**Metformin in Heart Failure: Documented Safety Outweighs Theoretical Risks**

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**Word Count (total): 534**

**Author Contributions:**

All authors comtributed substantially to interpretation of data, were involved in the Drafted the article or revised it critically for important intellectual content AND

• Gave final approval of the version to be published."

Heart failure is common in type 2 diabetes, yet treatment options for glycemic control are limited in this population. Metformin, first line treatment in Canada and around the world, has long been considered absolutely contraindicated for patients with heart failure because of the potential for fatal lactic acidosis – not so much because lactic acidosis has been reported with it but because of metformins’ pharmacologic relationship to phenformin (another biguanide removed from the market in the 1970s because it was associated with fatal lactic acidosis). There is still much debate regarding whether lactic acidosis is due to metformin *per se* or due to the underlying metabolic state of people with heart failure. [1, 2] Although lactic acidosis can on occasion be fatal, current evidence indicates that any risk associated with metformin itself is minimal.[3] It is noteworthy that in Canada, despite Health Canada’s excessively cautionary labeling, that more than half (58%) of patients with diabetes and heart failure are currently prescribed metformin ”off-label”.[4]

Thus, beginning in September 2009, Health Canada approved changes to product monographs for metformin that have explicitly removed the heart failure contraindication for metformin. Over the past year many of the major manufactures of metformin in Canada (10 out of 18) have updated their product monographs to reflect this change, although all still include a “warning,” for metformins use in those with acute heart failure despite no evidence to support the warning.

What is the evidence to support Health Canada’s labeling changes? In the absence of direct head-to-head trials evaluating metformin against other oral hypoglycemics in patients with heart failure, it comes from observational studies. Specifically, 2 reports published in 2007 [5, 6] were cited in revising the product monographs, with another six [7-12] confirming the same findings: metformin is as safe or safer than other oral hypoglycemics. Given the nature of these studies, it is difficult to say with certainty that metformin is indeed advantageous in heart failure; however, observational studies are most appropriate for the evaluation of rare adverse events, particularly in this case where there is also empiric evidence that randomized controlled trials are not feasible [4]. Although the scientific community is often focused on limiting the use of medications when benefits are unproven or potentially harmful, the story of metformin and lingering concerns caused by it’s predecessor phenformin, should remind us that there is another side to the patient safety coin - some medications currently considered unsafe may have been defined as such based on limited clinical evidence.

Perhaps because it is largely available as a generic drug, and there is little metformin-related pharmaceutical industry promotional activity, the aforementioned changes in metformin labeling are occurring very quietly in Canada, and busy clinicians may not be aware of these changes. We felt this information was important to share with Canadian readership. Of note, the 2008 Canadian Diabetes Association guidelines do recommend metformin as a first line therapy in patients with heart failure, and did so despite the fact this was a formal contraindication at the time. We hope these consensus based guidelines and these formal regulatory changes together will alleviate any lingering concerns clinicians may have with continuing or starting metformin in their patients with diabetes and heart failure.

**Funding**

There was no funding for this project.

**Competing Interest Statement**

All authors declare that they have no competing interests and therefore have none to declare.

**Author Contributions:**

All authors contributed substantially to interpretation of data, were involved in the initial draft and revised the article critically for important intellectual content, and gave final approval of the version to be published. DTE is the guarantor of the work and is responsible for the integrity of the work as a whole from inception to published article.

**References**

1. Fantus IG. Metformin's contraindications: needed for now. *Canadian Medical Association Journal*. 2005;173(5):505-507.

2. McCormack JK, Tildesley H. Metformin's contraindications should be contraindicated. *CMAJ*. 2005;173(5):502-504.

3. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care*. 2008;31(11):2086-2091.

4. Eurich DT, Tsuyuki RT, Majumdar SR et al. Metformin treatment in diabetes and heart failure: when academic equipoise meets clinical reality. *Trials* 2009;10:12.

5. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved Clinical Outcomes Associated With Metformin in Patients With Diabetes and Heart Failure. *Diabetes Care*. 2005;28(10):2345-2351.

6. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation*. 2005;111(5):583-590.

7. Inzucchi SE, Masoudi FA, Wang YF et al. Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction - Insights from the National Heart Care Project. *Diabetes Care*. 2005;28(7):1680-1689.

8. Shah DD, Fonarow GC, Horwich TB. Metformin therapy and outcomes in patients with advanced systolic heart failure and diabetes. *J Card Fail*. 2010;16(3):200-206.

9. Aguilar D, Chan W, Bozkurt B, Ramasubbu K, Deswal A. Metformin Use and Mortality in Ambulatory Patients with Diabetes and Heart Failure. *Circ Heart Fail* DOI: 10.1161/CIRCHEARTFAILURE.110.952556 (2010) (Epub ahead of print)

10. Roussel R, Travert F, Pasquet B et al. Metformin Use and Mortality Among Patients With Diabetes and Atherothrombosis. *Arch Intern Med*. 2010;170(21):1892-1899.

11. Evans JM, Doney AS, AlZadjali MA et al. Effect of Metformin on mortality in patients with heart failure and type 2 diabetes mellitus. *Am J Cardiol*. 2010;106(7):1006-1010.

12. MacDonald MR, Eurich DT, Majumdar SR et al. Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. *Diabetes Care*. 2010;33(6):1213-1218.