Disuse of Metformin by Patients with Type 2 Diabetes: A Medication Use Evaluation

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The American Diabetes Association (ADA) and European Association for the Study of Diabetes recommend that patients with type 2 diabetes initiate lifestyle changes and start metformin at the time of, or shortly after, diagnosis.[1] Despite this recommendation, a review of medications used for diabetes treatment in the US from 2003-2012 showed that between 33% and 48% of patients treating diabetes with medications did so with regimens that did not include metformin.[2] Similarly, a retrospective cohort study of 15,516 members of a major health plan from 2009 to 2013 showed that, of those who had initially been prescribed a medication to reduce blood glucose, only 58% received metformin.[3]

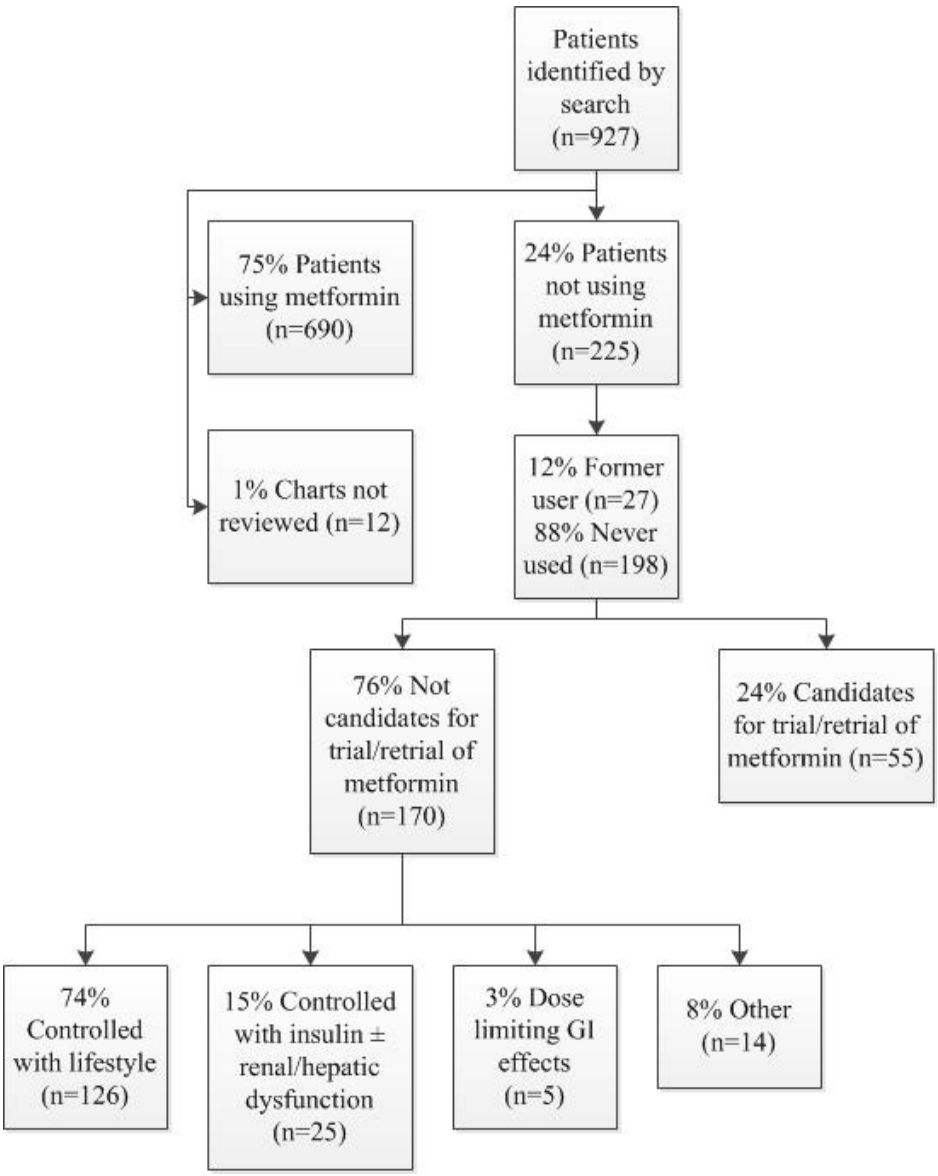
Little research has been conducted to explain reasons for the lack of metformin use. Metformin has historically been contraindicated in the elderly and in patients with various degrees of renal dysfunction. Additionally, some patients may discontinue metformin due to gastrointestinal side effects. In 2015, a retrospective review of the National Health and Nutrition Examination Survey data from 2007 to 2012 demonstrated that in approximately 1.6 million patients with estimated glomerular filtration rates (e-GFRs) between 30-60ml/min, metformin nonuse was around 50%.[4] In April of 2016, the Food and Drug Association (FDA) released information expanding the use of metformin in patients with various degrees of renal impairment.[5]

Because of the strong recommendation for use of metformin in patients with type 2 diabetes, the population data revealing relatively low use of metformin, and in light of the recent guidance in expanding use of metformin in patients with impaired renal function, a medication use evaluation was conducted to evaluate metformin use in two family medicine clinics.

Methods

A database query was completed in two family medicine clinics within the University of Wisconsin Department of Family Medicine and Community Health to determine the percentage of patients with type 2 diabetes not taking metformin and reasons for disuse. Patients with type 2 diabetes were stratified into three groups related to use of metformin: active users, former users and never users. Chart reviews were completed for patients who had never used metformin and had formerly used metformin to collect data on the current method of treatment and to identify goal hemoglobin A1c (HgbA1c).

FIGURE 1. Metformin Use Evaluation and Reasons for Nonuse



For those patients who had never used metformin, if an HgbA1c goal was not documented, it was assigned based on age and co-morbid conditions using ADA recommendations.[6] If no glucose-lowering medications were listed and HgbA1c was at goal, treatment was considered controlled with lifestyle, and these patients were not considered candidates for metformin. If HgbA1c was not at goal, trending upward over the past one to two years or nearing the loss of glycemic target, a more-in-depth chart review was done to look for renal dysfunction, evidence of hepatic impairment (e.g., documentation of liver disease or dysfunction on problem list) or other potential contraindications to metformin use.

Twenty-seven patients who had previously used metformin were also reviewed to determine reasons for discontinuation.

Finally, based on whether the documented or estimated HgbA1c goals were achieved and potential factors that might limit use of metformin, patients were assigned to one of two groups—those who might be considered as candidates for use of metformin and those for whom metformin use would not be considered. Descriptive statistics of means, standard deviations, and counts were used. As this medication use evaluation was undertaken as an evaluation of quality of care it was determined not to meet the federal definition of research and an IRB review was not required.

Results

There were 927 patients identified by the query (Figure 1). Of these, 690 (75%) were active users of metformin; chart reviews were not conducted for this group of patients. Twelve patients (1%) were not reviewed for a variety of reasons including: actual diagnosis of type 1 diabetes (n=5), patient expired (n=2), patient had begun metformin (n=2), and reviewer error (n=3).

There were 225 patients (24%) not using metformin. Of these, 198 patients had never used metformin and 27 were former, but not current, users of metformin.

A total of 55 patients were categorized as candidates for a trial or retrial of metformin. Of these, four were former users of metformin and 51 had never used metformin. The four former users had average HgbA1c values of 7.9% and average e-GFR values of 78ml/min (standard deviation ± 19.5ml/min). One of these patients had stopped metformin immediate release due to gastrointestinal issues and had not tried the extended release form. Another patient had previously achieved glycemic control with diet but was not currently at goal, and a different patient had discontinued metformin due to renal dysfunction that would no longer be a contraindication. Finally, the last patient in this group of four stopped metformin due to side effects not usually associated with that medication (e.g., weight gain, irritability). Of the 51 patients who had never used metformin, 31 were not using any medications. Overall, those who had never used metformin had average HgbA1c of 7.2% and average e-GFR of 79ml/min.

There were 170 patients who were not considered to be candidates for use of metformin, including 147 patients with no history of metformin use and 23 past users. Of the 147 patients who had never used metformin, 116 were successfully using lifestyle measures only to control blood glucose (average HgbA1c 6.5%), and therefore initiation of medication therapy was not warranted. Seventeen patients, currently using insulin, had an average e-GFR of 45 mL/min and therefore metformin initiation was not recommended per FDA guidance. Two other patients using insulin had hepatic dysfunction and 4 were in settings receiving end-of-life care. The remaining eight patients in this group of 147 included those with HgbA1c which appeared to trending downward over the last 1-2 years and approaching goal as well as patients who had successfully achieved their HgbA1c goal by starting different medications such as sulfonylureas, insulin or DPP4 inhibitors.

In the group of 23 former users who were not considered for metformin (average HgbA1c of 6.9%), 10 had achieved glycemic goals with lifestyle. Five patients in this group had dose-limiting gastrointestinal issues with metformin. The remaining eight patients in this cohort had evidence of diminishing renal function (average e-GFR 54ml/min) and the decision was made to not include them as candidates for metformin.

Results from the medication use review were presented to medical staff in each of the clinic settings. Information regarding patients who might potentially benefit from metformin use was also shared with diabetes nurse case managers.

Discussion

Of the patients with type 2 diabetes in these two practices, approximately 25% were not using metformin. Unlike some of the previously mentioned retrospective surveys, those patients who had never used metformin were generally not taking other oral medications, and most of those using insulin had diminished (average e-GFR ≤ 45ml/min) renal function or other contraindications.

Patients who had previously used metformin represented only a small percentage (12%) of those not using metformin. It was noteworthy that many of those who stopped taking metformin did so because of successful lifestyle intervention, and gastrointestinal adverse events were rarely associated with discontinuance.

It was of interest to find 126 (14%) of the total population of patients with type 2 diabetes were successfully maintaining glycemic control (average HgA1c in patients who never used or formerly used metformin of 6.5% and 6.9%, respectively) without any pharmacologic treatments. This finding is similar to data reported from the 2007-2009 National Health Survey, where 16% of patients with type 2 diabetes surveyed reported taking no medication to control blood glucose.[7]

Lifestyle modification improves glycemic control in many patients with type 2 diabetes. A four-year observational study of 4,503 adults with type 2 diabetes randomized to intensive lifestyle modification versus usual diabetes support and education resulted in 11.5% (95% CI 10.1%-12.8%) of those receiving lifestyle interventions achieving HgbA1c levels of less than 6.5% at one year, and 7.3% (95% CI 6.2%-8.4%) of the population were at this goal at year four.[7] A meta-analysis of 16 randomized, controlled trials (n=9,975) comparing a comprehensive lifestyle

intervention to standard care which varied by study (e.g., general advice about physical activity, monthly contact with study team, standard care by own clinician, diabetes support and education, usual clinical care for diabetes, standard leaflets, etc.) showed HgbA1c reduction of -0.37% (95% CI -0.59 to -0.14).[8]

Current practice guidelines promote the important foundation that diet and exercise play in framing treatment for patients with type 2 diabetes, but also recommend the use of metformin for all eligible patients with type 2 diabetes.[1] When pharmacologic treatment of type 2 diabetes is initiated, metformin remains the treatment of first choice based on its ability to lower HgbA1c, relatively low cost and lack of hypoglycemic adverse events.

Conclusion

The two most common reasons for metformin disuse included successful glycemic control with lifestyle intervention (56% of the 225 patients not using metformin) or contraindication due to renal dysfunction using the newly-defined FDA parameters. Use of other medications for glycemic control and discontinuation due to gastrointestinal effects were rarely associated with metformin disuse.•

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