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The Divergent Cardiovascular Effects of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Myocardial Infarction and Death

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ABSTRACT

The renin angiotensin aldosterone system (RAAS) plays a central role in the pathophysiology of hypertension and vascular disease. Angiotensin converting enzyme inhibitors (ACEis) suppress angiotensin II (ANG II) concentrations, whereas angiotensin receptor blockers (ARBs) block the binding of ANG II to AT_1 receptors. ACEis and ARBs are both effective anti-hypertensive agents and have similar risk reductions in stroke — a blood pressure dependent phenomenon. ACEis also reduce the risk of myocardial infarction (MI) and mortality in high risk hypertensive patients, as well as in diabetics, the elderly, those with vascular disease, and in congestive heart failure. ARBs, in contrast, do not reduce the risk of MI or death in clinical trials where the comparator has been another active therapy or even a placebo. Systematic reviews of ARBs that include meta-analyses or meta-regression analyses confirm that ARBs lack the cardiovascular protective effects of ACEis, which in part are "independent" of blood pressure lowering. Practice guidelines, especially those in high risk hypertensive patients, should reflect the evidence that ACEis and ARBs have divergent cardiovascular effects — ACEis reduce mortality, whereas ARBs do not. ACEis should be the preferred RAAS inhibitor in high risk patients.

Angiotensin converting enzyme inhibitors (ACEis) and angiotensin II type 1 (AT_1) receptor blockers (ARBs) are anti- hypertensive (HTN) agents that modulate the renin angiotensin aldosterone system (RAAS) by targeting angiotensin II (ANG II), each with a unique mode of action. ACEis suppress the production of ANG II, whereas ARBs block the ANG II stimulation of the AT_1 receptor; therefore each is a unique therapeutic class. ACEis and ARBs do have similar blood pressure (BP) lowering effects, with a positive impact on stroke,[1] diabetic kidney disease,[2] symptoms of congestive heart failure (HF),[3] and at least in *post hoc* analyses of large clinical trials, reduce the incidence of diabetes mellitus(DM) and atrial fibrillation.[4] This shared efficacy has led to the conclusions in many practice guidelines that ACEis and ARBs are equivalent, interchangeable, and alternative

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Abbreviations and Acronyms

ACEi = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

BP = blood pressure

CHD = coronary heart disease

CV = cardiovascular

CVA = cerebral vascular accident

DM = diabetes mellitus

HF = heart failure

HTN = hypertension or hypertensive

LV = left ventricular

MI = myocardial infarction

NYHA = New York Heart Association

QoL = quality of life

RAAS = renin angiotensin aldosterone system

SBP = systolic blood pressure

therapies, and to perhaps be viewed as a single pharmacologic class — "RAAS inhibitors".[5,6] This conclusion however, is not shared by all.

In the most recent iteration of the European Society of Hypertension (ESH) guidelines,[7] section 5.2.1.4 states that *"angiotensin receptor blockers may be inferior to ACE inhibitors in preventing myocardial infarction (424) or all-cause mortality (393)."* This statement might be viewed by many as controversial, if not heretical. However, if the BP reductions seen with ARBs do not translate into a reduction of "hard" cardiovascular (CV) endpoints similar to ACEis, then ACEis should be the preferred RAAS inhibitor in high risk patients. There is compelling and robust evidence to support this conclusion, such as clinical trial data in approximately 300,000 patients. The results are consistent whether from individual trials with a placebo or active comparator, or in meta-analyses,[8–10] or meta-regression analyses that adjust for BP within the trials[1,11]; ACEis reduce the risk of myocardial infarction (MI)and death above and "independent" of BP lowering, whereas ARBs do not.

This review will focus on the "hard" CV endpoints of ACEi and ARB trials – MI and death – in the context of the known impact of BP lowering per se on these endpoints. As well, the trial data will be evaluated from the perspective of its design and the statistical analysis used – prospective vs. retrospective trial, double blind vs. open label, active or placebo comparators, statistical "superiority" or "non-inferiority" – as any conclusion of therapeutic efficacy is predicated on the strengths and limitation of the statistical analysis used.

BP and CV endpoints

The CV endpoints of greatest clinical importance in the treatment of hypertension are mortality, MI, and stroke (CVA) — the "hard endpoints". The relationship of BP and mortality was assessed in a collaborative meta-analysis of prospective observational studies in 1,000,000 subjects with no known CV disease, thus evaluating the potential impact of BP reduction independent of any additional cardio-protective effects drugs might provide.[12] For every 10 mmHg reduction in systolic BP (SBP), it was predicted that the risk of coronary heart disease (CHD- MI plus CV death) would decrease by 25% and CVA by 36%. Although the risk reduction in CHD is less than CVA, death from CHD is three times more common than from CVA — confirming that CHD is the primary target for the greatest benefit to the population. This prediction was confirmed in a meta-analysis of 147 randomized anti-HTN trials by Law and Wald[13] — for every 10 mmHg reduction in SBP, CHD decreased 22% and stroke 41%. Although this meta-analysis includes a broad range of anti-HTN agents, each class may not provide equivalent reductions in the "hard endpoints"[1,11,14] which is an important consideration in the choice of therapeutic agents. It is also clinically relevant to consider the therapeutic benefits of anti-HTN on "soft" endpoints – microalbuminuria, insulin resistance, uric acid, tolerability, etc. – but primarily when the impact on "hard endpoints" is similar.

The ARB MI paradox – the evidence is there from 2004

A 2004 editorial in the *British Medical Journal*[15] (co-authored by one of us: MHS) was the first reference in the literature to suggest that ARBs may not provide similar CV protection as ACEis. Early ARB trials appeared not to reduce the risk of MI or death despite demonstrating good tolerability and effective BP lowering.[15] It was noted in the VALUE[16] trial that there was a statistically significant 19% excess of MI with the ARB valsartan as compared to the calcium channel blocker amlodipine in a large population of HTN patients. Other ARB trials also observed small increases in the risk of MI[4] — which achieved statistical significance in the CHARM-Alternative study.[17] There was biologic plausibility to explain this phenomenon – as discussed below – which was termed the "ARB MI Paradox".

The *BMJ* editorial[15] was controversial but resulted in tremendous discussion and debate which were addressed six months later at the 2005 European Society of Hypertension Meeting in Milan. The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC)[1] presented a parallel meta-regression analysis of ACEi and ARB trials where BP differentials within the trials were regressed against the risk of MI and death-CHD. Both ACEis and ARBs were shown to have identical BP "dependent" risk reduction of CHD. However, for any given BP reduction, ACEis reduce the risk of CHD an additional 9% (p = 0.002) above and "independent" of the effects of BP lowering with the 9% relative risk reduction apparent even in the absence of any BP reductions (Fig 1)[1] — a phenomenon confirmed by others.[11,18] In contrast, ARBs have no BP "independent" effects on CHD, rather there is a small non-significant increase in the risk of harm of 7% (95% CI; 24%–7%, p = ns) (Fig 1). For any given BP reduction, ACEis reduce the risk of MI and death an additional 15% (p = 0.0001) above that of an ARB, which was "independent" of BP lowering (Fig 1). In contrast, the risk reduction in stroke and HF for ACEis and ARBs were each identical and solely dependent on BP lowering. The BPLTTC meta-regression analysis[1] validated the hypothesis put forth in the *BMJ* editorial[15] – that ARBs lack the cardioprotective effects of ACEis on CHD – thus confirming the "ARB MI Paradox".

The divergent CV effects of ACEis and ARBs were confirmed in a 2006 *CIRCULATION* parallel meta-analysis of ACEi and ARB trials[4] (co-authored by these authors). ACEis vs. all comparators (active or placebo) (39 trials, n = 154,943) reduced the relative risk of total mortality by 9% ($p < 0.0001$) and MI by 14% ($p < 0.0001$), whereas ARBs (11 trials, n = 55,050) did not reduce mortality (OR 1.01; 95% CI, 0.96–1.06, p = 0.8) with the risk of MI actually increasing (OR 1.08; 95% CI, 1.01–1.16, p = 0.03) (Fig 2). In contrast, the risk reductions in CVA for both ACEis and ARBs were similar – where the risk of stroke is dependent on BP lowering alone – suggesting similar BP reductions in the parallel meta-analyses. As well, the risks of global death, MI, and stroke in the comparator arms of the ACEi and ARB parallel meta-analyses were similar (13% vs. 14%, 5.8% vs. 6.3%, and 4.2% vs. 4.4%, respectively) — suggesting similar at risk patients. Although other ARB meta-analyses have not demonstrated statistically significant increases in the risk of MI,[9,19,20] more importantly, they demonstrated no risk reduction in MI or mortality — a finding that should have been disconcerting to those investigators.

Angiotensin II, bradykinin, AT_1 and AT_2 receptors – how is it all connected?

The unique BP "independent" effects of ACE inhibitors have biologic plausibility.[4] ACEis suppress angiotensin II (ANG II) — ANG II not only plays a central role in the pathophysiology of HTN via vasoconstriction and fluid retention, but has direct tissue toxicity on the vasculature, heart, brain, and kidneys. ANG II induces CV damage by sustaining cell growth, inflammation, and fibrosis; has a direct effect on smooth muscle migration, vascular hypertrophy and formation of extracellular matrix resulting in vascular remodeling; and leads to endothelial dysfunction.[21] Suppression of ANG II levels with ACEis may attenuate the direct toxic tissue effects of ANG II "independent" of BP lowering. ACEis also prevent the breakdown of bradykinin; bradykinin is an important mediator of ischemic preconditioning, endothelial function, and fibrinolysis — all of importance for CV protection.[4]

In contrast to ACEis, ARBs do not up regulate bradykinin and therefore lack those potential CV protective effects.[4] ARBs do not suppress ANG II levels as do ACEis, but rather selectively block the AT_1 receptor — both drugs thereby attenuating the effects of ANG II, albeit by different mechanisms. AT_1 receptor blockade with ARBs is known to inhibit a negative feedback loop with a resulting increase in ANG II levels 200% to 300% from baseline with its attendant direct tissue toxicity. Increases in ANG II concentrations have also been hypothesized to play a beneficial role via stimulation of AT_2 receptors – which have opposing properties to AT_1 stimulation – with peripheral vasodilation as well as anti-growth and anti-inflammatory benefits.[21] Much less is known about the AT_2 receptor as there is low expression in adults, and its actions are over powered by AT_1 activation which is thought to have opposing properties.[21] Stimulation of AT_2 receptors in diseased coronary arteries is thought to lead to plaque rupture, myocardial infarction, and adverse vascular remodeling[22] (Fig 3). Clearly this could minimize or negate the potential CV benefit of BP lowering via AT_1 receptor blockade with ARBs.

ACEis and ARBs as compared to placebo

There are distinct advantages to clinical trials where the comparator is a placebo rather than another active comparator. Placebo controlled trials provide the most rigorous measure of treatment efficacy and harm, allows for trial conditions that maximize "treatment separation" thus increasing the likelihood of detecting beneficial or harmful effects, and can be an "add on" to standard care.[23] Three recent meta-analyses of ARB trials with placebo comparators provide insight into ARBs' therapeutic efficacy, or the lack thereof.

A parallel meta-analysis of ACEi and ARB trials with a placebo comparator in high risk patients excluded patients with HF (26 trials, n = 108,212) (Savarese[8]). ACEis (13 trials, n = 53,791) reduced the risk of MI by 17.7% ($p < 0.001$) and all-cause mortality by 8.3% (p = 0.008). ARBs (13 trials, n = 54,421) in contrast, had no significant risk reduction in MI or all-cause mortality (OR 1.006; 95% CI: 0.941–1.08, p = 0.866). These divergent results were seen despite ACEis and ARBs having similar reductions in stroke which were statistically significant – a risk reduction which is solely dependent on BP reduction[1,24] – suggesting similar BP reductions within the parallel meta-analyses. A more inclusive ARB meta-analysis of placebo controlled trials had similar results (17 trials, n = 67,374 patients) (Bangalore)[9] — MI and all-cause mortality had no risk reduction (OR 0.93; CI 0.81–1.07, OR 0.99; CI 0.95–1.03, p = 0.98, respectively). A meta-analysis limited to patients over the age of 65 (8 trials, n = 50,521) (Elgendy)[10] also found no risk reduction in MI or all cause mortality (HR 1.03; CI 0.88–1.21, HR 1.03; CI 0.98–1.08, respectively). As seen in the Savarese[8] meta-analysis, the risk of stroke in the Bangalore[9] and Elgendy[10] meta-analyses was also significantly reduced ((OR 0.91; CI 0.85–0.98), (HR 0.93; CI 0.86–1.0), respectively)).

The results of these 3 meta-analyses of placebo controlled trials are consistent: ARBs significantly reduce the risk of stroke, a CV benefit that is directly related to BP lowering.[1,24] Despite that, ARBs had no BP "dependent" risk reduction in MI and death, which at minimum should have been half the risk reduction seen for stroke.[12,13] This would suggest that ARBs may have direct deleterious CV effects, perhaps secondary to up regulation of ANG II levels that may attenuate the potential benefits of BP lowering.

ACEi vs. ARB trials

The direct comparison of ACEis and ARBs in head to head trials – some would say – is the optimum way to evaluate their relative CV protective effects. There are 4 large such trials, and although each was negative for the hypothesis of statistical "superiority" of the ARBs, they do provide a unique perspective. The ELITE II[25] trial in chronic HF (n = 3152, follow up 18 months)

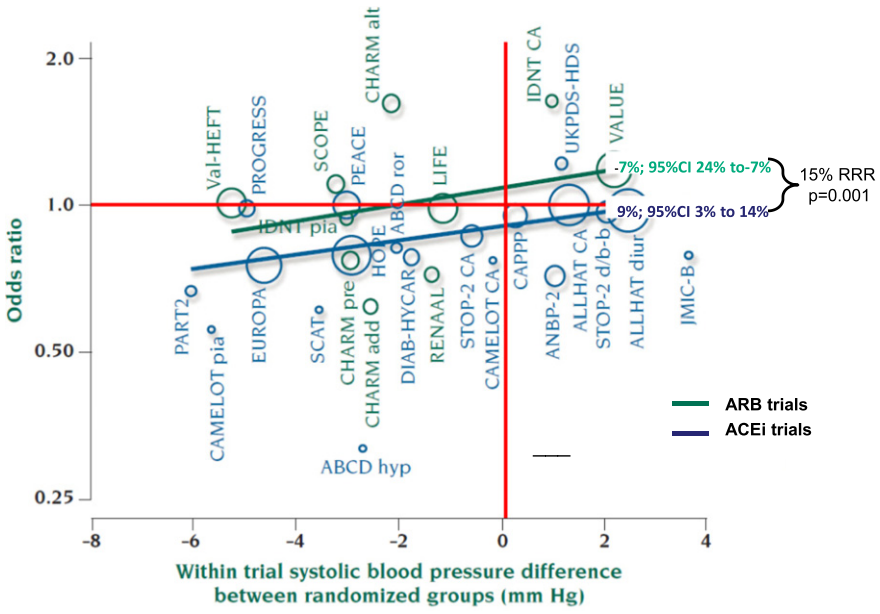

Fig 1 – Parallel meta-regression analyses of ACE inhibitor and ARB trials for the risk of MI and CV death adjusted for blood pressure reductions within the trials. There was a 15% risk reduction in MI and CV death (P = 0.0001) between ACE inhibitor trials (blue circles) and ARB trials (green circles). Modified from Turnbull et al. J Hypertens. 2007; 25(5):951–958.

compared losartan 50 mg vs. captopril 50 mg 3 times daily; the losartan treated group had a 13% higher total mortality than the captopril arm but was not statistically significant (280 versus 250 deaths, p = ns).

The OPTIMAAL[26] (n = 5477, follow up 32 months) and VALIANT[3] (n = 9818, follow up 25 months) were both trials in patients within 10 days of an MI and new onset HF. In OPTIMAAL,[26] losartan 50 mg had a significant increase in CV mortality as compared to captopril 50 mg three times a day (OR 1.17, 95% CI 1.01–1.34) with a trend for an increase in total mortality (relative risk 1.13, 95% CI 0.99–1.28, p = 0 · 07). In contrast, in VALIANT[3] the all cause mortality rates for valsartan 160 mg twice a day and captopril 50 mg three times a day were similar (HR, 1.00; 97.5% CI 0.90–1.11; P = 0.98), but not statistically equivalent. To prove statistical equivalence, a trial would require that as the *a priori* design, and the number of patients

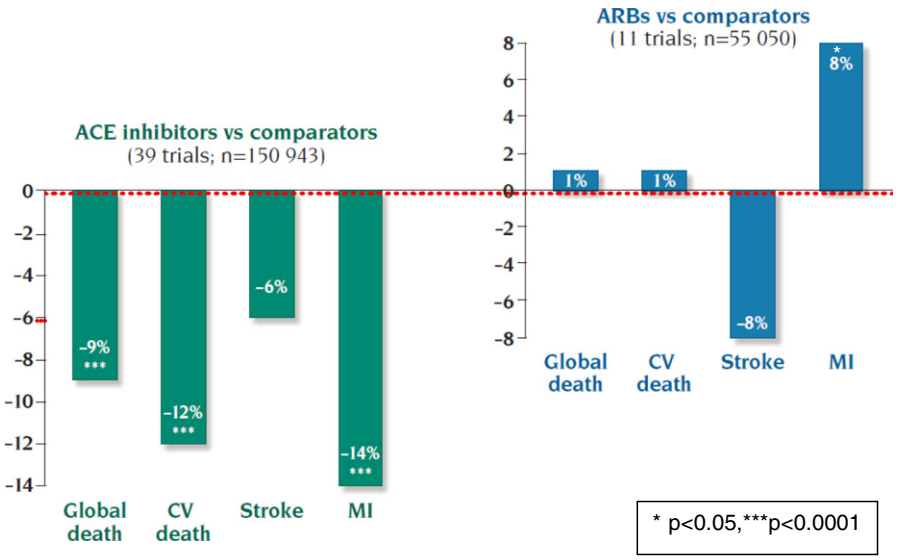

Fig 2 – A parallel meta-analysis of ACE inhibitors and ARB trials. ACE inhibitors reduced the relative risk of total mortality by 9% (P < 0.0001) and myocardial infarction by 14% (P < 0.0001), whereas ARBs (11 trials; n = 55,050) did not reduce mortality (OR, 1.01; 95% CI, 0.96–1.06; P = 0.8) and the risk of myocardial infarction actually increased (OR, 1.08; 95% CI, 1.01–1.16; P = 0.03). Modified from Strauss and Hall. Circulation. 2006: 114(8):838–854.

required would have been much larger. VALIANT is therefore a negative superiority trial and as such, even if the event rates of valsartan and captopril appear to be no different, it cannot prove statistical equivalence. A general axiom in statistics is that the *"absence of a difference does not mean a true difference does not exist"*. For example, the mean follow up in VALIANT[3] of 2 years was too short to show any potential "time-dependent" differences between 2 active comparators considering it took 3.5 years in the SAVE trial[27] for captopril to have a mortality benefit as compared to placebo. As well, potential benefit of captopril in VALIANT may have been masked as 39% of the patients received an average of 5 days of non-study ACEis post-MI and prior to randomization. ACEis are known to reduce mortality in the early post-MI period (7% RR reduction at 30 days[28]), with 85% of the benefit in the first week and therefore, early use of non-study ACEis in VALIANT may have influenced the results.

ONTARGET[29] (n = 17,118, follow up 56 months) compared telmisartan 80 mg vs. ramipril 10 mg in high risk patients with vascular disease or DM and excluded HF. There was no difference for the primary combined endpoint of CV death, MI, stroke, and hospitalizations for HF (HR 1.01; 95% CI 0.94–1.09) or for all cause mortality (HR 0.98; 95% CI 0.90–1.07). Telmisartan achieved a lower BP than ramipril (0.9/0.6 mmHg) and had a 9% lower risk of stroke, a BP dependent effect, but paradoxically had a 7% excess of MI — and although both risk reduction of stroke and MI are not statistically significant, the excess in MI is consistent with the "ARB MI Paradox". As in VALIANT,[3] ONTARGET[29] was designed and powered as a "superiority" trial, and despite numerically similar event rates in both arms of the trial, it was a negative superiority trial and therefore no conclusion of equivalence is possible. Despite that, the authors of ONTARGET[29] concluded in the abstract *"Telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes …for the primary cardiovascular combined endpoint"*[29] — a conclusion which is not valid.

The ONTARGET[29] trial – as did VALIANT[3] – included a statistical analysis for "non-inferiority", a relatively recent addition to the statistical armamentarium. "Non-inferiority" is a statistical concept that can prove that telmisartan is "not substantially worse than the gold standard (ramipril), by a pre-determined amount (equivalence margin)".[30] A statistically "non-inferior" therapeutic agent in no way determines that the therapy is therapeutically equivalent to the gold standard — rather at best, a statistically "non-inferior" therapy is a 2nd line therapy especially as it pertains to "hard" CV endpoints. This interpretation of statistical "non-inferiority" in the context of the results of ONTARGET[29] is validated by the recommendations of the Food and Drug Administration (NDA 20-850) and the Health Protection Branch of Canada — both approved telmisartan as a 2nd line therapy for those "high risk" patients who are ACEi intolerant. Despite the clear recommendations of these regulatory agencies, there is still much confusion amongst physicians in understanding what statistical "non-inferiority" can or – more importantly – cannot prove. This confusion is understandable given that the literal translation of the word "non-inferiority" defines things to be "equivalent" or "interchangeable" — definitely not what is proven by the statistical term of "non-inferiority"!

The above conclusions are also consistent with the European Medicines Agency (EMA) analysis of ONTARGET[29] in "The Assessment Report for Micardis" (London, 2009 #EMA/CHMP/768468/2009). That report concluded **"The data do not allow to conclude that the effect of ramipril is preserved (equivalence). Even superiority of telmisartan vs. placebo was not demonstrated neither when compared to a putative placebo in ONTARGET, nor when directly compared to placebo in TRANSCEND and pRoFESS"**.

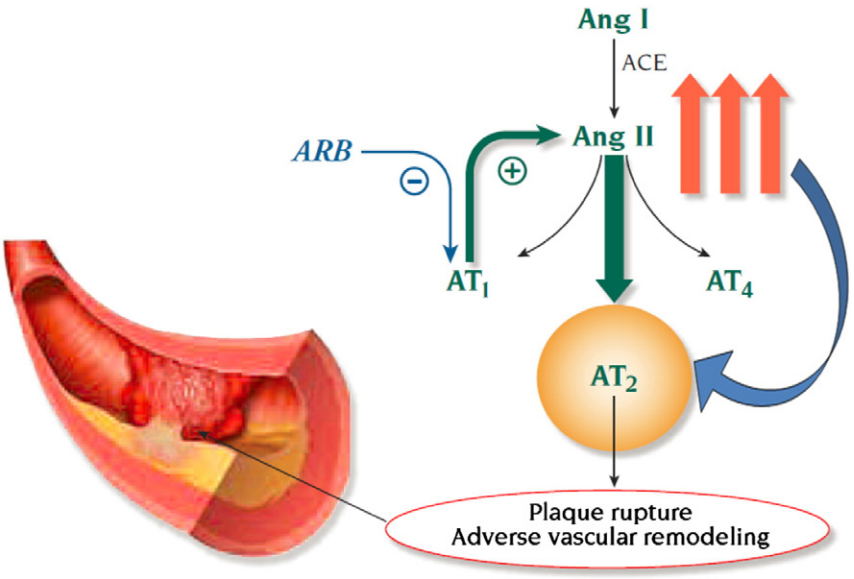

Fig 3 – Plaque rupture in coronary arteries with ARBs. Blocking AT_1 receptors with an ARB inhibits a negative feedback loop, increasing Ang II levels 2 to 3 fold, which leads to hyper stimulation of AT_2 receptors and plaque rupture in coronary arteries. Modified from Strauss and Hall. Circulation. 2006; 114(8):838–854.

What is indeed perplexing – and goes against the practice of evidence based medicine – is that despite the EMA concluding that telmisartan is not even superior to a placebo, approved telmisartan as a 1st line agent in high risk patients– as is ramipril – and can therefore be prescribed preferentially to an ACE inhibitor.

Hypertension – ACEis and ARBs – BP independent effects

A recent pooled meta-analysis of ACEi and ARB trials with any comparators included 20 trials with 158,998 patients (7 ACEis, n = 76,615 patients; 13 ARBs, n = 82,383 patients)[14] and had a high prevalence of HTN. The trials were contemporary – all published since 2000[14] – and as such, patients had similar co-morbidities, background medications, etc. The average follow up was 4.3 years, initial mean SBP was 153 mmHg, and at least 2/3 of the patients had a diagnosis of HTN. All cause mortality had a robust relative risk reduction of 5% (p = 0.05) in the 20 trials with either ACEis or ARBs. The ACEi and ARB trials were also analyzed each independent of each other — ACEis reduced all cause mortality 10% (p = 0.004), whereas ARBs were neutral (HR: 0.99, p = 0.683). Therefore all the mortality risk reduction in the combined ACEi/ARB meta-analysis was driven by the ACEi trials. The numbers needed to treat with an ACEi to prevent a single all cause mortality was 67 (HR 0.84–0.97) – a number that is clinically impactful – whereas with ARBs it was 335 (p = ns).[31] Although these results could be secondary to greater BP lowering within the ACEi trials as compared to the ARB trials, that does not appear to be so. In the ACEi trials only 19% of the patients had a placebo as the comparator whereas in the ARB trials, 51% of the patients had a placebo comparator — as blood pressure differentials would be greatest in trials with a placebo comparator as compared to another active comparator, BP lowering would have favored mortality reductions in the ARB trials.

This meta-analysis has several limitations that include variation between the studied populations, trial level data rather than individual patient data, and the assumption that there is a class effect amongst the different ACEis and ARBs. That being said, the strength of the evidence in HTN is that ACEi should be the preferred RAAS inhibitor, and not interchangeable with an ARB as is currently recommended in the 2011 UK National Institute for Health and Clinical Excellence (NICE) guideline 127 (www.nice.org.uk/guidance/CG127) and the Canadian Hypertension Education Program (CHEP).[5]

Diabetes mellitus

HTN is a common co-morbidity in DM, with ACEis and ARBs preferred therapies — in part, secondary to their unique nephroprotection.[2] Practice guidelines in diabetes mellitus do not distinguish between ACEis and ARBs[32] but the evidence does not support this conclusion. In a parallel meta-analysis of trials of ACEis and ARBs vs. any comparators (23 trials, n = 32,827; 13 trials, n = 23,867, respectively) in diabetes mellitus, ACEi significantly reduced all-cause mortality by 13% (RR 0.87; 95% CI 0.78–0.98) and MI by 21% (RR 0.79; 95% CI 0.65–0.95), whereas ARBs did not significantly reduce all-cause mortality or MI (RR 0.94; 95% CI 0.82–1.08; RR 0.89; 95% CI 0.74–1.07, respectively) (Table 1).[33] Both ACEis and ARBs were not associated with a decrease in the risk of stroke, suggesting minimal BP reductions in those trials and that the risk reduction with ACEis of MI and death was "independent" of BP lowering.

In trials where the comparator is a placebo,[33] ACEis (11 trials, n = 21,997) reduce all cause mortality 11% (HR 0.89; 95% CI, 0.89–0.99, p = 0.03), whereas ARBs (8 trials, n = 13,304) had no reduction in all cause mortality (HR 1.03; 95% CI 0.89–1.18). Of note, in the largest placebo controlled trial of an ACEi in DM, the ADVANCE[34] (n = 11,140), the combination perindopril–indapamide reduced BP by 5.6/2.2 mmHg over 4.3 years and reduced the risk of all cause mortality by 14% (p = 0.25). In contrast, in the largest ARB trial with a placebo comparator in DM, ROADMAP[35] (n = 4447), olmesartan reduced BP by 3.1/1.9 mmHg over 3.2 years, and resulted in a statistically significant increase in CV mortality (HR 4.94; CI 1.47–17.06, p = 0.01).

Renal disease – either a low eGFR or albuminuria – is a common co-morbidity in DM and an independent predictor for end stage renal disease and CV mortality.[36] ACEis and ARBs provide similar nephroprotection[2,37] and from the renal perspective are no different. However, mortality is 5–10 times more common than the risk of end stage renal disease in high risk patients including DM, with the absolute mortality rate highest in those patients with an estimated glomerular filtration rate < 60 and macroalbuminuria[36] — and as only ACEi reduces mortality and not ARB, the ACEi is preferred.[33]

Although the divergent CV effects of ACEis and ARBs in randomized trials are clear, randomized trials include a highly select patient group and may not reflect the total population at risk. Some would argue that "population-based retrospective cohort" studies are more inclusive, recognize a broader spectrum of patients, reflect "real world therapeutic experience", and therefore are as valid an assessment of therapeutic efficacy as a double blind trial. That assumption does not appear to be correct. For example, in a large population-based retrospective cohort trial of 87,472 DM patients that received either an ACEi or an ARB, it was concluded that ARB use was associated with a reduced risk of hospitalization/mortality relative to ACE inhibition[38] and as such *"endorse the use of ARBs interchangeably with ACE inhibitors"*. This conclusion is not credible as the endpoint was driven by hospitalizations and not mortality, the follow up of less than a year was too short to show the "time-dependent" benefit of the ACEis, mortality events were few, they were unable to adjust for additional potential cofounders, and it was retrospective. Retrospective data bases do provide information on event rates, medication usage, co-morbidities within populations, and contemporary patterns of practice — but as it relates to measuring therapeutic efficacy of non-randomized drugs, it is at best, hypothesis generating and does not refute the evidence from randomized double blind trials.

ACEis and ARBs in HF — placebo controlled trials

The head to head trials of ACEis vs. ARBs in HF have been reviewed – ELITE II,[25] OPTIMAAL,[26] and VALIANT[3] – supporting the conclusion that ACEi is preferred — a conclusion that is

supported in the placebo controlled trials. In the CONSENSUS-1 trial (n = 253, follow up 188 days), patients with severe HF (New York Heart Association/NYHA 4) were randomized to either the ACEi enalapril or a placebo — the 1 year mortality rate was reduced by 31% (36% vs. 52%, p = 0.001),[39] thus began a paradigm shift for the management of HF from a "hemodynamic" to a "neurohormonal" approach. In a meta-analysis of 5 long term trials of ACEi vs. placebo in patients with left ventricular (LV) dysfunction or symptomatic HF and normal BP (n = 12,763, follow up 35 months), ACE-inhibitors had lower rates of death (23.0% *vs.* 26.8%; OR 0.80, 0.74–0.87), re-MI (8.9% *vs.*11.0%; OR 0.79, 0.70–0.89), and readmission for HF (13.7% *vs.* 18.9%; OR 0.67, 0.61–0.74).[40] The benefits were observed early after the start of therapy and persisted long term. In the three of the five trials that were post-MI (SAVE, AIRE and TRACE), mortality was lower with ACEis than with placebo (23.4% *vs.* 29.1%; OR 0.74, 0.66–0.83), as were the rates of readmission for HF (11.9% *vs.* 15.5%; OR 0.73, 0.63–0.85), and re-MI (10.8% *vs.* 13.2%; OR 0.80, 0.69–0.94).

In the Val-Heft trial,[41] (n = 5010, follow up 23 months), the ARB valsartan 160 mg twice daily vs. placebo did not reduce the overall mortality rate (approximately 20% in both arms) but did significantly reduce hospitalizations for HF (18.2% vs. 13.8%, P < 0.001) and also resulted in significant improvements in NYHA class, LV ejection fraction, signs and symptoms of HF, and quality of life (QoL) as compared with placebo (P < 0.01).[41] The benefits of valsartan on QoL were apparent despite 93% of patients on background ACEis.

The CHARM program[42] (n = 7599) consists of 3 parallel placebo controlled ARB trials that compared 32 mg of candesartan in patients with symptomatic HF. Candesartan reduced all-cause mortality (HR 0.91, 95% CI 0.83–1.0, *P* = 0.055), but the benefits apparently all occurred in the first year of treatment. To quote the investigators, "this treatment difference in CV death was most striking in the first year without additional divergence in subsequent years[42]" suggesting an immediate but limited hemodynamic benefit of candesartan, with approximately 40% of patients having concomitant background therapy with an ACEi. It is intriguing to note that the CHARM investigators have also concluded that the mortality rate in the patients who were compliant with placebo were no different than those compliant with candesartan, which leads to the conclusion that in CHARM, it is compliance and not candesartan that reduces mortality.[43]

ACEis and ARBs in vascular disease

There are three large placebo controlled trials of ACEis in high risk patients with essentially normal BP (133/78–139/79 mmHg) that had inclusion criteria of either vascular disease or DM, with no symptoms of HF or LV dysfunction: HOPE,[44] EUROPA,[45] and PEACE.[46] In a meta-analysis of these three trials (n = 29,805, average follow up 4.5 years), ACEis reduced all-cause mortality (7.8 *vs.* 8.9%, p = 0.0004), cardiovascular mortality (4.3 *vs.* 5.2%, p = 0.0002), and non-fatal MI (5.3 *vs.* 6.4%, p = 0.0001), with only small associated reductions in BP (3/1–4/1 mmHg).[47] In the TRANSCEND[48] trial (n = 5926, follow up 56 months), the ARB telmisartan was compared to a placebo in similar at risk patients as in HOPE/EUROPA/PEACE with vascular disease or DM — all patients were previously ACEi intolerant. Telmisartan did not reduce CV death (7.7% vs. 7.5%, P = 0.78) despite SBP reductions favoring telmisartan of 3.2 mmHg[48] and with a CV mortality rate in the placebo arm essentially no different than in the placebo arm of HOPE (7.5% vs. 8.1%).[44] In the PRoFESS trial of post stroke patients (n = 20,232, follow up 30 months), telmisartan as compared to placebo also did not reduce the risk of CV death (13.5% vs. 14.4%, P = 0.11) again despite an SBP reduction in its favor of 3.8 mmHg.[49]

In the most recent AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease[50] their recommendation is as follows: "ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction of ≤40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated (Level of Evidence: A) and reasonable to use ACE inhibitors in all other patients (Level of Evidence: B). The use of ARBs is recommended in patients who have heart failure or who have had a myocardial infarction with left ventricular ejection fraction ≤ 40% and who *are ACE-inhibitor intolerant* (Level of Evidence: A)". At least as it pertains to HF and vascular disease, the guidelines appropriately distinguish the clear superiority of ACEis over ARBs.

ARB trial design

A trial design common amongst the ARB trials is the "Prospective Randomized Open-label Blinded Endpoint (PROBE)" trial — where both patients and physician are aware of their randomized treatment. Open label trials were introduced in 1992 as a potential alternative source of unbiased evidence.[51] The statistical integrity of "open label trials" is based on the premise that all primary analyses are performed using strictly objective end-points, such as death from all causes. Consequently, it has

Table 1 – Parallel meta-analyses of ACEi and ARB trials vs. all comparators in patients with diabetes mellitus.

	ACEis 23 trials N = 32,827 Relative Risk Reduction	ARBs 13 trials N = 23,867 Relative Risk Reduction
All-Cause Mortality	13% 0.87:95% CI 0.78–0.98	NS 0.94:95% CI 0.82–1.08
CV Deaths	17% 0.83:95% CI 0.7–0.99	NS 1.21:95% CI 0.81–1.8
Major CV Events	14% 0.86:95% CI 0.77–0.95	NS 0.94:95% CI 0.85–1.01
Myocardial Infarct	21% 0.79:95% CI 0.65–0.95	NS 0.89:95% CI 0.74–1.07
Heart Failure	19% 0.81:95% CI 0.71–0.93	30% 0.70:95% CI 0.59–0.82
Stroke	NS 0.95:95% CI 0.81–1.04	NS 1.0:95% CI 0.89–1.12

Adapted from Cheng et al. JAMA Intern Med. 2014; 174(5):773–785.

been widely accepted that if PROBE studies are carefully designed and conducted, the results will not be subject to systematic bias despite lack of "double blinding". This potential risk of bias in open label ARB trials was assessed in an all-inclusive ARB meta-analysis of high risk patients (37 trials, n = 147,020 patients), where a sensitivity analysis compared the CV endpoints in the "open label" trials as compared to the "double blind" trials.[9]

Twelve of the 37 ARB trials were "open label" (17,323 of the 147,020 patients) and had small reductions in global death, CV death, and MI that were not significant, but with significant reductions in angina, stroke, HF, and new onset DM ($p < 0.05$ for all) (Fig 4). In contrast, in the 25 "double blind" ARB trials (129,697 of the 147,020 patients) there was no observed reduction in global death, CV death, or MI, with a non-significant increase in angina and a non-significant decrease in CVA, with significant but less pronounced decreases in HF and new onset DM ($p < 0.05$) (Fig 4). The test for interaction was significant for angina, stroke, and heart failure proving that discordance between the "open label" and "double blind" trials exists (Fig 4).

The "open label" ARB trials – although contributing only 12% of the patients to the overall meta-analysis – demonstrated statistically significant benefits, or trends for benefit. In contrast, in the double-blind randomized prospective trials – the true measure of drug efficacy and the accepted "gold-standard" methodology for the unbiased assessment of limitations[52] – the CV benefits completely disappeared or were significantly attenuated. This is strong evidence that "open label" trials have a high risk of bias – even for hard endpoints such as mortality – as stated by the Cochrane group.[53] Rather than contributing to the "Evidence-Base", open label trials contribute to "Evidence-Bias". This apparent bias has multiple explanations: (i) the play of random chance, (ii) differential beneficial effects in ethnic groups recruited into the open as compared to double-blinded trials, (iii) subtle differences in concomitant treatment or investigation as might occur in an open label study or (iv) methodological weaknesses that have permitted differential identification, reporting, validation, or counting of trial end points[54] — with (iii) & (iv) the most probable. As it pertains to the potential for bias in "open label" trials, it is relevant to note that the JIKEI-Heart was retracted as the "data on BP are unreliable"[55] as was the KYOTO as "critical problems existed with some of the data reported in the above paper"[56] — both trials with the ARB valsartan.

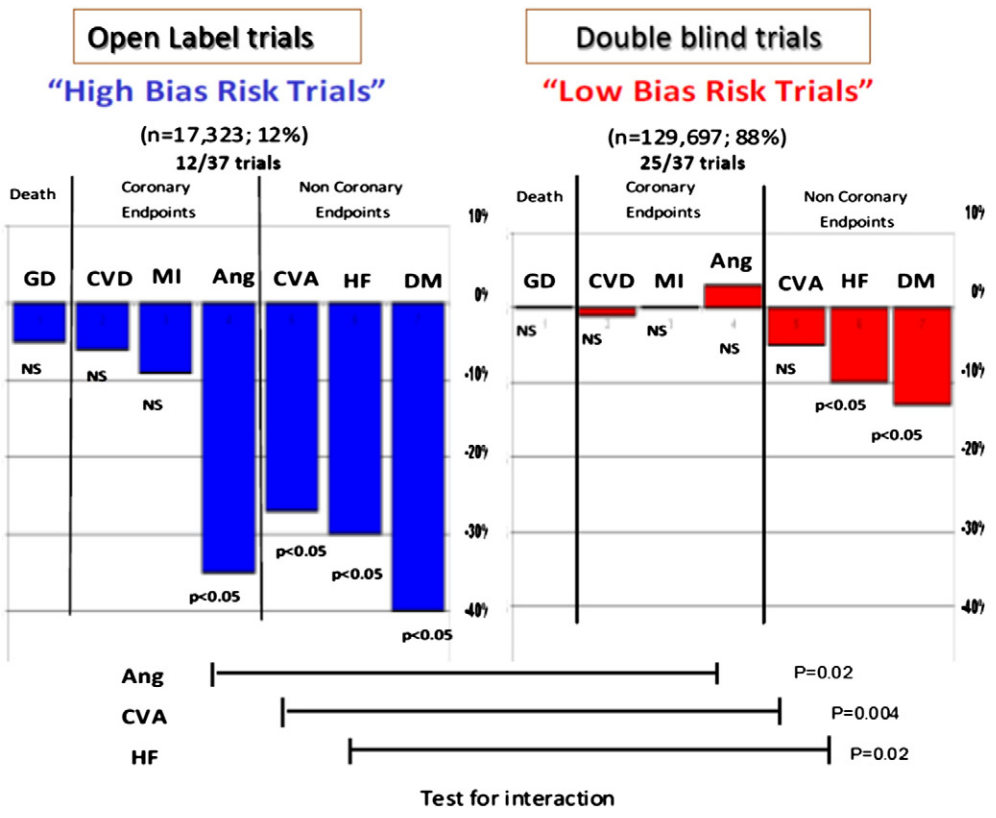

Fig 4 – The relative risk of global death (GD), cardiovascular death (CVD), myocardial infarction (MI), angina (Ang), cerebrovascular accident (CVA), heart failure (HF), & diabetes mellitus (DM) for ARBs vs. all comparators in "High Risk of Bias" trials as compared to "Low risk of Bias" trials (adapted from Bangalore et al. BMJ 2011; 342:d2234.) Open label trials: **Ecost, Ecost R, HIJ-Create, I-Preserve, Jikei, Kondo, Kyoto, Moses, Rass, Road, Suzuki, Takahushi;** Double Blind trials: **Case J, Charm, Elite, Gissi AF, IDNT, Irma-2, Life, Navigator, Ontarget, Optimal, Profess, Renaal, Scope, Transcend, Val-Heft, Valiant, Value.**

Conclusion

The parallel meta-analyses of ACEi and ARB trials vs. placebo or other active comparator, and the meta-regression analyses that adjust for BP within the trials, clearly and consistently demonstrate that ACEis reduce the risk of MI and death above and "independent" of BP lowering, whereas ARBs do not — the so called "ARB MI Paradox". This is a consistent finding amongst the different high risk populations: HTN, DM, those with vascular disease, and HF. This truth has been obscured by the open label trials with their high risk of bias, trials for statistical "non-inferiority" being misinterpreted as "equivalence" trials, and "population-based retrospective cohort" trials being touted as "real life experience" that can refute the findings in double blind prospective randomized trials.

If practice guidelines were to recognize the unique CV protective effects of ACEis as the preferred RAAS inhibitor over ARBs, the gain in "lives saved" would indeed be profound. In 1776 on the topic of "Common Sense" Thomas Paine stated that:

> " . . . *(A) long habit of not thinking a thing wrong, gives it a superficial appearance of being right, and raises at first a formidable outcry in defense of custom. But the tumult soon subsides. Time makes more converts than reason.*"

Perhaps that time has finally arrived!

Statement of conflict of interest

There is no conflict of interest.

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