METFORMIN: Is it a cardiovascular drug?

Gregory G. SCHWARTZ, MD PhD

Division of Cardiology
University of Colorado and Rocky Mountain Regional VA Medical Center
Aurora, Colorado, USA

gregory.schwartz@va.gov

Abstract

Metformin has been in clinical use for 61 years and is the most commonly prescribed medication for type 2 diabetes, taken by more than 100,000,000 people worldwide. Most international guidelines recommend metformin as the foundational drug therapy for type 2 diabetes. That guidance is based primarily on findings of reduced death and cardiovascular events with metformin in the United Kingdom Prospective Diabetes Study, an unblinded study with usual care control group performed in 753 patients between 1977 and 1991. Although subsequent observational data and meta-analyses of small trials have also suggested a clinical benefit of metformin, it has never been corroborated in a randomized, placebo-controlled cardiovascular outcomes trial.

Over the past 15 years, a growing body of experimental data has suggested that metformin, acting through AMP-activated protein kinase and possibly other mechanisms, has favorable cardiovascular effects in animal models with or without diabetes. These include anti-atherogenic effects, reduction of myocardial infarct size, improvement in vascular endothelial function, and attenuation of ischemic ventricular arrhythmias. Because placebo-controlled clinical trials of metformin are difficult to perform in patients with established type 2 diabetes, investigators have evaluated the drug's cardiovascular effects in patients without diabetes using surrogate endpoints. Metformin has been shown to improve coronary endothelial function, modify the progression of coronary arterial calcification, and reduce LV mass. However, other studies have shown neutral effects of metformin versus placebo on carotid intima-media thickness and left ventricular function after myocardial infarction. Thus, there is equipoise regarding metformin's role as a cardiovascular therapy.

The Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes (VA-IMPACT; clinicaltrials.gov NCT02915198; sponsored by VA Cooperative Studies Program) is testing the hypothesis that metformin, compared with placebo, reduces death and major adverse cardiovascular events in patients with pre-diabetes and established cardiovascular disease. Planned enrollment is 7868 patients followed for a median of 4 years to the accrual of 1360 primary endpoint events. Upon completion, this trial may provide an answer to the longstanding question of whether metformin is a cardiovascular drug.

Keywords

Metformin, AMP-activated protein kinase, cardiovascular disease, pre-diabetes, clinical trial