METFORMIN: NON-GLYCEMIC EFFECTS AND POTENTIAL NOVEL INDICATIONS

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Running title: Non-glycemic effects of metformin

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Abstract

Metformin is the most commonly prescribed drug for the treatment of type 2 diabetes because of its apparent robust effects in reducing cardiovascular risk. The United Kingdom Prospective Diabetes Study suggests that metformin reduces the risk of myocardial infarction, and more recent retrospective studies have shown an association between metformin and a reduction in stroke, atrial fibrillation and all-cause mortality. The mechanism(s) explaining these putative benefits are not clear but may involve decreased energy intake (with attendant weight loss), improvement in lipids, and lowering of blood pressure; a review of selected literature suggests that metformin lowers blood pressure when it is elevated, but not when it is normal. Metformin appears to be safe when given to patients with Stage 3 chronic kidney disease (CKD-3). In addition, there is evidence that individuals with CKD-3, who are at increased cardiovascular risk, stand to benefit from metformin therapy. Lactic acidosis is an extremely remote and probably avoidable risk; measurement of plasma metformin levels and more frequent monitoring of renal function may be useful in selected patients with CKD-3 who are treated with metformin. Finally, there is evidence that metformin is safe in patients with heart failure; metformin therapy is associated with a reduction in newly incident heart failure and in heart failure mortality.

Abbreviations:

CKD-3 = stage 3 chronic kidney disease; UKPDS = United Kingdom Prospective Diabetes Study; BP = blood pressure; MAP = mean arterial pressure; eGFR = estimated glomerular filtration rate; HF = heart failure.
Metformin and Cardiovascular Disease

Over the past 10 years, the biguanide metformin has emerged as the first line therapy for the treatment of type 2 diabetes; the American Diabetes Association, the European Association for the Study of Diabetes and the American Association of Clinical Endocrinologists have endorsed metformin in their consensus guidelines (1; 2). The chief reason for the ascendancy (and now primacy) of metformin in the treatment of type 2 diabetes is the belief that it reduces cardiovascular risk (3), based largely on the findings of the United Kingdom Prospective Diabetes Study (UKPDS) (4; 5). This is important considering that most people with type 2 diabetes ultimately succumb to a cardiovascular event (6). In the UKPDS, metformin had a robust effect on cardiovascular risk (4; 5), whereas a strategy of insulin provision (insulin or sulfonylureas) had a more modest (7) although ultimately significant (5) effect in reducing myocardial infarction. A prospective observational study of nearly 20,000 people with type 2 diabetes and atherosclerosis found that metformin use was associated with 24% lower all-cause mortality compared to patients who were not taking metformin (8). In addition, a retrospective cohort study of >250,000 people with type 2 diabetes found a >40% lower frequency of a composite endpoint of death or hospitalization due myocardial infarction or stroke among people taking metformin compared to those taking sulfonylureas (9). A recent retrospective study of ~15,000 Taiwanese patients with diabetes found that the risk of stroke over a 4-year period was 60% lower in those taking metformin compared with those who were not (10). Another recent DOI:10.4158/EP151145.RAR © 2016 AACE.
A retrospective 13-year study of over 600,000 patients with diabetes, also from Taiwan, found a 20% lower risk of atrial fibrillation among people taking metformin (11). A recent study found an increase in cardiovascular events and all-cause mortality among metformin-treated patients in whom insulin had been added (12).

The mechanism by which metformin might exert the effects observed in the UKPDS is likely independent of glycemic control, considering that glycemic control with metformin was nearly identical to that with insulin provision therapy (5; 13), which resulted in only equivocal reduction in myocardial infarction in the initial 11 year analysis (7). Animal studies show reductions in infarct size in non-diabetic rodents when metformin is given shortly before or during reperfusion (14; 15), an effect mediated by activation of AMP kinase and the Reperfusion Injury Salvage Kinase (RISK) pathway (16). A comparable acute effect of metformin has not been demonstrated in humans, however. Chronic therapy with metformin also may have favorable effects on lipids. A number of studies have shown a decrease in total cholesterol and triglycerides (17-20), in some cases accompanied by increases in HDL cholesterol (21-23), in patients treated with metformin. In addition, favorable effects on HDL cholesterol concentration and low density lipoprotein particle size in people who do not have diabetes have been described (24). In a large retrospective analysis of nearly 18,000 Veterans Administration patients with diabetes, patients receiving metformin had significantly lower triglyceride and higher HDL cholesterol levels than patients treated with sulfonylureas (25). However, reported effects of metformin treatment on lipids are somewhat inconsistent, and tend to be small (26). Studies have also shown improvement in endothelial function, possibly due to AMP kinase activation and improved insulin action (27). Other studies have shown improvement in the prothrombotic state that often accompanies diabetes (18) during metformin therapy.
possibly related to a reduction in fibrinogen level, activation of PAI-1, and inhibition of inflammation (28).

Effects on Energy Balance

It is noteworthy that metformin produces modest weight loss in the near term (4) and blunts weight gain when given chronically (5). It is conceivable that this phenomenon could be explained by malabsorption of ingested food and/or increased energy expenditure; in fact, some authors have suggested that metformin causes carbohydrate malabsorption (29; 30). However, careful tracer studies in humans have indicated that this is not the case, although metformin may delay carbohydrate absorption (31). Instead, weight loss produced by this medication is likely due to increase satiation; in a one year study, metformin therapy resulted in an estimated decrease in daily food intake of ~ 250-300 kcal (32). The absolute amount of weight loss produced by metformin is small, in part because decreased energy intake in type 2 diabetes results in improved glycemic control. Improved glycemic control, in turn, has an anti-glycosuric effect and also results in decreased energy expenditure; the combination of these two effects blunts weight loss, and can even result in weight gain (32). In a prospective observational study of ~5000 individuals with T2DM, intentional weight loss was associated with a reduction in cardiovascular mortality of up to 28% (33). It is not known whether the improved cardiovascular outcomes in people taking metformin are due to modest weight loss, or are a direct effect of metformin per se. Insulin provision generally causes weight gain (32).

Effects on Blood Pressure
Literature reviews have generally concluded that there is no effect of metformin on blood pressure (26; 30). In the Diabetes Prevention Program study, in which 70% of patients were normotensive, metformin had no apparent effect on blood pressure or on the frequency of newly incident hypertension compared to placebo (34). Because many of the negative studies appeared to us to have been conducted in individuals who were normotensive, we attempted to separate studies of patients with normal blood pressure from studies that had been conducted in people with hypertension. We excluded studies in which it was stated that the patient population included both people with hypertension and people without hypertension, and included only studies in which the baseline blood pressure in the population was provided. We reviewed in detail 13 studies that met these criteria (18; 19; 21; 22; 35-43). Because many of the studies did not state whether the population had hypertension or not, we calculated mean arterial pressure (MAP) for all of the studies from mean baseline blood pressure using an online calculator (http://www.physiologyweb.com/calculators/mean_arterial_pressure_calculator.html) and then separated the studies into two groups: “normal blood pressure” (MAP <107 mm Hg) and “elevated blood pressure” (MAP ≥107 mm Hg). A MAP of 107 was chosen because it corresponds with a blood pressure of 140/90 (44). The results are shown in Table 1. Although the criteria for defining the two groups of studies are arbitrary, there is a clear separation between the two groups with respect to systolic, diastolic and mean arterial pressure. There was no effect of metformin therapy in the seven studies of individuals with normal blood pressure, whereas metformin lowered blood pressure in 4 of the 6 studies of people with elevated blood pressure. Of the two negative studies in this group, metformin was given at a dose of 500 mg/day in one (43), and the other study had the lowest MAP in the group (42). Thus, these results suggest that metformin lowers blood pressure when blood pressure is elevated, but not when it is normal.
Metformin has also been directly compared to sulfonylureas with respect to blood pressure effects. A retrospective cohort study of ~3500 veterans with type 2 diabetes found that people who initiated metformin therapy had lower blood pressure at one year compared with individuals starting a sulfonylurea (45). Similar results were reported in prospective studies comparing the blood pressure effects of metformin versus glyburide in people with type 2 diabetes, both with normal (23) and elevated (46) blood pressure. It is difficult to determine whether the findings of these studies reflect hypotensive effects of metformin, hypertensive effects of sulfonylureas, or a combination of the two.

Taken together, these data indicate that metformin may lower blood pressure in individuals with elevated blood pressure, but most evidence suggests that this does not occur in people who have normal blood pressure. The mechanism for blood pressure lowering in the population with hypertension may be a reduction in sympathetic nervous system activity, as suggested by one study in which there were significant decreases in plasma norepinephrine levels in response to metformin therapy (22). Manzella, et al. administered metformin, 1700 mg daily in divided doses vs placebo for 4 months to 120 normotensive individuals with type 2 diabetes and found no change in blood pressure, but a significant increase in R-R interval variability, suggesting a decrease in cardiac sympathetic tone (47). Metformin therapy reduces cardiac work and myocardial fat oxidation (48), effects that are consistent with decreased myocardial oxygen consumption (mVO₂) and decreased myocardial sympathetic activity (see section on heart failure below).

Use in Patients with Kidney Disease

Essentially 100% of metformin absorbed from the gastrointestinal tract is excreted unchanged in
the urine (49). Because of this, blood levels of metformin are strongly influenced by renal function. Although chronic kidney disease (CKD) is common in type 2 diabetes and is associated with high cardiovascular risk (50), it can limit the use of metformin; abnormal renal function (defined as a serum creatinine $\geq 1.5 \text{ mg/dL}$ in men and $\geq 1.4 \text{ mg/dL}$ in women) is a contraindication to the use of the drug. Recent diabetes management guidelines from AACE/ACE recommended that metformin not be given when eGFR is less than 45ml/min/1.73m$^2$ (2). The British National Formulary and the Japanese Society of Nephrology recommended cessation of metformin if eGFR <30 mL/min/1.73 m$^2$ (51). When one takes into account the prevalence of type 2 diabetes, the prevalence of CKD Stage 3 (CKD-3, estimated glomerular filtration rate (eGFR) 30–59 ml/min/1.73 m$^2$) in type 2 diabetes, and the frequency of abnormal serum creatinine in CKD-3, it can be estimated that over 1 million people with type 2 diabetes and CKD-3 in the USA are ineligible for metformin treatment based on the serum creatinine (52).

The widespread belief that metformin cannot be used safely unless renal function is normal (53) is largely based on residual anxiety concerning cases of lactic acidosis precipitated by the use of phenformin (52; 54; 55). It should be emphasized that lactic acidosis does occur in people taking metformin; the vast majority of these cases are best described as metformin-associated lactic acidosis, as they are typically accompanied by hypoxia (type A lactic acidosis) and are thus not thought to be caused by metformin (56). Rare cases of metformin-induced lactic acidosis (56) (type B, or “normoxic”, lactic acidosis) have been described, including cases of metformin overdose (52). However, there is no evidence for an increased risk of lactic acidosis in large populations of patients taking metformin (>100,000 patient-years) (55; 57; 58). The explanation for the extreme rarity of lactic acidosis in patients treated with metformin, unlike the
situation with phenformin, lies in differences in the chemistry of the two compounds. Phenformin is lipophilic, binds avidly to mitochondrial membranes, and is hydroxylated in the liver, whereas metformin is hydrophilic, does not bind avidly to the mitochondrion, and is not metabolized in any tissue (49).

Thus a strong rationale exists for expansion of the use of metformin to patients with CKD-3 (52; 55; 59; 60). These individuals, who are at high cardiovascular risk (50), stand to benefit from metformin just as individuals with normal renal function. In a study of patients in the Swedish Diabetes Registry, metformin was well tolerated in people with CKD-3 and its use was associated with 13% lower all-cause mortality in this population (54). Moreover, metformin use is associated with an apparent decrease in the likelihood of a decline in renal function compared with sulfonylureas (61). However, there are no prospective, randomized trials examining metformin use in CKD-3 patients. The American Diabetes Association and the European Association for the Study of Diabetes have pointed out the desirability of expanding the use of metformin to patients with CKD-3 (59). Currently, two petitions which propose that use of metformin in patients with mild to moderate kidney function are being considered by the FDA (55).

Would a clinical test for the monitoring of plasma metformin levels in patients with kidney disease be useful to clinicians? The safety of the drug has been confirmed in large studies (55; 57; 58) and should be emphasized. Because of the rare occurrence of type B lactic acidosis in patients taking metformin, however, it is clear that there is a potential - however remote - for metformin-induced lactic acidosis when metformin is used therapeutically. At therapeutic doses in patients with normal renal function and in those with CKD-3, trough metformin blood levels are consistently less than 3.0 mg/L and average < 1.0 mg/L (52; 62-64) (Table 2). This appears to
be the case at metformin doses as high as 3000 mg/day (63; 65). There is relatively little information available on metformin pharmacokinetics in patients with CKD-3, and additional research is required to determine whether dose adjustment is warranted in selected patients.

In patients with metformin-induced lactic acidosis, metformin levels are generally 50-70 mg/L, with no values <30 mg/L (56; 62; 63) (Table 1). Thus, the therapeutic index (toxic level₅₀/therapeutic level₅₀) of metformin is in the 30-150 range. In contrast, for example, the therapeutic index of warfarin is roughly 2.0 (66). The availability of laboratory measures of warfarin action (prothrombin time) facilitates its safe use as an anticoagulant. In an analogous fashion, we believe that metformin could be used safely in CKD-3 (52; 55), and that its safety could be further ensured by the measurement of trough metformin levels in plasma in selected patients – especially those with eGFR in the 30-44 ml/min/1.73 m² range. HPLC (67) or liquid chromatography/tandem mass spectrometry (52; 63) measurement of metformin has been used for research studies with excellent sensitivity and precision. The selective use of a clinically available plasma metformin measurement to guide dose adjustment of the drug (perhaps targeting trough levels of <3 mg/L) would allow the practitioner to prescribe metformin to CKD-3 patients with confidence.

The practitioner should be aware of the possible risk of an acute change in renal function in any patient (whether CKD-3 is present or not) and the medication should be held in situations of acute illness, especially if the patient is not eating. Serum creatinine may not reflect GFR in the early hours of acute kidney injury. In addition, more careful monitoring of renal function in selected patients (e.g., quarterly or half-yearly serum creatinine measures in patients with eGFR in the 30-44 ml/min/1.73 m² range) may be warranted.
Use in Patients with Heart Failure

The prevalence of heart failure (HF), like that of type 2 diabetes, increases with age. The majority of heart failure patients are obese, and half or more have glucose intolerance or diabetes (52; 55). Patients with diabetes are much more likely to develop heart failure than patients without diabetes (incidence rate 30.9 vs 12.4 per 1000 person-years, RR = 2.5) (52; 55).

A number of studies have been conducted to investigate the possible relationship between the use of diabetes medications and the risk of heart failure. A retrospective study showed that initiation of insulin therapy was associated with a more than doubling of newly incident heart failure (68). The apparent risk of heart failure associated with the use of thiazolidinediones has been attributed to sodium retention (69).

Shortly after metformin was approved for use in the United States, heart failure was listed as a contraindication for its use in the package insert (70). Nonetheless, it was noted that metformin was used frequently for the management of diabetes in heart failure patients (71). Because of the availability of new information regarding the safety of metformin in patients with heart failure, the contraindication was subsequently withdrawn by the Food and Drug Administration (72).

Studies have also been conducted to investigate the relationship between metformin therapy and heart failure risks and outcomes. Individuals with type 2 diabetes who are treated with metformin have reduced newly incident heart failure (73; 74). Considering that blood pressure is lower in metformin-treated patients than in patients receiving sulfonylureas (23; 45; 46), it is of interest that heart failure mortality also appears to be lower in patients on metformin compared to people treated with sulfonylurea monotherapy (75). A cohort study of over 15,000 diabetes patients found a nearly one-third decrease in heart failure mortality in metformin-treated patients (76).
patients compared with people who were not taking metformin (71). A recent prospective observational study of nearly 20,000 people with diabetes showed similar findings (8).

As described above, metformin causes a decrease in food intake of 250-300 kcal/day (32). Is it possible that this effect is responsible for the apparent benefits of metformin in heart failure? Unintentional weight loss actually predicts poor outcomes in end-stage heart failure (76). On the other hand, weight loss results in improvement in both vascular stiffness and left ventricular stiffness (77). More dramatic weight loss, such as that produced by vertical banded gastroplasty, actually improves left ventricular function (78). Even modest weight loss, such as that achievable with lifestyle modification, can have favorable effects on ejection fraction and functional class in patients with heart failure (79).

Weight loss may decrease cardiac demand by the same mechanism that accounts for increased mVO2 with increasing BMI (80). Weight loss improves insulin sensitivity (81) and thus might be expected to decrease myocardial dependence on fat oxidation, in turn improving cardiac efficiency (82) as discussed above. A weight loss diet reduces left ventricular mass, cardiac work and myocardial fatty acid uptake (83). Decreased stroke volume, decreased cardiac output and decreased mVO2 has been reported in heart failure patients who achieve weight loss (79). Metformin therapy reduces myocardial fatty acid oxidation (48), an effect that would be expected to result in decreased mVO2.

Heart failure patients have increased sympathetic activity (84). In an investigation using MRI and MR spectroscopy to measure cardiac function and metabolism, van der Meer studied T2DM subjects before and during treatment with metformin or pioglitazone. Cardiac index and cardiac work decreased with metformin therapy, an effect that was not seen with pioglitazone; there were also modest decreases in stroke volume and left ventricular mass, as well as decreases...
in myocardial glucose uptake and free fatty acid oxidation (48). These findings are consistent
with decreases in myocardial VO$_2$ and sympathetic activity, and could be due to the generalized
downregulation of the sympathetic nervous system that occurs with a decrease in food intake
(85). Metformin therapy in people with obesity and type 2 diabetes results in an increase in heart
rate variability, suggesting decreased cardiac sympathetic tone (47). One study showed no effect
of metformin on muscle sympathetic nerve activity in patients with diabetes (86). This does not
rule out an effect on cardiac sympathetic activity, however, for several reasons. First, metformin
treatment reduces circulating norepinephrine concentrations (22), which have been shown to
increase with meals (85) and decrease with weight loss (87). Second, regional and systemic
sympathetic activity can diverge (85). Finally, in subjects who lose weight on a hypocaloric diet,
muscle sympathetic nerve activity rebounds, whereas norepinephrine spillover remains reduced
(87). Metformin treatment decreases postprandial concentrations of insulin (17), which is known
to activate the sympathetic nervous system (88). If metformin does have a favorable effect on
heart failure (and there have been no prospective, randomized trials that examine this question),
it is thus possible that either decreased sympathetic activity, weight loss \textit{per se}, or a combination
of the two could be responsible.

\textbf{Mechanism of Action}

Metformin acutely lowers glucose due to suppression of gluconeogenesis (89). There is
disagreement as to whether the drug is an insulin sensitizer, but when it is administered
chronically there is improvement in insulin sensitivity and a decrease in insulin levels (52).
Metformin results in reduction of hepatic gluconeogenesis by inhibiting mitochondrial
respiratory-chain complex 1 leading to activation of the AMPK-FOX03 pathway, reducing fatty

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acid oxidation and reactive oxygen species (90). This improves the bioavailability of nitric oxide, endothelial function and vascular blood flow (91). Biguanides suppress hepatic glucagon signaling by decreasing production of cyclic AMP (92).

There are other effects that could conceivably be more important in mediating the apparent long term benefits of the drug. Although metformin that is absorbed into the bloodstream has important effects on glucose metabolism, this does not explain the weight loss that occurs with metformin therapy. It has been estimated that half or more of metformin taken orally never reaches the bloodstream (49); instead, it is delivered to the terminal ileum, where it may induce bile acid malabsorption (93). Malabsorbed bile acids have the potential of stimulating the release of incretins in L-cells, which are highly concentrated in the rectum; this may delay gastric emptying and decrease gastric accommodation, ultimately increasing satiety (52; 93). This may provide an explanation for the decrease in energy intake that occurs in people who are treated with metformin (32). The relative contribution of decreased energy intake (accompanied by modest weight loss) versus effects on endogenous glucose metabolism to the overall improvement in glycemia is uncertain. The effect of metformin on postprandial glycemia is of interest. An early study by Wu, et al. showed no effect of metformin given twice daily on post-breakfast glucose excursion; however, in the same study there was a dramatic flattening of plasma glucose levels after lunch, accompanied by lower insulin levels (94). This suggests that the effect of metformin on postprandial glycemia does not manifest itself for several hours after an oral dose and may be due to an incretin-mediated effect on gastrointestinal motility, causing a delay in carbohydrate absorption (52; 93).

Clinical Considerations
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Metformin is most often prescribed as a twice daily dose in the USA, and a large study suggested that the maximum effective dose is 2000 mg/d (95). However, this observation pertains to glycemic effects; the maximum effective dose with respect to effects on cardiovascular outcomes is not known. In the only prospective, randomized study to demonstrate clear cardiovascular benefits, the medication was given in 3 divided doses totaling 2550 mg/day (4).

The most frequent side effects associated with metformin are gastrointestinal symptoms, especially diarrhea. Diarrhea occurs in ~30% of people who take metformin (96), and it has been reported that around 5% of patients are unable to tolerate metformin due to side effects (97). In our experience, gastrointestinal side effects are usually mild and transient; more severe diarrhea is often due to improper dosing (failure to start with a low dose) or administration (taking the medication on an empty stomach). Biochemical vitamin B12 deficiency has been reported to occur in ~6% of patients (98), but its clinical importance is not known (99).

Summary

Metformin has a dominant position in the treatment of type 2 diabetes that is deserved because of its favorable and robust effects on cardiovascular risk. The mechanism responsible for these benefits is not clear, but may include improvement in lipids and lowering of blood pressure (in people who have elevated blood pressure, but not in those with normal blood pressure) – effects that may relate in part to decreased energy intake and modest weight loss. Metformin appears to be safe for use in patients with CKD-3, and efforts to expand its use to these patients are warranted. Measurement of plasma metformin levels, along with more frequent monitoring of renal function, may be of value in selected patients, and may in some cases facilitate dose
adjustment. Metformin is also safe in patients with heart failure, and may actually have favorable effects on cardiac function in these patients.

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Table 1. Effect of metformin on blood pressure in patients with elevated blood pressure and normal blood pressure.

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<th>Reference</th>
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<td>141</td>
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*Individuals with treated hypertension. NS = not stated. MAP = mean arterial pressure.
Table 2. Average serum metformin levels (and corresponding renal function, where available) from the literature in patients with metformin-induced lactic acidosis (MILA), compared with therapeutic levels in “control” and CKD patients on chronic metformin therapy.

<table>
<thead>
<tr>
<th>Reference</th>
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<th>[57]</th>
<th>[57]</th>
<th>[59]</th>
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<td>Control</td>
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<td>eGFR 30-59</td>
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<td><strong>Avg. metformin</strong> (mg/L)</td>
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<td>55</td>
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NA = not available. *Creatinine clearance averaged 116 ml/min