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More on the Magic of Metformin

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Dear editor,

We read with interest the narrative review on "Cardiovascular Protection by Metformin: Latest Advances in Basic and Clinical Research" by Li and Li [1] and agree with the authors' main conclusion. Further preclinical studies and large-scale randomized clinical trials are needed to elucidate metformin's action on the cardiovascular system.

Over the last decade, we have made the following observations: (1) Metformin is safe and effective in diabetic patients with heart failure [2]. (2) The dual action of metformin on the liver (inhibiting gluconeogenesis) and the heart (activating AMP kinase) contributes to the unlocking of the failing heart from metabolic stress [3]. (3) In the inotropically stimulated isolated working rat heart studied ex vivo, prior metformin treatment in vivo, couples glucose uptake and oxidation and improves contractile function most likely by activating AMP kinase [4]. (4) Those initial observations have subsequently been extended to a model of pressure-induced cardiac stress, where metformin improves cardiac glucose metabolism and function, and where metformin prevents left ventricular hypertrophy in spontaneously hypertensive rats [5]. Lastly, and perhaps most importantly, is the cytostatic action of metformin [6, 7], most likely targeting metabolic mechanisms similar to those described in cardiac hypertrophy. In other words, the stressed heart hypertrophies and fails, while the stressed cancer cells hypertrophy and divide. We note that heart muscle cells are postmitotic

and do not divide, while the opposite is true for cancer cells. Our line of reasoning would then make metformin an attractive agent which protects the heart and kills the cancer. This, we would like to reason, is the magic of metformin. More work is needed, and the horizon seems endless.

Conflict of Interest Statement

The authors have no relevant financial or non-financial conflicts of interest to disclose.

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Author Contributions

E.K. and C.H.L. contributed to the review of the literature and writing of the letter. H.T. contributed to the conception of the idea, review of the literature, and writing of the letter.

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