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Impact of time to treatment intensification on glycemic goal attainment among patients with type 2 diabetes failing metformin monotherapy

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ABSTRACT

Background: Patients with type 2 diabetes on metformin monotherapy frequently require treatment intensification with another anti-hyperglycemic medication over time. Previous studies have indicated that a high proportion of patients with diabetes have a significant delay in the initiation of oral add-on therapy after metformin alone fails to achieve targeted glycemic control. In this study, we evaluated the impact of the timing of treatment intensification with oral add-on drug on glycemic goal attainment among diabetic patients failing metformin monotherapy.

Research design and methods: Using the General Electric (GE) Centricity Electronic Medical Record database (January 2004 through December 2009), we identified 5,870 patients with type 2 diabetes with treatment failure on metformin monotherapy - defined by a glycosylated hemoglobin (HbA1c) of ≥7.5% (index date). This cut-off of ≥7.5% (trigger HbA1c) was chosen rather than that of >7.0% to ensure that selected patients were more likely to be indicated for treatment intensification with add-on drug. Continuous enrollment of one year prior and two years after index date was required to be included in the study. Add-on treatment was defined as prescription of second oral agent from any available therapeutic classes while continuing metformin. Early treatment intensification was defined as initiation of oral add-on therapy within 3 months (n = 1,012) of index date while late intensification was defined as add-on initiation between 10 and 15 months after index date (n = 461). The study outcome was defined as glycemic goal attainment (HbA1c < 7%), which was evaluated between 18 and 24 months after index date.

Results: Our results suggested that at the end of the follow-up period, 47.2% of patients in the early add-on group were at glycemic goal compared to 41.7% in the late add-on group (p = 0.039). In a multivariable logistic regression model that accounted for age, gender, trigger HbA1c level, Charlson comorbidity index, anti-hypertensive and anti-hyperlipidemic drug use and history of cardiovascular disease, the adjusted odds ratio (OR) for glycemic goal attainment was 1.36 (95% confidence intervals [CI]: 1.09–1.72) comparing early add-on to late add-on treatment. This association was stronger among patients with higher trigger HbA1c at baseline; ORs of 1.53 (95% CI: 1.08–2.19) for HbA1c ≥8% and 2.63 (95% CI: 1.40–5.27) for HbA1c ≥9%.

Conclusion: These results suggest that earlier use of oral add-on drug in treatment regimen helps better achieve glycemic goal attainment in patients with metformin failure. Future studies should evaluate whether earlier treatment intensification is also associated with longer term health outcomes such as risk of microvascular and macrovascular complications.

Type 2 diabetes mellitus is a progressive disease characterized by insulin resistance and progressive loss of β-cell function, which affects 90%–95% of the 25.8 million Americans who have diabetes (Centers for Disease Control and Prevention, 2011). Because of its safety and efficacy, joint guidelines from the American Association of Clinical Endocrinologists (AACE) recommend that metformin be initiated as first line monotherapy unless contraindicated (Garber, Abrahamson, Barzilay, et al., 2013). Similarly, treatment guidelines by the joint task force convened by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) endorse metformin as the optimal first-line drug if not contraindicated and if tolerated (Inzucchi, Bergenstal, Buse, et al., 2012). Johansen (1999) reported the results of a meta-analysis of randomized controlled trials evaluating the efficacy of metformin against placebo in achieving glycemic control. Metformin monotherapy reduced fasting plasma glucose (FPG) levels by 2 mmol/L compared with placebo (95% Confidence Interval (CI): −2.4 to −1.7) and HbA1c values by 0.9 percentage points (95% CI: −1.1 to −0.7). In the studies included in the meta-analysis, the baseline HbA1c value in the metformin treatment group was 9.3 mmol/l (range 7.3 mmol/l to

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11.7 mmol/l) and that in the placebo group was 9.0 mmol/l (range 6.7 mmol/l–11.8 mmol/l).

However, oftentimes achieving or maintaining long-term glycemic control is difficult for many patients on metformin monotherapy, mostly because of a progressive reduction in the ability to produce insulin (Turner, Cull, Frighi, & Holman, 1999). Secondary failure with metformin is not uncommon and is dependent on the initial response to therapy (Nichols, Alexander, Girman, Kamal-Bahl, & Brown, 2006). Despite the improvement in diabetes care in recent times, as much as 40% of patients did not meet the recommended HbA1c target of < 7% in 2006 (Cheung et al., 2009) and more recently (2007–2010) this proportion seems to have increased to about 47% (Casagrande, Fradkin, Saydah, et al., 2013). Phillips, Branch, Cook, et al. (2001) attribute the failure to initiate or intensify therapy to clinical inertia, which the authors define as "recognition of the problem, but failure to act." The response of clinicians to treatment failure is an important contributor to glycemic burden (Brown & Nichols, 2003; Brown, Nichols, & Perry, 2004).

Despite existing treatment algorithms by AACE (Garber et al., 2013) and by ADA and EASD (Inzucchi et al., 2012), determining when to start combination therapy is often challenging. The position statement by ADA/EASD (Inzucchi et al., 2012) recommends that, in case of failure to achieve or sustain glycemic goals with metformin monotherapy and lifestyle modification, another medication should be added within ~3 months of the initiation of therapy or at any time when HbA1c goal is not achieved. However, among patients with type 2 diabetes failing metformin monotherapy, there is often a delay initiating add-on therapy. Recent U.S. data suggest that the median time to treatment intensification among those who failed on metformin monotherapy is more than one year (Fu, Qiu, Davies, Radican, & Engel, 2012). The question that naturally arises is: What is the effect of the timing of treatment intensification with oral add-on drug on glycemic goal attainment among patients with type 2 diabetes failing metformin monotherapy? Hence, we conducted a study to evaluate the impact of timing of treatment intensification with another oral agent on glycemic goal attainment among patients failing metformin monotherapy.

1. Research design and methods

1.1. Data source

A retrospective database study was conducted using the General Electric (GE) Centricity® Electronic Medical Records (EMR) database. The GE database consists of ambulatory data collected from over 1,300 mid- to large-size installations covering over 9,000 U.S. health care providers. Over 85% of the providers are general practitioners, internists, gynecologists and pediatricians. There are over 35 million patient records containing encounter information which includes problems, medications, prescriptions, clinical data, orders, demographics and laboratory results. All data are HIPAA-compliant and anonymized.

Patients with a diagnosis of diabetes constitute 7% of the database. About 75% of those patients have documented HbA1c results with an average of 4 HbA1c values per patient.

1.2. Study population

Our study included patients with newly diagnosed type 2 diabetes who failed to achieve an HbA1c level of 7.5% or less on metformin monotherapy between January 2004 and December 2009. The patients had at least 3 months of metformin therapy to ensure adequate opportunity to attain glycemic control. The cut-off of >7.5% (trigger HbA1c) was chosen rather than >7.0% (suggested treatment goal) to ensure that selected patients were more likely to be indicated for treatment intensification with add-on drug. Brown, Conner, & Nichols (2010) use a value of HbA1c ≥ 7.5 as an indicator of secondary failure. The date of trigger HbA1c (treatment failure) was considered the index date.

Patients were excluded if they: (1) were not continuously enrolled one year prior to and two years after the index date; (2) had a diagnosis of diabetes or a prescription for any diabetes medication during the year prior to the diagnosis date; (3) were ever on insulin; (4) had a second add-on or discontinued metformin after the first add-on; or (5) did not have an HbA1c measurement during the outcome assessment period. Add-on treatment was defined as prescription of a 2nd oral agent from any available therapeutic class while continuing metformin. Early treatment intensification was defined as initiation of oral add-on therapy within 3 months of the index date, intermediate intensification as initiation between 4 and 9 months and late intensification as add-on initiation between 10 and 15 months after the index date. Metformin monotherapy was a residual category that did not have any add-on until the final outcome measure (see Fig. 1).

1.3. Outcome measure and variable definitions

Study outcome was defined as glycemic goal attainment (HbA1c ≤ 7%), which was evaluated between 18 and 24 months after the index date. Comorbidities were identified using ICD-9CM codes. Charlson Comorbidities Index (CCI) was calculated and included in the analysis. Cardiovascular disease (CVD) and atherosclerotic vascular disease (AVD) were defined as the presence of acute coronary syndrome (ACS), coronary heart disease (CHD), peripheral vascular disease (PVD) or carotid artery disease (CAD). The CVD/AVD variable was also included in the analysis.

1.4. Statistical analysis

Descriptive statistics for all patients and for those in each therapy group were created. Bivariate associations were tested using Student's t test for continuous measures and the Fisher's exact statistic for categorical variables. We used multivariable logistic regression to estimate the odds ratio (OR) for attainment of glycemic goal using pair-wise comparisons of early add-on, intermediate add-on, late add-on and metformin monotherapy. All analyses were performed using SAS statistical software release 9.2 (SAS Institute, Cary, NC). Statistical significance was fixed at $p \leq 0.05$.

2. Results

There were 9,842 patients who failed metformin monotherapy after 3 months (HbA1c ≥ 7.5%) and who satisfied the continuous enrollment criteria. After eliminating patients who ever used insulin and those who did not have an outcome measure, 5,870 patients remained. After further exclusion of patients with modification of therapy (either discontinuing metformin or a second add-on) after the first add-on, we had 2,237 metformin monotherapy patients, 1,012 early add-on patients, 638 intermediate add-on patients and 461 late add-on patients. These patients formed the population for further analyses (see Fig. 1).

Comparison of baseline characteristics between different groups is provided in Table 1. In general, patients in the early, intermediate and late dual therapy groups were similar in terms of most factors. Early dual treatment patients had a slightly higher total cholesterol and a significantly higher HbA1c level ($p < 0.0001$ for early vs. late dual therapy and early vs. intermediate dual therapy) at baseline than patients in the other two groups. Fig. 2 shows the proportion of patients with goal attainment of HbA1c ≤ 7% at the end of 2 years by group. These proportions were 47.23% in the early dual therapy group, 43.33% in the intermediate dual therapy group, 41.65% in the late dual therapy group and 42.15% in the metformin monotherapy group (p for trend: 0.0155). Patients who got therapy escalation later were less likely to achieve HbA1c goal. Even in the early dual treatment group only 47% of the patients reached the target level.