Metformin Use May Moderate the Effect of DPP-4 Inhibitors on Cardiovascular Outcomes

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OBJECTIVE

To explore prevalent metformin use as a potential moderator of the cardiovascular effects of dipeptidyl peptidase 4 inhibitors (DPP-4i).

RESEARCH DESIGN AND METHODS

We performed a meta-analysis of the three major cardiovascular outcomes trials examining DPP-4i. We used meta-regression to examine how the cardiovascular effects of DPP-4i differ between prevalent metformin users and baseline nonusers.

RESULTS

While prevalent metformin users experienced a trend toward improved cardiovascular outcomes with DPP-4i (summary hazard ratio [HR] 0.92 [95% CI 0.84, 1.01]), baseline metformin nonusers showed a trend toward harm (HR 1.10 [95% CI 0.97, 1.26]). The difference in overall DPP-4i effect between metformin user and nonuser subgroups was statistically significant (P = 0.036).

CONCLUSIONS

Baseline metformin status may have a moderating effect on cardiovascular outcomes with DPP-4i use. This hypothesis-generating analysis suggests there is residual uncertainty as to how DPP-4i affect cardiovascular outcomes, depending on concurrently prescribed medications.

Dipeptidyl peptidase 4 inhibitors (DPP-4i), which are often added to background metformin therapy as next-line agents for type 2 diabetes, appear to have a neutral effect on cardiovascular outcomes relative to placebo (1–3). However, subgroup analyses of recent cardiovascular outcomes trials (CVOTs) suggest that baseline metformin use may serve as a moderator of the effectiveness of DPP-4i. Among prevalent metformin users, each of the three major DPP-4i CVOTs reported a trend toward better cardiovascular outcomes with DPP-4i; by contrast, each study reported a trend toward poorer outcomes with DPP-4i among baseline nonusers of metformin. Two of these studies reported a significant or near-significant interaction between baseline metformin status and DPP-4i status for the primary outcome (1,2). In order to further explore prevalent metformin use as a potential moderator of the cardiovascular effects of DPP-4i, we conducted a stratified meta-analysis of the three major DPP-4i CVOTs (1–3).

RESEARCH DESIGN AND METHODS

This analysis focused on three recently published CVOTs examining agents in the DPP-4i class (1–3). Each study's supplementary appendix reported relevant data for the subgroups of prevalent metformin users and baseline nonusers,

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including the number of patients in each subgroup, a hazard ratio (HR) for the primary composite study outcome associated with DPP-4i use in each subgroup, and a 95% CI for each subgroup HR.

Because these studies had good conceptual homogeneity in their design, populations, interventions, and outcomes, we performed quantitative synthesis using a DerSimonian-Laird random-effects model (4). As this analysis included only three studies, we conservatively used the Knapp-Hartung approach to adjust the SE of the estimated coefficients (5). In meta-analyses of ≤5 studies, the Knapp-Hartung approach is associated with acceptably low rates of type I error compared with the DerSimonian-Laird approach, particularly when studies are reasonably similar in size (as is the case in this analysis) (6). We performed meta-regression with metformin status as a covariate to establish the statistical significance of the difference in overall DPP-4i effect between prevalent metformin users and baseline nonusers. Subgroup summary HRs and 95% CIs were based on estimates from this meta-regression model. We evaluated statistical heterogeneity using Cochran Q and I^2 statistics. All quantitative analyses were performed using R (version 3.1.2), including R package "metafor" (version 1.9-7) for meta-analysis.

RESULTS

This analysis included three large, multinational trials, each of which randomized patients to receive a DPP-4i agent or placebo in addition to their existing diabetes therapy. Two studies exclusively included patients with known cardiovascular disease (1,2), while the third included patients with either established cardiovascular disease or multiple risk factors. Each study examined a particular DPP-4i agent: sitagliptin (1), alogliptin (2), or saxagliptin (3). The primary composite outcome for each of these studies comprised cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, with one study additionally including hospitalization for unstable angina (1). Only primary composite outcome data were presented by metformin subgroup. Median follow-up duration ranged from 1.5 to 3 years.

For the overall analytic population, DPP-4i had a neutral summary effect on the primary outcome (summary HR 0.99 [95% CI 0.87, 1.13]). However, prevalent metformin users (Fig. 1) experienced a trend toward reduction in the incidence of the primary study outcome with DPP-4i (summary HR 0.92 [95% CI 0.84, 1.01]). Individual study effects were consistent (Cochran Q P = 0.37, I^2 = 0.0%). By contrast, the baseline metformin nonusers showed a trend toward harm with DPP-4i (HR 1.10 [95% CI 0.97, 1.26]). Individual study effects were again consistent (Cochran Q P = 0.75, I^2 = 0.0%).

Using meta-regression, the difference in overall DPP-4i effect between prevalent metformin users and baseline nonusers was statistically significant (P = 0.036), indicating a difference in the relative effects of DPP-4i based on metformin status.

CONCLUSIONS

This stratified meta-analysis of three major DPP-4i CVOTs shows that baseline metformin status may be a moderator of the effect of DPP-4i on cardiovascular outcomes. Consistent with prior analyses (7), DPP-4i use had a neutral effect on the primary composite outcome in the overall population; however, prevalent users of metformin experienced a trend toward reduction of cardiovascular events with DPP-4i, while baseline nonusers showed a trend toward harm. This difference in the overall effect of DPP-4i between metformin user and nonuser subgroups was statistically significant, suggesting that the cardiovascular effects of DPP-4i agents may differ depending on whether these medications are coprescribed with metformin.

Because newer medication classes like DPP-4i are typically added to background metformin therapy (8), metformin's impact on the effectiveness of next-line drugs is of great interest. Currently, how diabetes medication classes interact to

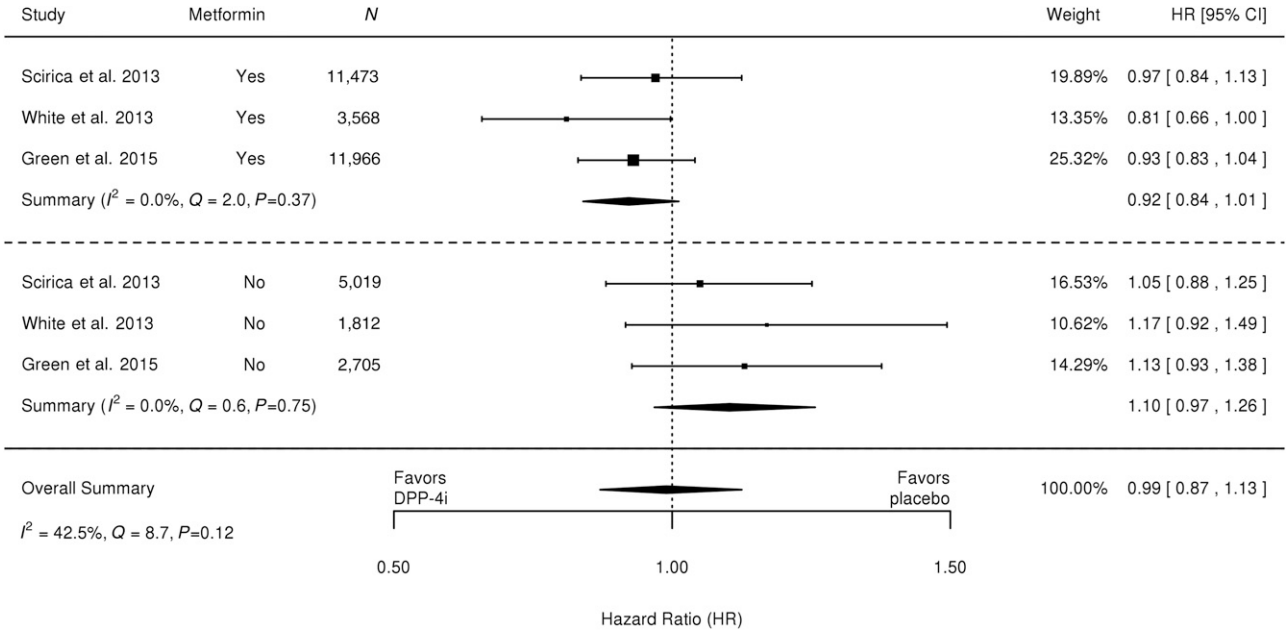

Figure 1—Forest plot depicting the effect of DPP-4i on primary composite study outcomes, stratified by metformin user/nonuser subgroups (P = 0.036 for difference in DPP-4i effect between prevalent metformin users and baseline nonusers). N = number of patients.

affect cardiovascular outcomes is not well understood. This hypothesis-generating analysis suggests that there is residual uncertainty as to whether DPP-4i are associated with cardiovascular neutrality, benefit, or even harm, depending on how these medications are used in clinical practice.

Prevalent metformin users showed a trend toward improved cardiovascular outcomes with DPP-4i in this analysis. One physiologic mechanism by which metformin could potentiate the effectiveness of DPP-4i is via glucagon-like peptide 1 (GLP-1); metformin raises GLP-1 levels (9,10), and DPP-4i act by inhibiting GLP-1 degradation. It is therefore plausible that these drugs could interact synergistically. Baseline nonusers of metformin showed a trend toward poorer outcomes with DPP-4i, raising the possibility that off-target effects may outweigh any benefits of DPP-4i use in the absence of metformin.

While the effect of DPP-4i differed significantly between prevalent metformin users and baseline nonusers, metformin use is likely not the sole difference between these subgroups. For example, metformin use may be a marker for baseline differences in rates of chronic kidney disease or congestive heart failure, for which this analysis does not account. For this reason, it is possible that metformin use itself does not mediate the observed difference in DPP-4i effect between metformin users and nonusers. Subsequent analyses should incorporate statistical adjustment for other population differences through use of patient-level data and should seek to assess available outcome measures individually rather than relying on composite outcomes.

We chose to focus exclusively on the three major DPP-4i CVOTs because these studies enrolled similar populations, used similar primary outcomes, and all reported data on metformin subgroups. The low heterogeneity on our stratified meta-analyses attests to these studies' similarity. Of note, specific agents within the DPP-4i class may interact with metformin differently. Future research should further examine metformin's moderating effects on individual DPP-4i agents and also explore how metformin may interact with other novel medication classes, such as GLP-1 receptor agonists and sodium–glucose cotransporter 2 inhibitors.

In summary, this hypothesis-generating analysis suggests that baseline metformin status may have a moderating effect on cardiovascular outcomes with DPP-4i use. These novel findings have great import for clinical application of DPP-4i and suggest intriguing areas for future investigation relating to DPP-4i and other diabetes medication classes.

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