ACHORD
Alliance for Canadian Health Outcomes Research in Diabetes

ACHORD Knowledge Translation Case Study:
Metformin for the treatment of patients with diabetes and heart failure

Metformin is currently considered the first line of treatment for the management of elevated blood sugar in patients with type 2 diabetes. Metformin has been available in Canada for almost 50 years. One major randomized controlled trial and several epidemiologic studies have suggested metformin can reduce the risk of cardiovascular (CV) events and mortality in patients with type 2 diabetes. This is important because CV disease is the leading cause of morbidity and mortality in patients with diabetes, and because no other blood-glucose lowering therapy has shown to have the same life-saving effects.

Like any drug, however, metformin has potential adverse effects. One adverse effect that has been a concern with metformin use is the potentially life-threatening complication of lactic acidosis. The evidence that metformin actually increases the risk of lactic acidosis is very limited, however (Misbin 2004). Rather, it has been considered a risk with metformin because of a number of deaths due to lactic acidosis associated with a related drug called phenformin, which was removed from the market in the 1960s. Based on this historical perspective, metformin has been formally contraindicated for use in patients with concurrent medical conditions also thought to increase the risk of lactic acidosis, such as heart failure and kidney disease. This presented a clinical dilemma because, as noted above, many people with diabetes have some form of heart disease, and metformin is the only glucose-lowering treatment shown to reduce CV events and mortality.

To address this clinical dilemma, we undertook an observational, population-based study using the administrative databases from Saskatchewan Health (Eurich 2005). This work was part of Dean Eurich's PhD thesis. Using administrative health care records, we identified people with diabetes and heart failure, then looked at what diabetes medications they received. We found that those who used metformin were less likely to be hospitalized or die compared to those who used other diabetes medication. Rather than presenting a risk, the life-saving effects of metformin may actually extend to this specific patient population with concurrent diabetes and heart failure.

We then engaged in discussions with officials at the Food and Drug Administration (FDA) in the US and the Therapeutic Products Directorate (TPD) of Health Canada. Based in part on our research, the FDA initiated a change in the prescribing information for metformin, removing heart failure as a contraindication, by 2006 (Inzucchi 2007). The process was quite different at TPD, however, where any changes to a product monograph need to be initiated by the manufacturer. We therefore approached Biovail Canada, manufacturer of Glumetza®, a sustained release metformin product, who subsequently submitted an application for a product monograph change in 2008, which was eventually approved and posted by Health Canada in September 2009. This prompted similar changes to remove heart failure as a contraindication in the other monographs for metformin products in Canada. As a final note, this research has also been incorporated into the 2008 clinical practice guidelines from the Canadian Diabetes Association (CDA 2008), which provides guidance that metformin is a safe and effective treatment for patients with diabetes and heart failure. Thus, our research has had clear and obvious impact on both policy and clinical practice for patients with type 2 diabetes.

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