Journal of Diabetes and Its Complications 33 (2019) 462–464

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Dethroning the king?: The future of metformin as first line therapy in type 2 diabetes

Most treatment guidelines recommend metformin as the first-line anti-hyperglycemic therapy for type 2 diabetes.[1] While metformin has several advantages, such a position in treatment algorithms is being challenged, due to data from clinical trials demonstrating benefits of newer medications beyond glucose lowering. This has prompted suggestions that other drugs may be more effective as foundational therapy. Further, it has encouraged scrutiny of the data that has supported the recommendations on metformin. More importantly, the new data raises the possibility of a more evidence-based approach to personalizing treatment choices for people with type 2 diabetes.

1. Evidence that metformin is still the best initial therapy for type 2 diabetes

Extensive clinical experience has supported the early use of metformin, a drug that has been available in many countries of the world for decades and which is actually based on a biguanide derived from the French lilac, (*Galega officinalis*) used in medieval times in Europe as a traditional diabetes treatment.[2]

It is generally accepted that the ideal anti-hyperglycemic medication should have high glucose-lowering efficacy with low risk of hypoglycemia and weight gain, be safe and well-tolerated and affordable.[1] Metformin meets many of these characteristics, which explains its position in current therapeutic paradigms. In addition, however, some clear benefit on long-term complications of diabetes beyond mere effects via reduction in hyperglycemia would also desirable.

Diabetes is a complex disorder with many pathophysiological abnormalities, one of which is the increased production of glucose by the liver secondary to hepatic insulin resistance and possibly abnormal glucagon secretion by the endocrine pancreas. Metformin is known to have insulin-sensitizing properties in the liver, whereas thiazolidinediones (such as pioglitazone) have a weaker effect at this site, exerting its predominate effect in skeletal muscle and fat.[3] Table 1 lists a number of proposed mechanisms underlying the glucose-lowering effects of metformin. However, the effect on glucose production in the liver [gluconeogenesis] is likely to be the most important. Recent work suggests that this suppression of gluconeogenesis may be mediated by inhibition of mitochondrial glycerophosphate dehydrogenase.[4]

The study that drove the popularity of metformin was the UKPDS,[5] where, in a subset of people who were overweight, metformin was shown to reduce myocardial infarction (HR 0.61, $P = 0.01$) and coronary heart disease mortality (HR 0.50, $P = 0.02$) significantly as compared to the control group which was assigned diet therapy alone.[5] Interestingly, this cardiovascular benefit was not found in the other randomized group, which was assigned to sulfonylureas or insulin. This benefit persisted even after long term (10-year) follow-up of patients who were previously treated with metformin. A smaller study by Kooy et al.[6] involving 390 patients demonstrated a reduction in major adverse cardiovascular events with metformin in combination with insulin (HR 0.61; $P = 0.02$), but this was not the primary endpoint of the study.[6] A third, and also quite small (N = 308) trial examined cardiovascular outcomes after randomization to metformin or the sulfonylurea glipizide for 3 years. Despite equal control of HbA1c, those in the metformin group experience less events (HR 0.54, 0.30–0.90).

Several studies have also demonstrated the cardiovascular benefits of metformin in patients with type 2 diabetes and coronary artery disease, particularly in comparison with sulfonylureas[7] as well as in patients with cardiomyopathy.[8] Interestingly, metformin was initially contraindicated in patients with heart failure, although some observational studies showed that patients with heart failure treated with metformin experienced reduced mortality.[9] These data eventually lead to the rescinding of this contraindication in patients whose heart failure is clinically stable.

Metformin was also previously contraindicated in people with mild-moderate chronic kidney disease (CKD), but the FDA changed these guidelines in 2016, allowing for cautious use in those with estimated glomerular filtration rates (eGFR) between 30 and 60 mL/min/1.73 m^2. Although there are no randomized trials in patients with CKD, Solini et al.[10] demonstrated that patients with mild to moderate CKD treated with metformin had lower cardiovascular events than those not so treated. Another observational study by Crowley et al. demonstrated that in both CKD and CHF patients, there was a clinical benefit of treatment with metformin.[11] As a result, use of metformin is appropriately expanding beyond those individuals with normal GFR.[12]

Finally, metformin is generally safe and well tolerated with low risk of hypoglycemia and may cause a small degree of weight loss. Most importantly, it is now generally easily affordable and widely available as a generic compound. In the US, large retailers offer the drug at a cost of just $4 per month or less.

Thus, this time-tested remedy is clearly well positioned to continue as foundation therapy for patients with type 2 diabetes, including those with CV disease. Yet, its so-called cardiovascular benefits, while likely present, given the overall consistency of the findings, is based on a comparatively modest database when contrasted to modern, large CV outcomes trials, several of which have shown clear CV benefits of newer glucose-lowering drugs.[13–15] Importantly, however, all of these trials have included metformin as background therapy in approximately 3 out of 4 patients.

2. Should other drugs be considered as first-line therapy as compared to metformin?

Although metformin is considered to have high efficacy, these data are based on older studies with the patients having very high baseline A1c[16]

https://doi.org/10.1016/j.jdiacomp.2019.03.003

Table 1
Proposed mechanisms of action of metformin.

- ↑ hepatic glucose production (gluconeogenesis)
- ↑ peripheral insulin sensitivity; stimulating AMP kinase
- ↑ free fatty acid oxidation (Randle cycle)
- ↑ gut glucose absorption; é gut glucose utilization pr changing microbiome
- ↑ bile salt absorption; ê reduced bile acid transport
- ↑ severity of islet amyloid formation, with delayed progression of insulin secretory failure
- ↑ expression of the GLP-1 receptor in islet cells
- ↑ incretin release from gut neuroendocrine cells

levels. Trials with newer medications have enrolled patients with lower baseline A1c. Since the degree of fall in A1c is related to the baseline A1c, newer medications appear to be as efficacious. Head to head, metformin has equal glucose lowering efficacy as many other drugs, at least in the short term. Metformin does have greater efficacy than DPP-4 inhibitors, but is inferior to insulin and GLP-1 receptor agonists. In the long term, glycemic control is inferior to that of a thiazolidinedione[17] and any weight loss appears to be less than that observed when a GLP-1RA or an SGLT-2 inhibitor is used. More importantly, secondary failure of metformin therapy is quite common[18] and relates to the fact that it does not improve beta cell function substantially, as do drugs like thiazolidinediones and possibly GLP-1RAs.[19,20]

Although the effect of metformin on cardiovascular events was quite clear in the UKPDS study, it occurred only in a small subgroup of obese subjects in comparison to diet therapy and was not statistically significant in comparison to sulfonylureas and insulin, where any differences were not statistically significant (with the exception of fewer strokes.) Furthermore, there was no reduction in microvascular disease with metformin, unlike that benefit seen with the other medications, although this was likely due to reduced power in this smaller subgroup. Even after long-term follow-up of the metformin group, however, patients initiated on this agent did not experience a microvascular benefit, unlike sulfonylureas and insulin.[5] Such a lack of benefit is supported by data from the study by Kooy where the primary endpoint, which was a composite of microvascular and macrovascular events, was not significantly reduced by a combination of metformin and insulin. Observational studies with metformin also showed limited benefit for microvascular events.[21] It is unclear why this potent glucose-lowering medication does not reduce microvascular complications.

Although some data have shown the *safety* of metformin in patients with mild-moderate CKD, there are no data concerning potential benefits on the *progression* of renal dysfunction. In contrast, the benefits of SGLT2 inhibitors in patients with mild CKD have recently been demonstrated[14]. Further, in patients treated with a GLP-1 receptor agonist liraglutide in the LEADER study, there were a large number of patients with moderate and severe renal impairment who demonstrated not only safety of the drug but also benefit in terms of prevention of cardiovascular events.[15,22]

Although there has been no large cardiovascular outcome trial with metformin compared with placebo as first-line therapy (other than UKPDS), the ORIGIN trial[23,24] was a comparison of early use of insulin glargine and the standard stepped therapy often utilizing metformin as first-line therapy in patients with newly diagnosed diabetes, following the recommended guidelines.[1] Although the study was negative in terms of the primary endpoint of preventing cardiovascular events with insulin, the data could also be interpreted to suggest that there was no difference between approaches using insulin first as compared with metformin. In a recent trial in type 1 diabetes, metformin also failed to show any cardiovascular benefit.[25]

The side effect profile of metformin is not trivial. Although serious side effects such as lactic acidosis are very rare, diarrhea is very common[26] and can be quite distressing in some patients, leading to nonadherence to therapy.[26] More insidious is the development of vitamin B12 deficiency[27] which could conceivably contribute to worsening neuropathy[28] as well as cognitive dysfunction.[29] Consideration of these side effects of metformin is important from a public health perspective as a large proportion of the population is being treated with metformin, particularly older individuals due to increased prevalence of diabetes in that population. Interestingly, one study of high-dose vitamins demonstrated an improvement in symptoms and signs of peripheral neuropathy, particularly in patients treated with metformin.[28]

3. Are there alternatives to metformin as first line therapy?

Recent data points to several alternatives, particularly if a personalized approach is used. In patients with atherosclerotic cardiovascular disease, a GLP-1 receptor agonist such as liraglutide or semaglutide or an SGLT2 inhibitor, such as empagliflozin, canaglflozin or dapagliflozin, may carry additional benefits.[15] In patients with congestive heart failure, or CKD (so long as there is sufficient glomerular filtration), an SGLT2 inhibitor is now consider a potentially more appropriate agent.[13,14] And finally, for patients with stroke, pioglitazone may be particularly beneficial, as seen in the PROactive and IRIS trials,[30,31] although admittedly the latter was conducted in patients with insulin resistance but not diabetes. The majority of IRIS subjects had prediabetes, however, and in this subgroup the benefits of pioglitazone appeared even larger[32].

It is important to recognize the powerful effects of these newer agents in preventing cardiovascular events, as summarized in Table 2. However, overall data on these medications in patients with newly diagnosed diabetes, using these drugs as first-line therapy, is still very limited. In most of the trials, participants had long duration diabetes and were on several other agents, including insulin. Only in the IRIS trial could pioglitazone be considered to be first line. In contrast, in the major CVD outcome trials most patients had long standing disease and were previously on metformin, which was usually continued during the trial.

Table 2
Selected clinical trials in diabetes showing CV benefit.

Drug	Study	Duration (years)	HR for primary endpoint (MI/MACE) (95%CI)	HR for CV mortality (95% CI)	Population/notes
Metformin	UKPDS 34	7.1	0.61 (0.41–0.89)	0.64 (0.45–0.91)	• Obese, newly diagnosed T2DM
Empagliflozin	EMPA-REG OUTCOME	3.1	0.86 (0.74–0.95)	0.62 (0.49–0.77)	• T2DM + established CVD Significant reduction in CHF hospitalization
Canagliflozin	CANVAS	3.6	0.86 (0.75–0.97)	0.87 (0.72–1.06)	• T2DM + CVD or CV risk factors. • Significant reduction in CHF hospitalization
Dapagliflozin	DECLARE	4.2	0.93 (0.84–1.03)	0.93 (0.82–1.04)	• T2DM + CVD or CV risk factors • Significant reduction in CHF hospitalization
Liraglutide	LEADER	3.8	0.87 (0.78–0.97)	0.78 (0.66–0.93)	• T2DM + CVD or CV risk factors
Semaglutide	SUSTAIN 6	2.0	0.74 (0.58–0.95)	0.98 (0.65–1.48)	• T2DM + CVD or CV risk factors

In order to establish another drug as an alternative first line therapy for type 2 diabetes a comparative trial in patients with newly diagnosed disease would be needed. Such a trial would need to demonstrate superiority over metformin based on hard clinical outcomes. Given the established role of metformin in clinical practice and the duration of treatment needed to show benefits beyond glucose lowering, it is unlikely that such a trial will be conducted soon. Such a trial may be possible, using a "precision medicine" approach. Such an approach was used in the IRIS trial which targeted patients with previous stroke and insulin resistance. However, in that trial the comparator was placebo rather than metformin.

It may be similarly possible to select patients with the specific characteristics to take advantage of the benefits from some of the newer agents, thereby targeting an appropriate patient population. For example, if a comparison between an SGLT2 inhibitor and metformin is done in patients with congestive heart failure and newly diagnosed diabetes, it is conceivable that the former is more likely to reduce hospitalizations and mortality. Similarly, in patients with newly diagnosed diabetes and CVD, a GLP-1 RA with proven benefit, such as liraglutide or semaglutide may be more successful than metformin in preventing not only glycemic failure but also disease progression.

However, it is unlikely that for most people (especially those without CVD) that metformin will be displaced as the first line therapy. To establish another drug as the "first line for all" would require a very large, long term comparative trial with hard end points, over a relatively long duration. Such a trial would be prohibitively expensive and logistically challenging.

4. Summary

Metformin remains well established as the first-line treatment for type 2 diabetes for several reasons, although its position may be considered somewhat flimsy, based on a CV data base that is far from robust. It may be time to reconsider this drug's position as foundation therapy, particularly in light of emerging data with other glucose-lowering drug classes, such as SGLT 2 inhibitors, GLP-1 receptor agonists, and even pioglitazone, although side effects of the latter have limited its used over the past decade. Of course, large clinical trials would need to be conducted in order to dethrone this 'king' of type 2 diabetes management. We are hopeful that future clinical trials will eventually be conducted to inform evidence-based personalized approaches to management, so that, with initial therapy, the best drug is prescribed or an individual patients.

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