Metformin and Heart Failure

Innocent until proven guilty

Throughout the world and for many years, metformin has been a mainstay of therapy for patients with type 2 diabetes. This highly effective and usually well-tolerated oral agent is, to date, the only one demonstrated to reduce cardiovascular disease (CVD) complications in newly diagnosed type 2 diabetic patients (1). It's precise mechanism of action remains enigmatic, although it clearly results in a reduction of endogenous glucose production, primarily hepatic gluconeogenesis, most likely involving the stimulation of AMP-activated protein kinase activity (2). A peripheral insulin-sensitizing effect in skeletal muscle has also been demonstrated by some, but not all, investigators (3). In small studies, metformin appears to exert benefit on various other fundamental biological processes that influence atherogenesis, such as lipid metabolism, inflammation, and vascular endothelial function (4). Another insulin sensitizer category, the thiazolidinediones (TZDs), has also been proposed to reduce CVD risk, but that class carries with it concerns of weight gain and fluid retention. As a result, TZDs remain more popular in combination therapy regimens. Perhaps of greatest import to clinicians is the recognition that metformin is the only oral antidiabetic agent associated with weight loss. Accordingly, metformin remains, in the eyes of many authorities, the optimal initial drug choice in most type 2 diabetic patients if diet and exercise have not succeeded in adequately reducing blood glucose levels (5).

Approval of metformin in the U.S. was delayed because of previous experience with phenformin, which was associated with lactic acidosis. Although the risk of such metabolic decompensation with metformin was known to be significantly lower than with the earlier biguanide, a fair amount of debate occurred during the approval process (6). The Food and Drug Administration (FDA) eventually sanctioned metformin's use, with the stipulation that strong warnings be included in the package insert regarding potential risks (7). Since metformin accumulates in the setting of renal failure, and since toxic biguanide levels have been implicated in lactic acidosis, the drug was deemed contraindicated in those with even modest renal impairment, defined as a serum creatinine concentration ≥1.4–1.5 mg/dl. Pharmacokinetic data, however, suggest that metformin levels increase only when the creatinine clearance is reduced to <60 ml/min (8). Indeed, the vast majority of cases of metformin-associated lactic acidosis pertain to patients with acute renal failure, typically in the setting of severe hemodynamic compromise (9). Nonetheless, the FDA deemed it prudent to incorporate a margin of error in the prescribing guidelines to ensure that the risk of acidosis would be held to an absolute minimum. Other original contraindications included those conditions in which acid-base status, lactate metabolism, or renal function might be compromised, including hypoxia, liver dysfunction, alcoholism, and during radiocontrast studies.

Following the initial U.S. clinical experience with metformin, postmarketing surveys indicated that reported cases of lactic acidosis frequently involved patients with heart failure (10). Accordingly, the package insert was later revised to include this new contraindication when the condition had progressed to the point of requiring medical therapy. Practically, this essentially excluded all heart failure patients as potential candidates for this increasingly popular antidiabetic agent. The rationale was reasonable, particularly in light of these emerging reports. Patients with heart failure often have coexisting renal dysfunction. They are frequently hospitalized with circulatory embarrassment, a time at which lactate levels might be expected to rise. Additionally, these individuals are commonly treated with potent loop diuretics, which require careful titration to avoid volume contraction and diminished renal blood flow. Such risks could be increased in heart failure patients with diabetes, who often have coexisting nephropathy. In the face of this growing list of rigid contraindications, several studies have confirmed that a sizable percentage of patients are prescribed metformin appropriately (11–14). Interestingly, though, few adverse clinical outcomes have been demonstrated despite these practices (12,15). Admittedly, such good outcomes may actually be a vindication of the clinical vigilance encouraged by the restrictive prescribing guidelines.

The importance of heart failure as a cause of morbidity and mortality in diabetic patients is now apparent. Diabetes more than doubles the relative risk of prevalent heart failure (16). In addition, heart failure patients with diabetes are at increased risk of adverse outcomes compared with their nondiabetic peers (17). Despite this increasingly recognized association, the underlying link between diabetes and heart failure remains incompletely understood. Clearly, the multitude of CVD risk factors in diabetic patients, particularly those with type 2 diabetes, predispose them to coronary artery disease, increasing the likelihood of myocardial infarction. Not infrequently, the resulting cardiac injury is disturbingly silent. However, many patients with coexisting diabetes and heart failure have preserved systolic function but with impaired left ventricular relaxation (18). This “diastolic dysfunction” also often goes clinically unrecognized. Proposed contributors include hypertension, diabetic microcirculatory disease, oxidative stress, and the deleterious influences of hyperglycemia and insulin resistance on inflammatory mediators, growth factors, vascular endothelial function, and the renin-angiotensin system. Ultimately, maladaptive ventricular remodeling occurs (19). It is also recognized that heart failure may itself lead to insulin resistance (20), primarily through sympathetic nervous system activation, chronically impaired systemic blood flow, decreased skeletal muscle mass, and a consequential sedentary lifestyle. However, irrespective of the directionality of this association, as the population ages, the number of patients with both diabetes and heart failure is expected to grow substantially. Optimal
therapeutic strategies are therefore of utmost importance in this group of patients.

Given the association between diabetes and ventricular dysfunction, a link that likely involves both atherosclerosis and a number of other mechanisms, the potential effects of antihyperglycemic therapies on heart failure outcomes is of significant interest. Unfortunately, to date, despite the increased CVD mortality in diabetes, the benefit of antihyperglycemic therapy on overall cardiac end points has been, at best, modest. It is unclear whether this is a manifestation of a more complex relationship between hyperglycemia and CVD than currently recognized, our inability to reduce glucose levels low enough, or a misdirected emphasis on treatment strategies that do not adequately address insulin resistance. Certainly, epidemiological analyses both in observational studies (21) and from clinical trials (22) provide unequivocal evidence that higher glucose levels are associated with higher CVD risk. Yet, admitted, we’ve been dramatically more successful thus far in improving clinical cardiovascular outcomes in our diabetic patients by focusing on their blood pressure and lipid levels. Nonetheless, drugs with insulin-sensitizing properties may benefit patients with heart failure, given the association between insulin resistance, type 2 diabetes, and ventricular dysfunction. But herein lies the therapeutic conundrum: the classes of antihyperglycemic drugs that improve insulin sensitivity and have beneficial impact on cardiovascular risk factors, metformin and the TZDs, are both contraindicated in patients with advanced heart failure. Their treatment is therefore a major challenge, with therapeutic options severely limited. Because of the reticence of many diabetic patients to use insulin, it is likely that many with coexisting heart failure remain suboptimally treated on sulfonylureas alone. Moreover, insulin itself may cause significant fluid retention and has been recently associated with increased mortality in this group of patients (23). Therefore, while the prohibition of using metformin in those with decompensated heart failure is logical, preventing its use in patients with compensated, chronic heart failure may be less so.

In light of a series of recent studies, including the one by Eurich et al. (24) in this issue of Diabetes Care, the case is mounting for a reanalysis of the current prescribing indications for metformin, at least for the subset of patients with heart failure. These same investigators recently reported decreased total mortality from Saskatchewan, Canada, in patients with type 2 diabetes managed with metformin over those treated with sulfonylureas (25). In that retrospective analysis, a hazard ratio for mortality of 0.63 was reported, a finding consistent across all treatment groups, with varying baseline characteristics. Masoudi et al. (26) recently demonstrated that, in a group of Medicare recipients discharged from U.S. hospitals with a principal diagnosis of heart failure, the prescription of an insulin-sensitizing agent, either metformin or a TZD, was associated with a 13% lower risk of death at 1 year. Metformin-treated patients were also hospitalized less frequently, whereas TZD-treated patients had a borderline increase in all-cause Readmission, primarily due to a modest increase in heart failure readmissions. In the current study, the Saskatchewan Healthcare database was again analyzed, with a focus on the relationship between antihyperglycemic therapy and heart failure. In this group of >12,000 new users of antihyperglycemic drugs, −1,800 developed heart failure during the observation period. Patients treated with metformin were compared with those treated with sulfonylureas and those on combination therapy. (The study period [1991–1996] did not allow for analysis of the then-unavailable TZDs.) After multivariable adjustment, fewer deaths occurred in the metformin (hazard ratio 0.70 [95% CI 0.54–0.91]) and combination therapy (0.61 [0.52–0.72]) groups than in the sulfonylurea group. The similar reductions in the combination therapy group, which typically includes patients with more advanced disease, support the contention that the association of improved outcomes with metformin is real and not simply due to any treatment-related selection bias. A reduction in the composite end point of death or hospitalization was also observed, although without an effect on first hospitalization itself.

If a benefit from metformin therapy in heart failure does exist, then are there plausible pathophysiological explanations? Since both the link between diabetes and heart failure and the actual mechanism of action of metformin remain incompletely understood, this remains a difficult question to fully answer. Generally, many of the characteristics common to diabetes and heart failure, such as insulin resistance, endothelial dysfunction, inflammation, and oxidative stress, are improved by metformin. At a more fundamental level, the contracting heart appears to elaborate most of its energy from the metabolism of nonesterified fatty acids, an adaptation that may be further heightened in the insulin-resistant diabetic heart due to an increased availability of this substrate (27). Notably, in conditions of cardiac ischemia or increased ventricular wall stress, the availability of the more metabolically efficient glucose as an energy source becomes increasingly important. Accordingly, drugs that enhance insulin-mediated glucose uptake by the myocardium may improve the function of the failing ventricle. In addition, stimulation of AMP-activated protein kinase in the heart may augment cardiac energy dynamics (28), as might metformin’s modest effect to lower circulating nonesterified fatty acid levels.

It is certainly difficult to derive any firm conclusions from retrospective analyses, particularly when their methods involve predominately administrative databases or even chart reviews. Unrecognized confounding variables may substantially influence the results of such investigations, and therefore prospective studies are sorely needed to confirm the provocative findings of observational studies. However, until such data become available, the FDA, in conjunction with the diabetes and cardiology communities, should at least begin to readdress the current package labeling that constrains the use of metformin in stable heart failure patients, as has been suggested by others (29,30). For instance, in those with treated, compensated ventricular dysfunction, and normal renal function, the cautious use of metformin may be advisable as part of a comprehensive glucose-lowering program. The evidence is clearly accumulating that this agent may actually benefit type 2 diabetic patients with this comorbidity. Some might propose that drug labeling should be altered only based on the results of randomized clinical trials and not influenced by observational databases. Yet it should be recalled that it was, to a large extent, precisely this inferior level of evidence that led to the initial contraindication of metformin in heart failure patients in the first place. For now, to optimize glycemic control in this growing group of patients with type 2 diabetes and heart failure, rational guidelines must be developed, using the best available evidence. Based on this, at least in heart failure patients, one might say...
that metformin should be considered “innocent until proven guilty.”

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