. By using meta-regression estimates such as these, the modeler can bridge the discrepancy between the desired setting and the available evidence without having to make arbitrary decisions on which existing studies to consider relevant. In addition, efficacy of rescue treatment can be tailored to reflect a hypothetical patient’s characteristics at the simulated time of insulin initiation. We illustrate the intended usage of these findings in a Numerical Example and in Appendix Table 10 in Supplemental Materials 2 found at http://dx.doi.org/10.1016/j.jval.2016.10.004.

A potential limitation of the meta-regression approach is its reliance on aggregated study results and not actual patient-level data (which offer better statistical power, estimates of patient-level variability, and the ability to confirm hypothesized relationships at the individual level). Patient-level Diabetes Control and Complications Trial study data [14] have been used to estimate proportional hazard equations for severe hypoglycemic event rates for T1DM, when a clear negative relationship with baseline HbA1c and positive relationships with HbA1c lowering and insulin dose were found. Although useful, these estimated relationships are specific to a single trial (and patient population) and specific to T1DM, and so they are poorly generalizable to parameterizing insulin rescue therapy in economic modeling of T2DM. Patient-level analyses can be useful to overcome potential endogeneity problems when explanatory variables are available at the population level only, but by restricting the set of explanatory variables to those in which the direction of the effect is clear a priori, we minimized the risk of endogeneity problems. Another potential limitation could be the absence of good, standardized reporting of participants’ diet and lifestyle practices in the trials. A meta-analysis of individual patient data from as many studies as considered here would also have imposed a large set of administrative challenges ranging from obtaining access to the data to imposing a common data structure to all studies, and this was unfeasible with the large number of studies identified here.

Restricting the search to the PubMed database only may be seen as a limitation, but as many additional articles were identified through reference lists of existing review articles, we believe that the evidence base is representative.

Similar to the present study, Esposito et al. [15] compared the glucose lowering of eight types of AHAs (including insulin) using trial-level results. Mean HbA1c change and the proportion of patients meeting HbA1c levels of less than 7% were stratified by intervals of baseline HbA1c. The results for insulin concord well with our results because both studies confirmed a strong relationship between HbA1c lowering and baseline HbA1c. Our study extends the Esposito et al. [15] analysis by including insulin dose, weight change, and hypoglycemic events and by using meta-regression techniques to estimate prediction equations.

McEwan et al. [13] estimated log-linear prediction equations for the frequency of severe and nonsevere hypoglycemic events for insulin-treated patients with T2DM. Their literature search identified 82 studies containing a total of 155 study arms. Although there was an inverse relationship between HbA1c change and event rates, insulin dose was not considered. The covariates explained between 20% and 30% of the variability in outcomes. The McEwan sample included more studies than ours because reporting of insulin dose was not an inclusion criterion (we excluded 65 studies on this basis). The studies included in the McEwan study and the present study matched closely, however, with respect to descriptive statistics though the mean rates of hypoglycemic events in the McEwan study were higher than in ours (e.g., 9.30 per patient-year vs. 6.37 for symptomatic hypoglycemic events). Methodological differences may also explain some of the differences in results. For example, McEwan et al. used a linear model on the log-transformed event rates, whereas we used a generalized linear model with an assumption on heteroscedastic variances in the event rates. Perhaps more importantly, McEwan et al. did not control for insulin dose, and much of this effect was likely captured by the proxy measure of HbA1c change (which was highly statistically significant).

A number of questions remain unanswered. Foremost, what explains the absence of a relationship between hypoglycemic event rates and insulin dose and HbA1c, which was found in the
Diabetes Control and Complications Trial for patient-level T1DM data [14]? Standardization of hitherto heterogeneous study definitions of hypoglycemia would aid comparability of results across studies. Heterogeneity between the study populations, details of study data collection or reporting, or unreported treatment features could also be a confounding factor.

Conclusions

Parsimonious and robust multivariate prediction equations were estimated for HbA1c and weight change, separately for insulin-naive and insulin-experienced patients, which are suitable for use in improving realism and flexibility in modeling insulin rescue medication in economic simulation modeling in T2DM. Prediction equations were also estimated for symptomatic, severe, and nocturnal hypoglycemic events, though considerable heterogeneity in definitions limits their usefulness.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2016.10.004 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES