Metformin

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Metformin: still the sweet spot for CV protection in diabetes?

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Glossary

ASCVD Atherosclerotic cardiovascular disease
CVOT Cardiovascular Outcome Trial
HHF Hospitalisation due to heart failure
MACE Major Adverse Cardiovascular Event
RCT Randomised control trial

Abstract
Metformin remains the first-line drug treatment for type 2 diabetes (T2D) in most guidelines not only because it achieves significant reduction in HbA1c but also because of a wealth of clinical experience regarding its safety and observational data that has shown that metformin use is associated with lower mortality rates when compared to sulphonylureas or insulin. Recently other diabetes drugs, particularly SGLT2 inhibitors (SGLT2i) and GLP1 receptor agonists (GLP1RA), have attracted considerable attention for their cardioprotective benefits reported in cardiovascular outcome trials (CVOTs). Randomised control trials on these newer drugs are on a larger scale but have shorter follow-up than UKPDS, the main study supporting metformin use. In a recent change to the European Society of Cardiology guidelines, metformin was replaced by SGLT2i and GLP1RA as first-line for T2D with atherosclerotic cardiovascular disease, whereas American Diabetes Association and UK-wide guidelines maintain metformin as first choice drug pharmacotherapy for all T2D. A definitive evidence-base for prioritisation of these drugs is currently missing because there are no head-to-head clinical trial data. Without such trials being forthcoming, innovative, pragmatic and low-cost 'real-world' trial approaches based on electronic health records may need to be harnessed to determine the correct priority, combinations of drugs and/or identify specific patient populations most likely to benefit from each one.

Introduction

Metformin is the cornerstone of drug therapy in type 2 diabetes mellitus (T2D). Its widespread priority in guidelines is largely supported by the United Kingdom Prospective Diabetes Study (UKPDS) that reported reduced cardiovascular death and morbidity in metformin-treated patients compared with alternative drugs available at that time, despite similar glycaemic control (1), supported by an abundance of observational data (2, 3). Observational data is vulnerable to confounding however and UKPDS was open-label, not blinded, with small patient numbers compared with more recent trials on newer drugs. Other aspects of the design have been criticised (4) and in addition, recent meta-analysis could not replicate the cardiovascular benefit of metformin reported in UKPDS, although other included trials were smaller with shorter follow up (5, 6). A recent Cochrane Library systematic review concluded that there was no clear evidence whether, compared with no intervention, behaviour

changing interventions, or other glucose-lowering drugs, metformin monotherapy influences patient-important outcomes (7). Metformin is generally well-tolerated although up to a third of patients are unable to tolerate gastro-intestinal side-effects. Metformin can be provided in doses up to 2g to achieve a large reduction in HbA1c.

A particular strength of UKPDS was its head-to-head comparison of all the major licensed T2D drugs available at the time. In the following 25 years many promising newer agents have arrived but a head-to-head analysis akin to UKPDS is missing for these drugs, which include thiazolidinediones, SGLT2 inhibitors (SGLT2i), glucagon like peptide-1 receptor agonists (GLP1RA) and dipeptidyl peptidase-4 (DPP4) inhibitors. In terms of cardiovascular benefits, much research and recent changes in guidelines are particularly focused on two drug types, SGLT2i and GLP1RA (8) in which drugs in these classes have shown cardiovascular benefit compared to placebo. These two drug classes will be the additional focus of this review besides metformin.

Molecular mechanisms underlying cardioprotective properties of metformin

The anti-hyperglycaemic action of metformin was identified in the 1920s, well before the era of target-driven drug discovery, and its mechanism(s) are only now becoming established. There is much focus on doses of metformin used in cell culture experiments to justify greater physiological relevance of some targets of metformin over others; however, the unproductiveness of these arguments is underlined by recent studies indicating that something as simple as glucose concentrations have a substantial effect on cell culture dose responses to metformin (9). Other approaches besides simple dose comparisons, including gene-knockout and/or clinical validation studies where possible, are proving to be more reliable ways of establishing physiological significance of observed effects of metformin. Targets of interest besides

the liver have recently broadened to include inflammatory cells (10), the gastro-intestinal tract (11), and changes in glucose handling (12-14). The most likely intracellular target is generally accepted to be mitochondrial metabolism (15). The precise intra-mitochondrial mechanism(s) remain uncertain and lacking genetic validation but are likely to involve inhibition of complex I (16-19), leading to activation of sensors of energy-stress that are responsive to increases in cellular AMP levels and other metabolites. AMP-activated protein kinase (AMPK) activation was the first of these sensors to be studied in detail (20) but more recently the importance of AMPK-independent mechanisms has been recognised (21). Recently for example, Sakamoto and co-workers used an AMP-insensitive knockin of fructose bisphosphatase-1 (FBP1) to establish that AMP-dependent regulation of FBP1 mediates the acute effect of metformin on glucose in mice (22). AMPK dependent and independent targets may also contribute to beneficial effects in CVD and these may be different to the targets mediating the metabolic actions of the drug. In our recent work for example, we have studied the immunomodulatory properties of metformin, including suppression of NF-κB (nuclear factor κB) inflammatory signaling pathway (10). The effects on NF-κB are understood to owe mainly to mitochondrial inhibition (10). These molecular studies were followed up in observational analysis of a large, treatment-naive diabetes mellitus population cohort. In comparison with sulfonylureas (another T2D drug), metformin suppressed the neutrophil-to-lymphocyte ratio, which is a known predictor of all-cause mortality and cardiovascular events. We also found that metformin suppressed plasma cytokines in patients without diabetes mellitus who had heart failure, including the aging-associated cytokine CCL11 (C-C motif chemokine ligand 11). In earlier molecular studies, blockade of CCL11 suppressed age-related cellular dysfunction (23). Studies on the immune-modulatory effects of metformin irrespective

of diabetes provide a rationale for testing of metformin in non-diabetic CVD but further investigation is ongoing to establish to what extent any cardioprotective effects of metformin can be attributed to this aspect. More broadly, control of immunity through changes in metabolism, increasingly known as immunometabolism, is becoming recognized as a novel disease therapy node (24, 25). Perhaps the best exemplar of harnessing immunity to target CVD hitherto targeted by drugs mainly altering metabolism is the CANTOS trial, which demonstrated efficacy in treatment of CVD with an anti-inflammatory drug for the first-time (26).

Newer agents: trials and mechanisms

SGLT2 inhibitors

Sodium-glucose transport protein 2 (SGLT2) transporters are expressed in kidney proximal convoluted tubules and are an ideal target for T2D as they contribute approximately 90% of filtered glucose reabsorption (27). A number of individual CVOTs have demonstrated cardioprotective benefits of SGLT2i. Meta-analysis (28) on four of the most significant trials, the EMPA-REG OUTCOME (29) study, CANVAS (30), DECLARE-TIMI 58 (31) and CREDENCE (32) comprised 38723 patients. This meta-analysis found SGLT2i reduced major adverse cardiovascular events (MACE) by 12% (HR 0·88 [95% CI 0·82-0·94], p<0·001). Benefit was seen most strongly in patients with atherosclerotic cardiovascular disease (ASCVD) (HR 0·86 [0·80-0·93]) rather than those without (HR 0.94 [0·82-1·07]). SGLT2i had a more robust effect on cardiovascular death (HR 0·83 [0·75-0·92], p<0·001) and particularly hospitalisation for heart failure (HR 0.68 [0.60-0.76]) p<0.001). In earlier meta-analysis (33), SGLT2i also markedly attenuated progression of renal disease (HR 0·55 [0·48-0·64], p<0·0001). These latter two effects occurred irrespective of existing ASCVD or heart failure. The very latest meta-analysis presented at the American Diabetes Association

(ADA) 2020 meeting, during the drafting of this review, is similar to these earlier findings. This meta-analysis includes the VERTIS trial which reported recently (34). In terms of side effects, in the earlier meta-analysis, SGLT2i were associated with amputations (HR 1.26 [1.06-1.51]), although this effect was largely contributed by one trial, CANVAS. In addition, there was about a 2-fold signal for diabetic ketoacidosis across all three studies, (HR 2.2 [1.25-3.87]) (28). This latter effect has prompted advice to withdraw SGLT2i in patients severely ill with active COVID-19 infection (35). Metformin is also advised to be withdrawn in severely ill COVID-19 patients due to potential risk of lactic acidosis (35). Contrary to this advice, some observational evidence suggests a protective effect of metformin in COVID in women (36)

To establish the mechanism of the protective effect of SGLT2i on CVD, further experimental work needs to be done and it may be that there are multiple factors in play. Besides direct renal sodium and glucose effects there are knock-on effects including on fuel usage, weight, uricosuria, hypertension and wider kidney physiology (37). The CV benefits of SGLT2i are believed to be due to more than simple glucose lowering, as SGLT2i have a relatively modest impact on HbA1c compared with other drugs. Indeed, in the DAPA-HF trial, treatment with dapagliflozin was associated with a significant reduction in the risk for worsening heart failure or cardiovascular death in people with heart failure and reduced ejection fraction regardless of T2D status (38). The rapid separation of placebo and drug arms in heart failure outcomes in Dapa-HF and in most of the SGLT2i CVOTs suggest as well that glucose-lowering and weight loss is unlikely to be the main action. Rather, it has been suggested that the main driver may be the effects of changes in renal sodium, glucose and water handling on

diuresis and improvements in maladaptive renal arteriolar responses in T2D (39, 40). Effects on adverse left ventricular remodelling may also be involved (41, 42)

GLP1RA drugs

GLP1 agonists include injectable peptides as well as oral preparations. They mimic the incretin effect, lost in diabetes, which is mediated by insulinotropic peptide hormones including GLP1 secreted by the gut following a meal, and which then potentiate glucose-stimulated insulin secretion (43). There have now been several CVOTs of GLP1RA, including ELIXA (44), EXSCEL (45), LEADER (46), SUSTAIN6 (47), PIONEER6 (48), HARMONY (49) and REWIND (50). A recent meta-analysis of five of these trials, ELIXA, EXSCEL, LEADER, SUSTAIN6 and HARMONY, found that GLP1RAs reduce three-point MACE by 12% (HR 0.88, 95% CI 0.84-0.94; $P < 0.001$) (51). In addition, they reduced CV death in ASCVD (HR 0.87, 95% CI 0.82-0.92 $P = 0.028$) but unlike SGLT2i, there was no impact on HHF (HR 0.93, 95% CI 0.83-1.04) (51). GLP1RA are generally understood to have a favourable safety profile.

Akin to both metformin and SGLT2i, the molecular mechanisms through which GLP-1RAs reduce CV outcomes may be complex, judging by mechanistic studies in model organisms. GLP1 receptors are expressed in cardiovascular tissue so that direct CV and vascular effects of GLP1R could contribute (52, 53). Bio-activity of truncated versions of the endogenous GLP1 peptide (52, 54) and preservation of cardioprotective benefit in GLP1R-knockout animals adds to the likely complexity of this system (52). The long half-lives of the peptides may be important to their CV benefit, compared for example with DPPIV-targeting agents. The divergence of placebo and treatment curves in trials seems more gradual than for SGLT2i. Besides

effect on HbA1c, GLP1RAs consistently lower systolic blood pressure and lower weight in RCTs (53, 55), which may contribute to the cardioprotective effect. Favourable effects on lipids are commonly but less consistently observed in trials (53).

The lack of head-to-head randomised trials

The evidence gathered in large-scale CVOTs with SGLT2i and GLP1RA has not been matched by large-scale CVOTs on metformin, predominantly due to the ubiquity of its use as first-line T2D therapy. In response to the new evidence on SGLT2i and GLP1RA, recently ESC changed its guidance and now recommends SGLT2i or GLP1RA, not metformin as first-line for patients with ASCVD, or high / very high CV risk (56). Nevertheless, ADA (57) and UK NICE guidelines remain unchanged, with metformin as first-line for all patients. It has been noted for example that on the basis of existing trials, it is not possible to rank competing treatments reliably with regard to their effects on cardiovascular outcomes (58, 59). Without large-scale metformin CVOTs, the magnitude of any CV-protective effects of this drug will not be determined free of confounding and ultimately, randomised head-to-head trials would be the best evidence with which to define drug priority. Consistent with this, recent systematic review and network meta-analysis of trials studying all major diabetes drugs indicated that use of metformin as first-line treatment of drug-naive patients at low cardiovascular risk still seemed justified (59). It is important to note that in the CVOTs described for SGLT2i and GLP1RA drugs, efficacy was compared with placebo and not subjected yet to the stronger challenge of demonstrating efficacy above other drugs in head-to-head comparisons. Nevertheless, some inference regarding the impact on CV outcomes of metformin can be made, bearing in mind the limitations of such post-hoc analyses. One approach is to examine event rates in patients taking

metformin in these trials vs. those not taking metformin. As would be expected, in the CVOTs the percentage on metformin was high (~70%). In a post-hoc analysis of the LEADER trial, after adjustment, patients on metformin at baseline had significantly reduced incidence of the primary outcome compared to individuals not taking metformin (HR 0.72; 95% CI 0.64-0.81)(60). In unpublished analysis of CANVAS (presented at the American Association of Clinical Endocrinologists 28th Annual Scientific & Clinical Congress 2019) (61), 22.8% of patients in the study were not treated with metformin. In patients on metformin, canagliflozin had no significant effect on the primary outcome of CV mortality, nonfatal MI or nonfatal stroke (HR 0.91, 95% CI 0.77-1.06) whereas in those not on metformin, canagliflozin did cause improved outcome compared to placebo (HR 0.76, 95% CI 0.35-0.78). In another post-hoc analysis of CANVAS, the beneficial effect of canagliflozin for the outcome of CV death or hospitalisation for HF was also significantly attenuated in patients with metformin (p for interaction 0.03) (62). A directionally similar result was also seen in EMPA-REG, although the interaction did not quite reach significance (p=0.07) (63). These results provide some evidence that the benefit of the SGLT2 drugs may be attenuated by baseline prescription of metformin. It has been argued that interactions between these two drug types imply shared targeting of AMPK by metformin and SGLT2i (64), although more investigation will be required to establish the extent to which other AMP-regulated enzymes such as FBP1 contribute to any shared mechanism, rather than AMPK. Assuming that there is not a detrimental interaction between the study drug and metformin, it would be reasonable to assume that CV benefits of these SGLT2 inhibitors might be attenuated because metformin is already providing beneficial effects through this shared mechanism. In contrast to these findings though, in VERTIS (34) and DECLARE (65), there was no clear difference in patients

with/without baseline metformin. The reasons for this variation between studies is currently unclear and further study is required.

In meta-analysis of recent CVOTs, consistent with a CV-protective effect of metformin, metformin use at baseline is associated with a lower risk of CV death (HR 0.64 95% CI 0.56-0.74), in both the placebo and active drug groups (interaction p value 0.94) (Figure 1). Like all observational data, our analysis is vulnerable to confounding due to bias, as the patients were not randomised to metformin. Larger effects of metformin than other drugs might be due to confounding by indication, as it is now typically prescribed first, in people whose diabetes is less severe and with a better prognosis. In addition, as we only used study-level data, we were unable to adjust the results for likely confounding factors such as renal function, however this does provide additional supportive evidence for the presence of CV benefit with metformin. Our analysis is consistent with another recent post-hoc analysis by Bergmark and colleagues, which investigated metformin in the saxagliptin SAVOR-TIMI 53 trial (66). This work found that metformin use, after adjustment for clinical variables and biomarkers, was associated with lower rates of all-cause mortality (HR 0.75 [95% CI, 0.59-0.95]). However, there was no significant impact on the composite end point of cardiovascular death (HR 0.92 [95% CI, 0.76-1.11]). Together with these previous findings, our analysis of recent CVOTs reinforce earlier studies that metformin has a significant benefit to CVD patients with T2D, in lieu of novel randomised trials of metformin vs. placebo. In the past, head-to-head RCTs would have been deployed to address comparative effectiveness of two or more agents. It has been argued previously (67) that the lack of recent head-to-head trials to determine comparative effectiveness of diabetes drugs may be an inadvertent consequence of the requirement of the USA FDA and European Medicines Agency on CVOTs for new drugs, following CV

concerns associated with rosiglitazone. Issues such as relative effectiveness, long-term drug-related adverse events and consequent risk/benefit analysis over time, may in comparison have become inadequately addressed (67). Consequently, there is comparatively little data on metformin compared to SGLT2i and GLP1RA (Fig. 2), a gap that regulatory authorities might consider obliging drug developers to close in future trials.

New head-to-head trials akin to UKPDS or if cost proves prohibitive, innovative new pragmatic trial approaches based on electronic health records, may now be needed to definitively establish the correct priority of these three drug classes or best combinations and/or to identify specific patient populations most likely to benefit from each. Moreover, promising results with these diabetes therapies, coupled with the growing realisation that glucose-lowering may be providing only a small fraction of their cardioprotective effects, supports their ongoing investigation in selected non-diabetic patients (68). Recently in the MET-REMODEL RCT for example, we have provided proof-of-principle findings, establishing that metformin can regress left-ventricular hypertrophy in patients with coronary artery disease and insulin resistance without diabetes. In this study, metformin treatment significantly reduced left ventricular mass indexed to height compared with placebo group (absolute mean difference -1.37 (95% CI: -2.63 to -0.12, P = 0.033) (69). Forthcoming large-scale metformin vs. placebo trials in non-diabetic hyperglycaemia such as VA-Impact (NCT02915198) and GLINT (70) may also be informative for these non-diabetic contexts.

Conclusion

In conclusion, there have been promising findings with newer agents and recent changes in guidelines for metformin, SGLT2i and GLP1RA in CV protection in T2D. In

the absence of traditional head-to-head randomised control trials, innovative new low-cost trial approaches exploiting electronic health records may help address currently unanswered questions around relative effectiveness and risk/benefit of these three drug classes. Investigation of nondiabetic cohorts is also ongoing.

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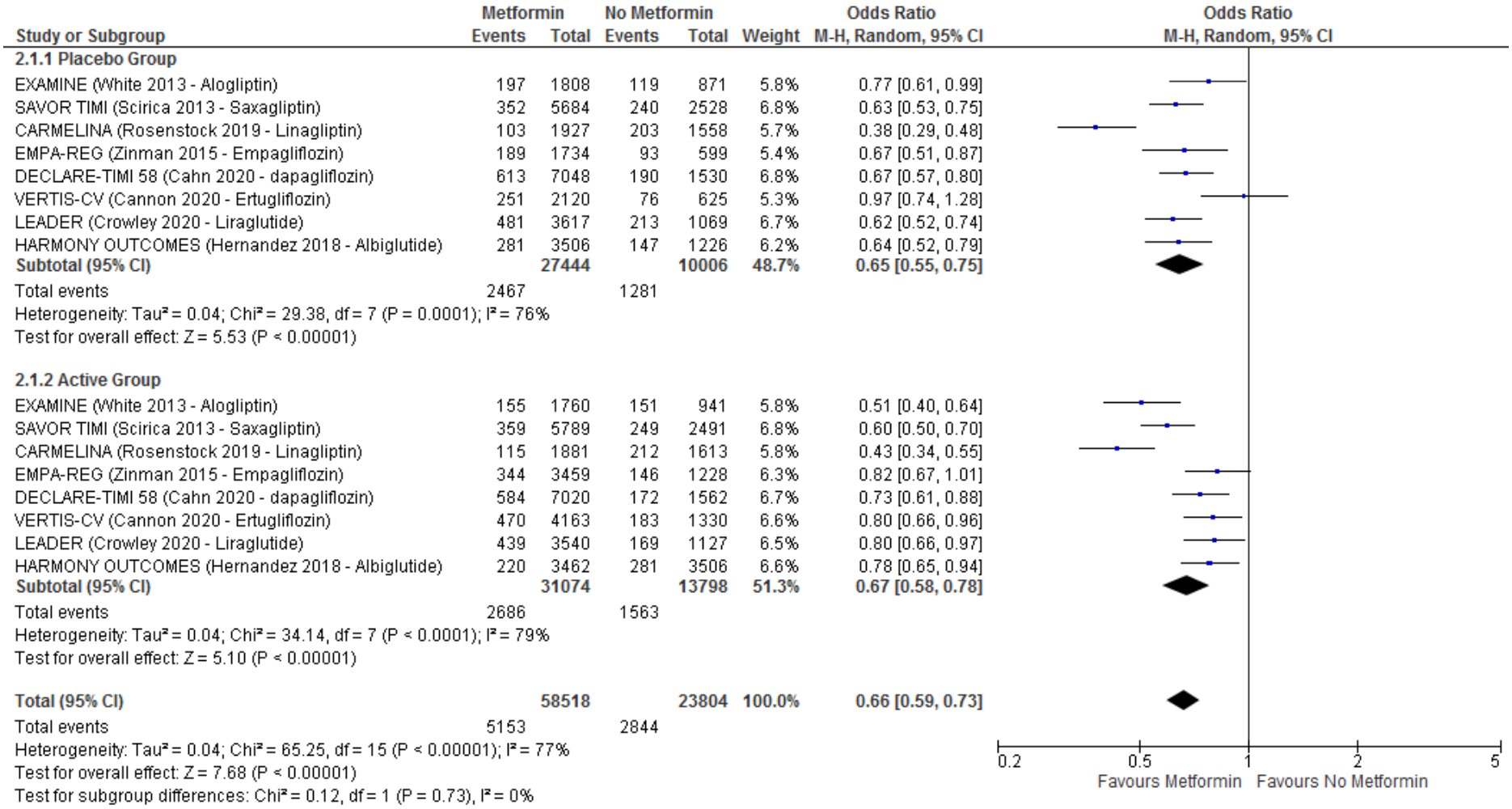
Figure 1. Primary Outcome Events in Recent Type 2 Diabetes CV Outcome Trials Stratified by Metformin Use.



Results derived from study-level data where available.

Fig 2

	Metformin	SGLT2 Inhibitors	GLP-1 RAs
Publication	Griffin (Diabetologia 2017)	Arnott, JAHA 2020	Kristensen, Lancet Diabetes 2019
Number of Studies	13 (4 metformin vs. placebo only)	4 (all vs. placebo)	7 (all vs. placebo)
Number of Patients	3,815 (CV Death Endpoint)	38,723	56,004
MACE	n/a	0.88 (0.82-0.94)	0.88 (0.82-0.94)
CV Death	0.97 (0.80-1.16)	0.83 (0.75-0.92)	0.84 (0.76-0.93)
Fatal/Non-fatal MI	0.89 (0.75-1.06)*	0.88 (0.80-0.97)	0.91 (0.84-1.00)
Fatal/Non-fatal Stroke	1.04 (0.73-1.48)*	0.96 (0.86-1.09)	0.84 (0.76-0.93)
HF Hospitalisation	n/a	0.68 (0.60-0.76)	0.91 (0.83-0.99)

*Only 7 studies reported myocardial infarction; 4 reported stroke