Assessing the risk of angiotensin receptor blockers on major cardiovascular events: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Angiotensin receptor blockers (ARBs) are commonly used as a treatment for many cardiovascular diseases, but their safety has been called into question. The VALUE trial found an increased risk of myocardial infarction in participants receiving ARBs compared to other antihypertensive. The aim of the meta-analysis was to synthesize the available evidence of randomised controlled trials (RCTs) and elucidate if ARBs increase the risk of cardiovascular events.

Methods: A comprehensive search was conducted to identify RCTs that assessed the safety of ARBs. Titles and abstracts of all papers were independently screened by two authors. Data extraction and quality assessment were also performed independently. The relative risk (RR) of all-cause mortality, myocardial infarction, and stroke were pooled using the IVhet model. Multiple sensitivity analyses were conducted to assess the effect of ARBs by restricting the analysis to different participants’ characteristics.

Results: Forty-five RCTs comprising of 170,794 participants were included in the analysis. The pooled estimates revealed that ARBs do not increase the risk of all-cause mortality (RR 1.00; 95%CI 0.97–1.04), myocardial infarction (RR 1.01; 95%CI 0.96–1.06), and stroke (RR 0.92; 95%CI 0.83–1.01). The sensitivity analysis did not yield a particular group of patients at increased risk of cardiovascular events with ARBs. Risk of all-cause mortality and stroke decreased with ARB when the proportion of smokers in a population was < 25% (RR 0.91; 95%CI 0.84–0.98) and in females (RR 0.76; 95%CI 0.68–0.84), respectively.

Conclusions: ARBs do not increase the risk of major cardiovascular events and are safe for use in patients.

Keywords: Cardiovascular events, Angiotensin receptor blockers, Meta-analysis, Risk
Background
Cardiovascular diseases (CVDs) remain one of the most prevalent non-communicable diseases and impose a great burden on the healthcare systems. Globally, an estimated 16.7 million deaths in the year 2010 were attributed to CVD with projections showing a staggering 23.3 million deaths by 2030 [1]. Hypertension is the leading risk factor for CVD and it is associated with 57 million disability adjusted life years (DALYs) worldwide [2].

It is well known that the risk of major cardiovascular events can be reduced by a wide spectrum of antihypertensive drugs including angiotensin receptor blockers (ARBs) [3]. This type of drug works by inhibiting the angiotensin II receptors, thus causing systemic vasodilatation, thereby aiding in the reduction of blood pressure [4]. ARBs are one of the most common drugs used for controlling blood pressure, treating heart failure, and preventing kidney failure in people with diabetes or hypertension [5]. However, the safety of ARBs in comparison to other anti-hypertensive medications has been called into question.

The VALUE trial found that ARBs (valsartan) increased the risk of myocardial infarction (fatal and non-fatal) by 19% compared with calcium channel blockers (amlodipine) [6]. This observation led many researchers to examine cautiously the evidence surrounding ARBs and myocardial infarction. For example, the point estimate of the CHARM-alternative trial suggests a 36% increase in myocardial infarction with candesartan (versus placebo) regardless of the reduction in blood pressure [7]. On the other hand, the TRANSCEND trial found an 8% decrease in risk of cardiovascular admissions for those on telmisartan compared to placebo [8].

Angiotensin-converting-enzyme (ACE) inhibitors are known to have a cardioprotective effect and the safety profile of ACE inhibitors have been shown not to differ from ARBs [9]. Hence it was unclear the mechanism that could explain an increase in risk of myocardial infarction with ARBs. Due to the wide use of ARBs for many CVDs and the contradictory results, we decided to conduct a systematic review and meta-analysis of randomised controlled trials (RCTs) to elucidate the cardiovascular safety profile of ARBs.

Methods
Findings of this systematic review and meta-analysis are presented according to PRISMA reporting guidelines [10].

Search strategy and selection criteria
A systematic search was conducted in PubMed in September 2018. The following search terms were included: randomized controlled trial, angiotensin receptor antagonist, cardiovascular disease, and mortality. The full search strategy is shown in the supplementary material (S1). To achieve a comprehensive evaluation of the published evidence, the systematic search was supplemented with a similarity search (i.e. the first 20 related citations of each included paper) as well as hand search of the reference lists of relevant studies. Titles and abstracts were uploaded on Rayyan (http://rayyan.qcri.org/) [11] for the screening process. Two authors (YW and RB) independently screened all the records by title and abstract. Disagreements were resolved through author consensus and involvement of a third author (LFK).

![Fig. 1 PRISMA flow diagram of study selection](image-url)
| Trial name, year publication | Population | Setting | Intervention | Control | Follow up (in months) | Male (%) | Mean / median age (years) | Mean BMI (kg/m²) | Mean cholesterol (mg/dL) |
|------------------------------|------------|---------|--------------|---------|----------------------|----------|--------------------------|-----------------|-------------------------|
| 4C (2016) [16]               | Patients with IHD after coronary stent implantation | 39 centres in Japan | Candesartan | Standard care without ARB | 36 | 73 | 69 | 24 | NR |
| ACTIVE I (2011) [17]         | Patients with atrial fibrillation | 600 centres worldwide | Irbesartan | Placebo | 54 | 61 | 70 | 29 | NR |
| CARP (2011) [18]             | Patients that received a coronary stent | 5 centres in Hiroshima, Japan | Valsartan | Non-ARB therapy | 48 | 79 | 65 | 24 | NR |
| CASE-J (2008) [19]           | Patients with high-risk hypertension | 527 physicians from Japan | Candesartan | Amlodipine | 41 | 55 | 64 | 25 | NR |
| CHARM-Added (2003) [20]      | Patients with CHF and LVEF< 40 | 618 centres in 26 countries | Candesartan | Placebo | 41 | 79 | 64 | 28 | NR |
| CHARM-Alternative (2003) [7]  | Patients with symptomatic CHF and LVEF< 40% | 618 centres in 26 countries | Candesartan | Placebo | 34 | 68 | 67 | 28 | NR |
| CHARM-Preserved (2003) [21]  | Patients with HF and LVEF> 40 | 618 centres in 26 countries | Candesartan | Placebo | 37 | 60 | 67 | 29 | NR |
| Cice et al. (2010) [22]      | Patients with CHF and in haemodialysis | 30 clinics in Italy | Telmisartan | Placebo | 36 | 90 | 63 | NR | NR |
| DETAIL (2004) [23]           | Patients with diabetes mellitus and nephropathy | 39 centres in northern Europe | Telmisartan | Enalapril | 60 | 73 | 61 | 31 | 223 |
| DIRECT-Prevent 1 (2008) [15] | Patients with type 1 diabetes a no retinopathy | 309 centres worldwide | Candesartan | Placebo | 56 | 56 | 30 | 24 | 184 |
| DIRECT-Protect 1 (2008) [15] | Patients with type 1 diabetes and retinopathy | 309 centres worldwide | Candesartan | Placebo | 56 | 57 | 32 | 25 | 186 |
| DIRECT-Protect 2 (2008) [24] | Patients with type 2 diabetes and retinopathy | 309 centres worldwide | Candesartan | Placebo | 56 | 50 | 57 | 29 | 205 |
| E-COST (2005) [25]           | Patients with hypertension | Centres in Saitama, Japan | Candesartan | Non-ARB therapy | 37 | 48 | NR | NR | NR |
| E-COST-R (2005) [26]         | Patients with hypertension and mild renal impairment | Centres in Saitama, Japan | Candesartan | Non-ARB therapy | 37 | 59 | 67 | NR | 181 |
| ELITE (1997) [27]            | Patients with CHF and LVEF< 40% | 125 centres in the USA, Europe, and South America | Losartan | Captopril | 13 | 67 | 74 | NR | NR |
| ELITE II (2000) [28]         | Patients with CHF and LVEF< 40% | 289 centres in 46 countries | Losartan | Captopril | 23 | 69 | 71 | NR | NR |
| GISSI-AF (2009) [29]         | Patients with history of atrial fibrillation | 100 centres in Italy | Valsartan | Placebo | 12 | 62 | 68 | 28 | NR |
| HU-CREATE (2009) [30]        | Patients with coronary artery disease and hypertension | 14 centres in Japan | Candesartan | Non-ARB therapy | 50 | 80 | 66 | 25 | 193 |
| Trial name and year publication | Population | Setting | Intervention | Control | Follow up (in months) | Male (%) | Mean / median age (years) | Mean BMI (kg/m²) | Mean cholesterol (mg/dL) |
|--------------------------------|------------|---------|--------------|---------|-----------------------|----------|--------------------------|-----------------|------------------------|
| HOPE-3 (2016) [31]            | Patients with intermediate cardiovascular risk | 228 centres in 21 countries | Candesartan + hydrochlorothiazide | Placebo | 67 | 54 | 66 | 27 | 201 |
| IDNT (2003) [32]              | Patients with diabetes mellitus and nephropathy | Centres in the North America, Europe, Latin America, South East Asia, and Oceania | Irbesartan | Amlodipine or placebo | 31 | 64 | 59 | 31 | NR |
| I-PRESERVE (2008) [33]        | Patients with CHF and LVEF > 45% | Centres in 25 countries | Irbesartan | Placebo | 50 | 40 | 72 | 30 | NR |
| IRMA-2 (2001) [34]            | Patients with hypertension, diabetes mellitus, and micro-albuminuria | 96 centres worldwide | Irbesartan | Placebo | 24 | 69 | 58 | 30 | 224 |
| J-RHYTHM II (2011) [35]       | Patients with hypertension and atrial fibrillation | 48 centres in Japan | Candesartan | Amlodipine | 12 | 69 | 66 | NR | NR |
| Kondo et al. (2003) [36]      | Patients with history of coronary intervention | Ogaki Municipal Hospital in Japan | Standard care + Candesartan | Standard care without candesartan | 24 | 76 | 65 | 24 | 187 |
| KYOTO HEART (2009) [37]       | Patients with uncontrolled hypertension | 31 centres from Kyoto, Japan | Valsartan | Non-ARB therapy | 39 | 57 | 66 | 39 | NR |
| LIFE (2002) [38]              | Patients with hypertension and left ventricular hypertrophy | 830 centres from the USA, the UK, and Scandinavia | Losartan | Atenolol | 58 | 46 | 67 | 28 | 232 |
| MOSES (2005) [39]             | High-risk hypertensive patients | Centres in Germany and Austria | Eprosartan | Nitredipine | 45 | 54 | 68 | 28 | NR |
| NAVIGATOR (2010) [40]         | Patients with impaired glucose tolerance | 806 centres in 40 countries | Valsartan | Placebo | 60 | 49 | 64 | 31 | 210 |
| OCTOPUS (2013) [41]           | Patients with hypertension and in haemodialysis | 66 dialysis centres in Okinawa, Japan | Olmesartan | Non-ARB therapy | 60 | 62 | 60 | 24 | 155 |
| ONTARGET (2006) [42]          | Patients with coronary, peripheral, cerebrovascular disease or diabetes with end-organ damage | 733 centres in 40 countries | Telmisartan | Ramipril or ramipril + telmisartan | 56 | 77 | 66 | 28 | 190 |
| OPTIMAAL (2002) [43]          | Patients with acute myocardial infarction and heart failure | 329 centres in 7 European countries | Losartan | Captopril | 35 | 69 | 67 | 27 | 212 |
| ORIENT (2011) [44]            | Patients with diabetes mellitus with proteinuria | Centres in Japan and Hong Kong | Olmesartan | Placebo | 38 | 69 | 59 | 25 | 208 |
| PrOFESSIONAL (2008) [45]      | Patients with a recent ischaemic stroke | 695 centres in 35 countries | Telmisartan | Placebo | 30 | 64 | 66 | 27 | NR |
| RENAAL (2001) [46]            | Patients with diabetes and nephropathy | 250 centres in 28 countries | Losartan | Placebo | 41 | 63 | 60 | 30 | 228 |
| ROAD (2007) [47]              | Patients with proteinuria and chronic renal insufficiency | Nanfang Hospital Renal Division in China | Losartan | Benazepril | 44 | 63 | 50 | 23 | 97 |
| SCAST (2011)                  | Patients with acute stroke | 146 centres in Europe | Candesartan | Placebo | 6 | 58 | 71 | NR | NR |
Table 1 Characteristics of the RCTs included in the meta-analysis (Continued)

| Trial name, year publication | Population | Setting | Intervention | Control | Follow up (in months) | Male (%) | Mean / median age (years) | Mean BMI (kg/m²) | Mean cholesterol (mg/dL) |
|-----------------------------|------------|---------|--------------|---------|-----------------------|----------|--------------------------|-----------------|--------------------------|
| [48] SCOPE (2003) [49]       | Patients with mild to moderate elevated blood pressure | 527 centres in Europe | Candesartan | Placebo | 45 | 36 | 76 | 27 | 239 |
| SUPPORT (2015) [50]         | Patients with hypertension and CHF | 17 centres in Tohoku, Japan | Olmesartan | Non-ARB therapy | 53 | 75 | 66 | 25 | NR |
| Suzuki et al. (2008) [51]   | Patients with kidney failure treated with haemodialysis | 5 dialysis centres in Saitama, Japan | Losartan, candesartan, or valsartan | Non-ARB therapy | 36 | 59 | 60 | 21 | 157 |
| Takahashi et al. (2006) [52] | Patients with kidney failure treated with haemodialysis | Enshu General Hospital in Japan | Candesartan | Nothing | 19 | 58 | 61 | 20 | NR |
| TRANSCEND (2008) [53]       | Patients with coronary, peripheral, cerebrovascular disease or diabetes with end-organ damage, and intolerant to ACE inhibitors | 630 centres in 40 countries | Telmisartan | Placebo | 56 | 57 | 67 | 28 | 197 |
| T-VENTURE (2009) [54]       | Patients with acute myocardial infarction | 4 centres in Japan | Valsartan | ACE inhibitor therapy | 6 | 83 | 63 | NR | NR |
| Val-HeFT (2001) [55]        | Patients with heart failure | 302 centres in 16 countries | Valsartan | Placebo | 23 | 80 | 63 | NR | NR |
| VALIANT (2003) [56]         | Patients with recent myocardial infarction and LVEF < 35% | 931 centres in 24 countries | Valsartan | Captopril | 25 | 78 | 65 | 27 | NR |
| VALUE (2004) [6]            | Patients with hypertension and high risk of cardiac event | Centres in 31 countries | Valsartan | Amlodipine | 50 | 58 | 67 | 29 | NR |

ACE Angiotensin-converting enzyme, ARB Angiotensin II receptor blockers, CHF Congestive heart failure, IHD Ischaemic heart disease, LVEF Left-ventricular ejection fraction, NR Not reported

aIDNT (2003): Two control groups, placebo group was excluded
bIRMA-2 (2001): Two intervention groups, irbesartan 150 mg daily and irbesartan 300 mg daily were combined
cONTARGET (2008): Three intervention groups, ramipril + telmisartan group was excluded
dVALIANT (2003) Three intervention groups, valsartan + captopril group was excluded
| Trial name, year publication | Mean LDL (mg/dL) | Mean HDL (mg/dL) | Mean triglyceride (mg/dL) | Non-smoker (%) | Hypertension (%) | Heart failure (%) | Diabetes mellitus (%) | Ischaemic / coronary artery disease (%) | Chronic kidney disease (%) |
|-----------------------------|-----------------|-----------------|--------------------------|----------------|-----------------|-------------------|-----------------------|----------------------------------------|--------------------------|
| CASE-J (2008) [19]          | NR              | NR              | NR                       | 79             | 100             | 0                 | 43                    | 43                       | 24                       |
| CHARM-Added (2003) [20]     | NR              | NR              | NR                       | 83             | 48              | 100               | 30                    | 68                       | NR                       |
| CHARM-Alternative (2003) [7] | NR              | NR              | NR                       | 86             | 50              | 100               | 27                    | 62                       | NR                       |
| CHARM-Preserved (2003) [21]  | NR              | NR              | NR                       | 87             | 64              | 100               | 28                    | 56                       | NR                       |
| Cice et al. (2010) [22]     | NR              | NR              | NR                       | 86             | 50              | 100               | 27                    | 62                       | NR                       |
| DETAIL (2004) [23]          | 137             | 48              | 207                      | 37             | 100             | 0                 | 100                   | NR                      | 100                      |
| DIRECT-Prevent 1 (2008) [15]| NR              | 66              | NR                       | 74             | NR              | NR                | 100                   | NR                      | 0                        |
| DIRECT-Protect 1 (2008) [15]| NR              | 66              | NR                       | 74             | NR              | NR                | 100                   | NR                      | 0                        |
| DIRECT-Protect 2 (2008) [24]| NR              | NR              | NR                       | 73             | 62              | NR                | 100                   | 5                       | 0                        |
| E-COST (2005) [25]          | NR              | NR              | NR                       | 86             | 50              | 100               | 27                    | 62                       | NR                       |
| E-COST-R (2005) [26]        | NR              | NR              | NR                       | 86             | 50              | 100               | 27                    | 62                       | NR                       |
| ELITE (1997) [27]           | NR              | NR              | NR                       | 88             | 57              | 100               | 25                    | 50                       | 7                        |
| ELITE II (2000) [28]        | NR              | NR              | NR                       | 88             | 57              | 100               | 25                    | 50                       | 7                        |
| GISSI-AF (2009) [29]        | NR              | NR              | NR                       | 81             | 57              | NR                | 100                   | NR                      | 7                        |
| HIJ-CREATE (2009) [30]      | 45              | 128             | 64                       | 100            | 21              | 38                | 100                   | NR                      | 0                        |
| HOPE-3 (2016) [31]          | 128             | 128             | 72                       | 38             | 0               | 5.8               | 0                     | 0                       | NR                       |
| IDNT (2003) [32]            | NR              | NR              | NR                       | 100            | 0               | 0                 | 0                     | NR                      | 0                        |
| I-PRESERVE (2008) [33]      | NR              | NR              | NR                       | 89             | 28              | 28                | 0                     | 0                       | 0                        |
| IRMA-2 (2001) [34]          | 44              | 180             | 81                       | 100            | 21              | 100               | 6                     | 0                       | 0                        |
| J-RHYTHM II (2011) [35]     | NR              | NR              | NR                       | 100            | 21              | 100               | 6                     | 0                       | 0                        |
| Kondo et al. (2003) [36]    | 49              | 126             | 76                       | 44             | 2               | 100               | 21                    | NR                      | 0                        |
| KYOTO HEART (2009) [37]     | 122             | 55              | 149                      | 78             | 100             | 7                 | 27                    | 23                       | NR                       |
| LIFE (2002) [38]            | NR              | NR              | NR                       | 84             | 100             | 0                 | 13                    | 16                       | NR                       |
| MOSES (2005) [39]           | NR              | NR              | NR                       | 100            | 26              | 37                | 26                    | 5.4                      | NR                       |
| NAVIGATOR (2010) [40]       | 50              | 151             | 89                       | 78             | NR              | 49                | 12                    | 11                       | NR                       |
| OCTOPUS (2013) [41]         | NR              | 155             | 65                       | 100            | NR              | 32                | 7                     | 100                      | NR                       |
| ONTARGET (2008) [42]        | 112             | 50              | 151                      | 36             | 69              | 0                 | 37                    | 75                       | NR                       |
| Trial name, year publication | Mean LDL (mg/dL) | Mean HDL (mg/dL) | Mean triglyceride (mg/dL) | Non-smoker (%) | Hypertension (%) | Heart failure (%) | Diabetes mellitus (%) | Ischaemic / coronary artery disease (%) | Chronic kidney disease (%) |
|-----------------------------|------------------|-----------------|--------------------------|----------------|-----------------|-------------------|-----------------------|-------------------------------------|------------------------|
| OPTIMAAL (2002) [43]        | 130              | 45              | 168                      | NR             | 36              | 6                 | 17                    | 100                                | NR                     |
| ORIENT (2011) [44]          | NR               | NR              | NR                       | NR             | NR              | NR                | NR                    | NR                                 | NR                     |
| ProfESS (2008) [45]         | NR               | NR              | NR                       | NR             | 75              | 100               | 4                     | 100                                | 5                      |
| RENAAL (2001) [46]          | 142              | 45              | 219                      | 82             | 93              | 0                 | 100                   | NR                                 | 11                     |
| ROAD (2007) [47]            | NR               | NR              | NR                       | NR             | 77              | 63                | 0                     | 0                                  | 100                    |
| SCAST (2011) [48]           | NR               | NR              | NR                       | NR             | NR              | NR                | NR                    | NR                                 | NR                     |
| SCOPE (2003) [49]           | NR               | NR              | NR                       | NR             | NR              | NR                | NR                    | NR                                 | NR                     |
| SUPPORT (2019) [50]         | 108              | NR              | NR                       | NR             | NR              | 100               | 100                   | 50                                 | 47                     |
| Suzuki et al. (2008) [51]   | NR               | NR              | NR                       | 78             | 93              | 16                | 52                    | 2                                  | 100                    |
| Takahashi et al. (2006) [52]| NR               | NR              | NR                       | NR             | 81              | 0                 | 33                    | 0                                  | 100                    |
| TRANSCEND (2008) [53]       | 117              | 49              | 158                      | 47             | 76              | 0                 | 36                    | 74                                 | NR                     |
| T-VENTURE (2009) [54]       | NR               | NR              | NR                       | 40             | 57              | 0                 | 34                    | 100                                | NR                     |
| Val-HeFT (2001) [55]        | NR               | NR              | NR                       | NR             | NR              | 100               | 25                    | 57                                 | NR                     |
| VALIANT (2003) [56]         | NR               | NR              | NR                       | NR             | NR              | 56                | 15                    | 23                                 | 100                    |
| VALUE (2004) [57]           | NR               | NR              | NR                       | NR             | 93              | 6                 | NR                    | 45                                 | NR                     |
The inclusion of studies was restricted to human studies; RCTs comparing ARBs versus a control (either a placebo or another antihypertensive medication); follow-up of at least 12 months; and reported all-cause mortality, myocardial infarction, and stroke as outcomes. Recurrent myocardial infarction and stroke were also considered if the study only included patients that have had recently experienced myocardial infarction or stroke. Observational studies, studies where ARBs were not the first line of treatment, and conference abstracts were excluded.

Data extraction and quality assessment
The number of participants and the number events (i.e., all-cause mortality, myocardial infarction, and stroke) in each intervention group (ARBs [active] and non-ARBs [control]) were extracted. In addition, study characteristics (e.g., study sites and follow-up period) and participants’ characteristics (e.g., mean age, proportion of males, mean BMI) were extracted. The Cochrane Collaboration’s tool for assessing risk of bias in randomized trials [12] was used to assess the risk of bias of the included studies.

Statistical analysis
The outcomes of interest were the relative risks (RRs) of all-cause mortality, myocardial infarction, and stroke with ARBs compared to the control group. The inverse variance heterogeneity (IVhet) model was used to pool the effect size [13]. The $I^2$ index was used to assess heterogeneity among studies, an $I^2 > 50\%$ was considered significant heterogeneity.

Sensitivity analyses were conducted to identify potential scenarios where ARBs increase the risk of all-cause mortality, myocardial infarction, and stroke. The following analyses restricting the meta-analysis to: control group (active medication, only ACE inhibitors, or placebo); follow-up period ($\leq$40 weeks or > 40 weeks); proportion of males ($\leq$50% or > 50%); age ($\leq$65 years or > 65 years); BMI (normal range or overweight/obese); elevated total cholesterol ($\geq$200 mg/dL); elevated LDL ($\geq$120 mg/dL); decreased HDL (< 50 mg/dL); elevated tri-glyceride ($\geq$150 mg/dL); proportion of smokers ($\geq$25%); only patients with hypertension; only patients with or without chronic heart failure; only patients with or without diabetes mellitus; only patients with ischaemic/coronary artery disease; and only patients with chronic kidney disease.

Publication bias was assessed through visual inspection of funnel and Doi plots and statistically through the Egger’s regression $p$-value and the LFK index [14]. All the analyses were conducted in Stata MP 14 (StataCorp, College Station, TX, USA).

Result
Study selection and study characteristics
One thousand seven hundred and eighty-six unique records were identified through the search strategy and the similarity search. Four hundred and seventy-four records remained after the title and abstract screening and 44 publications remained after the full-text screening.

![Fig. 2 Forest plot depicting the relative risk of ARBs on a) all-cause mortality, b) myocardial infarction, and c) stroke](image-url)
### Table 2: Sensitivity analyses

|                                | All-cause mortality | Myocardial infarction | Stroke |
|--------------------------------|---------------------|-----------------------|--------|
|                                | RR (95%CI)          | I² N                  | RR (95%CI) | I² N | RR (95%CI) | I² N |
| Type of control                |                     |                       |         |       |           |      |
| Placebo                        | 0.99 (0.95–1.04)    | 13 18                 | 0.96 (0.88–1.10) | 0 14 | **0.91 (0.85–0.98)** | 7 14 |
| Active                         | 1.01 (0.95–1.08)    | 28 21                 | 1.03 (0.96–1.11) | 7 23 | 0.93 (0.79–1.08) | 54 22 |
| Active only ACE inhibitors     | 1.04 (0.95–1.13)    | 46 8                  | 1.01 (0.93–1.09) | 0 9  | 0.98 (0.88–1.10) | 0 8 |
| Follow-up period               |                     |                       |         |       |           |      |
| ≤ 40 weeks                     | 1.01 (0.91–1.14)    | 51 19                 | 0.98 (0.88–1.10) | 12 18 | 0.94 (0.74–1.20) | 40 18 |
| > 40 weeks                     | 1.00 (0.96–1.03)    | 0 20                  | 1.03 (0.96–1.10) | 0 19 | 0.90 (0.82–1.00) | 45 18 |
| Proportion of males            |                     |                       |         |       |           |      |
| ≤ 50%                          | 0.93 (0.86–1.00)    | 0 6                   | 1.02 (0.85–1.22) | 37 5 | **0.76 (0.68–0.84)** | 0 5 |
| > 50%                          | 1.02 (0.97–1.06)    | 23 33                 | 1.01 (0.95–1.07) | 0 32 | 0.96 (0.87–1.05) | 28 31 |
| Age                            |                     |                       |         |       |           |      |
| ≤ 65 years                     | 0.98 (0.88–1.09)    | 32 18                 | 0.95 (0.85–1.06) | 0 15 | 1.03 (0.80–1.34) | 22 12 |
| > 65 years                     | 1.01 (0.98–1.05)    | 10 20                 | 1.04 (0.98–1.10) | 0 21 | 0.92 (0.84–1.00) | 41 23 |
| BMI                            |                     |                       |         |       |           |      |
| Normal range                   | 0.84 (0.60–1.19)    | 31 7                  | 0.81 (0.41–1.57) | 0 6  | 1.21 (0.77–1.90) | 0 5 |
| Overweight and obese           | 1.01 (0.98–1.04)    | 0 24                  | 1.01 (0.96–1.07) | 5 24 | 0.92 (0.83–1.01) | 49 23 |
| Elevated total cholesterol     |                     |                       |         |       |           |      |
| ≥ 200 mg/dL                    | 0.98 (0.91–1.05)    | 15 10                 | 0.99 (0.91–1.08) | 0 8  | **0.82 (0.74–0.91)** | 6 7 |
| Elevated LDL                   | 1.01 (0.90–1.14)    | 36 7                  | 0.97 (0.87–1.07) | 0 6  | 0.86 (0.70–1.07) | 45 5 |
| Decreased HDL                  | 1.01 (0.95–1.08)    | 15 11                 | 0.99 (0.89–1.09) | 20 10 | **0.90 (0.82–0.98)** | 0 8 |
| Elevated triglyceride          | 1.01 (0.94–1.08)    | 13 8                  | 0.99 (0.90–1.09) | 16 8 | 0.92 (0.83–1.01) | 0 7 |
| Proportion of smokers          |                     |                       |         |       |           |      |
| < 25%                          | **0.91 (0.84–0.98)** | 2 12               | 0.99 (0.88–1.11) | 0 13 | 0.81 (0.67–0.99) | 41 12 |
| ≥ 25%                          | 0.99 (0.95–1.05)    | 7 15                  | 0.99 (0.91–1.01) | 0 12 | 0.92 (0.87–0.98) | 0 12 |
| Hypertension                   |                     |                       |         |       |           |      |
| Only patients with hypertension| 0.98 (0.89–1.07)    | 0 12                  | 1.02 (0.80–1.29) | 27 12 | 0.82 (0.66–1.03) | 57 13 |
| Chronic heart failure (CHF)    |                     |                       |         |       |           |      |
| Only patients without CHF      | 0.97 (0.92–1.03)    | 0 11                  | 0.99 (0.83–1.18) | 43 12 | 0.85 (0.73–1.00) | 47 11 |
| Only patients with CHF         | 1.00 (0.85–1.19)    | 75 6                  | 1.06 (0.86–1.32) | 0 8  | 1.04 (0.81–1.32) | 14 8 |
| Diabetes mellitus (DM)         |                     |                       |         |       |           |      |
| Only patients without DM       | 0.99 (0.38–2.61)    | 0 2                   | 0.65 (0.26–1.59) | 48 3  | 0.72 (0.50–1.04) | 37 3 |
| Only patients with DM          | 1.04 (0.88–1.23)    | 0 7                   | 0.99 (0.53–1.80) | 67 4  | 1.31 (0.73–2.35) | 30 3 |
| Ischemic/coronary artery disease |                   |                       |         |       |           |      |
| Only patients with ischemic/coronary artery disease | 1.06 (0.91–1.22) | 25 7                  | 0.97 (0.88–1.07) | 0 7  | 1.02 (0.84–1.24) | 0 5 |
| Chronic kidney disease         |                     |                       |         |       |           |      |
| Only patients with chronic kidney disease | 0.86 (0.66–1.12) | 50 8                  | 0.99 (0.71–1.41) | 20 9  | 1.08 (0.83–1.39) | 0 8 |

CI confidence interval; N number of studies; RR relative risk; ACE angiotensin-converting-enzyme
Statistically significant results are emboldened
The 44 publications reported data from 45 RCTs and 170,794 participants (85,544 participants in the ARB group and 85,250 participants in the placebo/control group) (Fig. 1). The publication by Chaturvedi et al. [15] reported findings from two RCTs, the DIRECT-Prevent 1 and DIRECT-Protect 1 studies.

Twenty-four RCTs compared ARBs versus placebo, while 21 RCTs against an active medication. The majority of RCTs (n = 39) included a larger proportion of males (ranging from 54 to 90%). Only two RCTs, DIRECT-Prevent 1 and DIRECT-Protect 1 enrolled participants with a median age < 50 years. Among the studies that reported the median BMI, only 22% had participants with a normal BMI (< 25 kg/m²). Fourteen, nine, and eight RCTs included only patients with hypertension, chronic heart failure, and diabetes mellitus, respectively (Table 1). All-cause mortality, myocardial infarction, and stroke were assessed in 39, 37, and 36 RCTs.

Quantitative synthesis

After pooling all the available evidence, it was found that ARBs do not increase the risk of all-cause mortality (RR 1.00; 95% CI 0.97–1.04), myocardial infarction (RR 1.01; 95% CI 0.96–1.06), or stroke (RR 0.92; 95% CI 0.83–1.01) (Fig. 2). Sensitivity analyses based on different study and participants characteristics showed no increase in risk of any of the three outcomes of interest. However, it was also noticed that ARBs did not reduce the risk of all-cause mortality (RR 0.99; 95% CI 0.95–1.04) or myocardial infarction (RR 0.96; 95% CI 0.88–1.05) when compared to placebo, ARBs only decreased the risk of stroke (RR 0.91; 95% CI 0.85–0.98) (Table 2). Sensitivity analyses also revealed a decreased in all-cause mortality risk with ARBs when the proportion of smokers is small (< 25%) (RR 0.91; 95% CI 0.84–0.98); and stroke in females (RR 0.76; 95% CI 0.68–0.84), patients with elevated total cholesterol (RR 0.82; 95% CI 0.82–0.91) and lower levels of HDL (RR 0.90; 95% CI 0.80–0.98) (Table 2).

The most common deficiencies were no blinding of participants and personnel (n = 14; 31%), followed by no blinding of the outcome assessor (n = 10; 22%) and incomplete outcome data (n = 10; 22%). Overall, the RCTs showed low risk of bias except for E-COST [25], E-COST-R [26], and Kondo et al. [36] (S2).

The Doi plots revealed minor asymmetry for all-cause mortality (LFK index = −1.24) and myocardial infarction (LFK index = −1.33) for RCTs reporting favourable results for ARBs. No asymmetry was observed for stroke (supplementary material S3).

Discussion

Findings from previous RCTs were controversial, the VALUE [6] and the CHARM-alternative [7] trials found increase in myocardial infarction with ARBs compared to amlodipine and placebo, respectively. While other large RCTs such as the LIFE [38] and the RENAAL [46] trials found a decrease in all-cause of death and myocardial infarction with ARBs. In 2011, Bangalore et al. [57] conducted a meta-analysis on ARBs and the risk of myocardial infarction and found that ARBs do not increase the risk of cardiovascular events. Since then, multiple RCTs have been published; in our meta-analysis we pooled the most updated evidence (45 RCTs comprising of 170,794 participants – 8 RCTs and 23,000 more participants that Bangalore et al.) and corroborated that ARBs are safe medications as they do not increase the risk of all-cause mortality, myocardial infarction, or stroke. It is worth pointing out that our meta-analysis (in line with previous studies [57, 58]) also found that ARBs do not reduce the risk of all-cause mortality and myocardial infarction when compared to placebo.

In addition, the safety profile of ARBs was examined in multiple scenarios by restricting the analysis to different study and participants characteristics (i.e. sensitivity analyses). In none of the cases, ARBs were found to increase the risk of all-cause mortality, myocardial infarction, and stroke. ARBs reduce the risk of all-cause mortality by 9% in populations with low prevalence of smokers and exerts a cerebrovascular protective effect in female patients and patients with abnormal total cholesterol or HDL.

Findings from our study are reassuring for patients and clinicians as ARBs are widely used to treat conditions such as hypertension, chronic kidney disease/kidney failure (especially in patients with diabetes mellitus), and heart failure. However, the findings need to be understood in light of some of the limitations. Only RCTs were included, but the possibility of confounding not accounted during the analysis of the RCTs cannot be completely ruled out. There was heterogeneity in the RCTs protocols (e.g. inclusion criteria, different ARBs, different doses, follow-up) that needs to be accounted in future research synthesis studies through individual patients meta-analysis.

Conclusion

In conclusion, our meta-analysis provides reassuring evidence for patients and clinicians that ARBs are safe drugs, and do not increase the risk of death, myocardial infarction, and stroke.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12872-020-01466-5.

Additional file 1: S1. Search strategy. S2. Risk of bias of the included studies S3. Doi (top) and funnel (bottom) plots for the studies assessing a) all-cause mortality, b) myocardial infarction, and c) stroke S4.
Abbreviations
ARB: Angiotensin receptor blocker; ACE: Angiotensin-converting-enzyme; CVD: Cardiovascular disease; DALYs: Disability adjusted life years; IVhet: Inverse variance heterogeneity; RCT: Randomised controlled trial; RR: Relative risk

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Authors’ contribution
Conception and design of the study: LFK. Collection and assembly of the dataset: YW, RB, LFK. Analysis of the dataset and interpretation of results: YW, RB, NI, LFK. Manuscript writing: YW, RB, NI, LFK. Final approval of manuscript: YW, RB, NI, LFK

Availability of data and materials
He data used in the study was extracted from published studies.

Ethics approval and consent to participate
Not applicable, this is a systematic review and meta-analysis of published papers.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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