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## **Repurposing metformin for cardiovascular disease**

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## **Signposts for repurposing from sixty years of metformin use**

Although introduced for use as a diabetic medication in 1957, metformin remains the cornerstone of diabetic drug management in patients with type 2 diabetes mellitus (T2D). Its widespread use has largely been underpinned by the United Kingdom Prospective Diabetes Study (UKPDS) that reported lower cardiovascular mortality and morbidity in patients treated with metformin compared with alternative glucose-lowering drugs, despite similar glycemic control. Recent meta-analysis suggests that the cardiovascular effects of metformin could be smaller than that reported by UKPDS; however, this should be interpreted with caution as there has only been a small number of randomized controlled trials (1). While CVD patients with T2D comorbidity are likely to benefit most from metformin, indications of CV benefit over other diabetes treatments has driven interest in repurposing metformin to treat CVD, irrespective of diabetes status.

Identified before the era of target-driven drug discovery programs, metformin's cellular mechanism is poorly established. The most likely cellular effect underlying antihyperglycemic responses is inhibition of mitochondrial enzymes, including complex I. Mitochondrial suppression by metformin activates AMP-activated protein kinase (AMPK); however, AMPK-independent targets also contribute to effects on glycemia and in addition, benefits of the drug in CVD may also be exerted by mechanisms distinct from its metabolic actions. In our recent work for example, we have been studying anti-inflammatory effects of the drug through suppression of the NF- $\kappa$ B inflammatory signalling pathway (2). We traced these effects back to mitochondrial inhibition, consistent with other evidence of mitochondrial regulation of inflammation (3). Following up these studies in a large, treatment-naive diabetes mellitus population cohort, we confirmed this effect

in humans by observing that compared with sulfonylureas (another T2D drug), metformin suppressed the systemic inflammation marker, **neutrophil to lymphocyte ratio (NLR)**, which is a known predictor of all-cause mortality and cardiovascular events. We also found that metformin suppressed plasma cytokines in patients without diabetes who had heart failure, including the aging-associated cytokine CCL11 (C-C motif chemokine ligand 11). Blockade of CCL11 can suppress aspects of age-related cellular dysfunction and further investigation is required to determine whether observed effects of metformin on mammalian longevity, where suppression of NF- $\kappa$ B is also observed, owe at least in part to cardioprotective benefits arising from suppression of this and other cytokines.

### **Immunometabolism as a drug target for metformin in CVD?**

Inflammation is understood to contribute to CVD but existing non-steroidal anti-inflammatory drugs (NSAIDs) and anti-TNF drugs have shown limited utility in CVD treatment. There is still a strong belief however that anti-inflammatory strategies are worth pursuing, key exemplars of which are the recent CIRT (NCT01594333) and CANTOS (NCT01327846) trials. If inflammation is to be targeted successfully in CVD it is likely that other agents, with different anti-inflammatory mechanisms will need to be studied. Control of immunity through changes in metabolism-‘immunometabolism’ (4), such as is exhibited by metformin, is becoming recognized as an additional potential site of therapy even in non-diabetic age-related disease.

### **RCTs in patients without T2D**

Despite encouraging data in T2D, recent findings on CVD benefit from prospective studies in groups without T2D have so far been mixed. In subjects without diabetes who have cardiac syndrome X with normal coronary arteriography but two consecutive positive

exercise tolerance tests, an 8-week period of metformin treatment improved maximal ST-segment depression, Duke score and chest pain incidence compared with placebo (5) (Table 1). The 'proof of concept' TAYSIDE trial in patients without diabetes who have heart failure and insulin resistance found a beneficial effect of metformin on its secondary outcome of VE/VCO<sub>2</sub> slope, a prognostic measure of exercise capacity (NCT00473876). However, the CAMERA trial (NCT00723307) on patients with insulin resistance but without diabetes who had coronary artery disease already taking statins showed no effect of metformin on carotid artery intima-media thickness (CIMT). In addition, the GIPS-III trial (NCT01217307) on metformin in ST-segment elevation myocardial infarction (STEMI) patients without diabetes showed little or no effect of metformin. In contrast, the recent REMOVAL trial (NCT01483560) in type 1 diabetes did show an effect on the pre-specified tertiary endpoint of maximal carotid-artery intima-media thickness, despite no sustained effect on glycemia, possibly consistent with a CV effect of the drug that is not due to changes in glycemia. Further studies with metformin are ongoing (Table 1). Recent evidence from the EMPA-REG OUTCOME trial (NCT01131676) showed that the SGLT2 inhibitor, empagliflozin, another T2D drug, lowered CVD mortality in T2D patients with prevalent ASCVD. This may largely be independent of effects on glycemia, similar to the multifactorial picture emerging with metformin.

### **Future prospects**

The present clinical equipoise for metformin in CVD without T2D has led to a call for CV endpoint trials of metformin in the absence of diabetes (1) and it is timely to consider how

future repurposing RCTs might be designed. Since pharmaceutical companies are unlikely to fund large-scale trials of metformin, public funding agencies should give consideration to supporting these. New diabetes-independent plasma markers of drug response might find utility as surrogate endpoints in trials, such as inflammatory biomarkers. Such biomarkers might be especially useful in short-term trials where 'hard' endpoints, such as mortality, are delayed. Arguably, an even more critical role for such inflammatory biomarkers may ultimately prove to be better stratification of patient groups, before their entry into trials. A compelling exemplar of the power of this approach is the recently completed CANTOS trial (NCT01327846) of an IL-1 $\beta$  antibody, which selected for trial only those individuals with persistently high inflammatory burden. Where others have not succeeded in the past, this study has established inflammation as a viable target in CVD.

### **Concluding remarks**

In conclusion, a variety of evidence suggests that metformin has potential as a treatment for CVD irrespective of diabetes status but prospective randomized trials to repurpose the drug in individuals without diabetes have so far been largely neutral on CV-related outcomes. Future RCTs, incorporating better stratification/targeting, using novel preclinical markers of diabetes-independent inflammation might establish the utility of metformin and therefore help to prioritize metformin repurposing over other emerging CVD treatments.

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## Disclosure Statement

None