Antihypertensive treatment and risk of cancer: an individual participant data meta-analysis

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Summary

Background Some studies have suggested a link between antihypertensive medication and cancer, but the evidence is so far inconclusive. Thus, we aimed to investigate this association in a large individual patient data meta-analysis of randomised clinical trials.

Methods We searched PubMed, MEDLINE, The Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from Jan 1, 1966, to Sept 1, 2019, to identify potentially eligible randomised controlled trials. Eligible studies were randomised controlled trials comparing one blood pressure lowering drug class with a placebo, inactive control, or other blood pressure lowering drug. We also required that trials had at least 1000 participant years of follow-up in each treatment group. Trials without cancer event information were excluded. We requested individual participant data from the authors of eligible trials. We pooled individual participant-level data from eligible trials and assessed the effects of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β blockers, calcium channel blockers, and thiazide diuretics on cancer risk in one-stage individual participant data and network meta-analyses. Cause-specific fixed-effects Cox regression models, stratified by trial, were used to calculate hazard ratios (HRs). The primary outcome was any cancer event, defined as the first occurrence of any cancer diagnosed after randomisation. This study is registered with PROSPERO (CRD42018099283).

Findings 33 trials met the inclusion criteria, and included 260 447 participants with 15 012 cancer events. Median follow-up of included participants was 4·2 years (IQR 3·0–5·0). In the individual participant data meta-analysis comparing each drug class with all other comparators, no associations were identified between any antihypertensive drug class and risk of any cancer (HR 0·99 [95% CI 0·95–1·04] for ACEIs; 0·96 [0·92–1·01] for ARBs; 0·98 [0·89–1·07] for β blockers; 1·01 [0·95–1·07] for thiazides), with the exception of calcium channel blockers (1·06 [1·01–1·11]). In the network meta-analysis comparing drug classes against placebo, we found no excess cancer risk with any drug class (HR 1·00 [95% CI 0·93–1·09] for ACEIs; 0·99 [0·92–1·06] for ARBs; 0·99 [0·89–1·11] for β blockers; 1·04 [0·96–1·13] for calcium channel blockers; 1·00 [0·90–1·10] for thiazides).

Interpretation We found no consistent evidence that antihypertensive medication use had any effect on cancer risk. Although such findings are reassuring, evidence for some comparisons was insufficient to entirely rule out excess risk, in particular for calcium channel blockers.

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Introduction

Although evidence for the benefits of antihypertensive medication in the prevention of cardiovascular disease is well established,[1] low adherence to treatment is a major barrier to effective blood pressure control.[2] Non-compliance with antihypertensive medication is often due to concerns about possible adverse effects,[3] including an increased risk of developing cancer.[4–7] Several pathways have been hypothesised to explain possible associations between raised blood pressure and cancer risk, but findings have been inconsistent and mainly based on observational studies.[7,8] Most concerns have been associated with off-target effects of specific drug classes, such as possible carcinogenic effects of angiotensin II receptor blockers (ARBs) on lung tissue and the photosensitising effect of thiazide diuretics that could increase the susceptibility of the skin to the effects of sunlight exposure.[9,10]

A series of meta-analyses of randomised controlled trials, based on aggregate data, have investigated the association between class-specific antihypertensive treatment and risk of cancer, but findings have been conflicting. One study has suggested that using ARBs increases the risk of cancer,[4] whereas two subsequent meta-analyses showed no such association.[11,12] Another meta-analysis of randomised controlled trials found no evidence linking any drug class with the incidence of any cancer,[12] but an increased risk of cancer with the use of angiotensin-converting enzyme inhibitors (ACEIs) in combination with ARBs could not be ruled out. However,

Research in context

Evidence before this study

We searched PubMed, MEDLINE, The Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from Jan 1, 1966, to Sept 1, 2019, without language restrictions, for randomised controlled trials and meta-analyses investigating blood pressure lowering treatment. We searched MEDLINE using and expanding on the MeSH terms for "hypertension", "blood pressure", and "antihypertensive agents" including possible variations thereof and relevant antihypertensive drug classes. Our search identified 100 trials eligible for inclusion in the Blood Pressure Treatment Trialists' Collaboration. Of the trials and meta-analyses that reported cancer outcomes, no consistent associations were identified between any antihypertensive drug class and cancer risk.

Added value of this study

In this meta-analysis of individual patient-level data from 33 randomised controlled trials, to our knowledge, the one with the largest sample size to date, we found no compelling evidence that the use of any antihypertensive drug class had a significant effect on the risk of cancer when compared with placebo. Furthermore, we found no consistent evidence that the use of any antihypertensive drug class had a material effect on the risk of developing breast, colon, lung, prostate, or skin cancer. We found no association between risk estimates and longer durations of treatment (up to 4 years on average). The effect also did not vary across groups stratified by age, sex, body-mass index, smoking status, or previous antihypertensive use at baseline.

Implications of all the available evidence

Our study addresses a gap in the evidence for the safety of antihypertensive medication. Together with the established benefits of antihypertensive medication for the prevention of cardiovascular disease, our study provides evidence against antihypertensive treatment being associated with increased cancer risk. These findings are reassuring for patients and clinicians using these drugs and should encourage an improvement in adherence to antihypertensive medications. However, evidence for some cancer types was insufficient to entirely rule out the possibility of some excess risk, in particular, after a duration of treatment longer than that considered in our study.

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See **Online** for appendix

findings from existing meta-analyses based on summary statistics are limited by the study design, because such methods could not account for competing risks. Additionally, these analyses could not assess the timing of cancer events, since events occurring shortly after treatment initiation are unlikely to be causally linked to treatment since it is biologically plausible that a latency period exists between exposure to the medication and cancer occurrence.

The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) is a collaboration of the principal investigators of major global clinical trials of pharmacological blood pressure lowering treatment, coordinated by the University of Oxford (Oxford, UK). The collaboration provides the most extensive individual patient-level dataset of blood pressure lowering trials currently available worldwide. Using the BPLTTC database, we aimed to investigate class-specific effects of antihypertensive drugs on the outcomes of cancer, cancer deaths, and site-specific cancers.

Methods

Study governance and data source

For this meta-analysis of individual participant-level data, we used the BPLTTC database,[13,14] which currently has access to individual participant data from randomised controlled trials identified as described in the search strategy and selection criteria section and the study protocol.[13,14] The study protocol was approved by the Steering Committee and Collaborators before the data was released for analysis and is available in the appendix (pp 29–39). Ethical approval for the current study was obtained from the Oxford Tropical Research Ethics Committee (OxTREC Reference 545–14).

Search strategy and selection criteria

The search strategy and primary criteria for inclusion in the BPLTTC have been published previously[14] and are reported in the appendix (pp 2–4). Briefly, we searched PubMed, MEDLINE, The Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for randomised controlled trials investigating pharmacological blood pressure lowering treatments published between Jan 1, 1966, and Sept 1, 2019. We searched MEDLINE using and expanding on the MeSH terms for "hypertension", "blood pressure", and "antihypertensive agents", including possible variations thereof and relevant antihypertensive drug classes, without language restrictions. The full search strategy for MEDLINE is included in the appendix (p 10). Eligible trials for this study were randomised controlled trials comparing one blood pressure lowering drug class with a placebo, inactive control, or other blood pressure lowering drug. We also required that trials had at least 1000 participant years of follow-up in each treatment group and reported individual participant data on cancer events and timing of diagnosis during follow-up. We excluded trials that did not provide cancer event information.

Data extraction

Two investigators (DC, MN) independently screened titles and abstracts for eligibility and any conflicts were

resolved through discussion with a third investigator (KR). Individual participant data were requested from all eligible trials (full list of variables requested is reported in the appendix [pp 11–12]). Some trials included in the collaboration had previously reported numbers of cancer events, whereas others had not published this information previously. Analyses were confined to studies that compared one main drug class with a control group (or groups) and studies that compared more versus less intensive treatment regimens without a specific drug class group were excluded. All participants from eligible trials were included in the analysis. We used the Revised Cochrane risk-of-bias tool[15] to assess the risk of bias of individual trials.

We extracted individual participant data for baseline characteristics (appendix pp 11–12) and follow-up blood pressure measurements, cancer events, and cancer deaths.

Outcomes

The primary outcome was any cancer event, defined as the first occurrence of any cancer diagnosed after randomisation. Cancer events in the trials were reported using Classification of Diseases codes and Medical Dictionary for Regulatory Activities classifications. These cancer events include those prespecified as outcomes and those reported as adverse events in each trial. Secondary outcomes were deaths with cancer as the underlying cause and site-specific cancers. The site-specific cancers analysed included common cancers and subtypes that have previously been reported to be associated with blood pressure lowering treatment, comprising of breast, colorectal, lung, prostate, and skin cancers.[5–10,16] We describe the source of these outcomes for each trial, and whether or not these outcomes have been adjudicated by an endpoint committee on the basis of certain criteria, in the appendix (pp 13–17).

Data analysis

Characteristics of the participants included in each drug class comparison at baseline were described using summary statistics. All analyses were time-to-event analyses done using Cox proportional hazards models, stratified by trial, and were based on the intention-to-treat principle. In some trials, the exact dates of cancer diagnosis were not recorded in the trial database. In the absence of exact dates, the date of cancer diagnosis was approximated using the closest date to diagnosis on the basis of the date the cancer was first reported in the study or the date of death in participants for whom cancer had not been diagnosed or recorded before death with the underlying cause reported as cancer. Individuals were censored at date of death or last follow-up date. We used cause-specific fixed-effects Cox regression models for cancer events, with additional censoring for non-cancer deaths, to account for the competing risks. We fit cause-specific hazard models and Fine and Gray subdistribution hazard models to account for competing risk of non-cancer death. The primary analyses were done using data from cause-specific models, because they are considered more appropriate for assessing the causes of an event than Fine and Gray models.[17] Proportional hazard assumptions were tested by plotting log-log plots and by assessment of Schoenfeld residuals.

We examined the effects of each antihypertensive drug class using the one-stage individual participant data meta-analysis framework.[18,19] In these prespecified analyses, the active group included participants who were randomly assigned to a specific antihypertensive drug class (ACEI, ARB, β blockers, calcium channel blockers, or thiazide diuretics) and the control group includes participants randomly assigned to all other comparator groups, including placebo, standard treatments, or other drug classes (or drug class combinations). Further details of treatment comparison groups are described in the appendix (pp 18–19). We estimated the heterogeneity of cancer risk effects across each of these comparisons using χ^2 tests. We also did a network meta-analysis to investigate the class-specific effects of antihypertensives compared with a placebo reference group.[20–23] In this prespecified analysis, the effects of drug classes were analysed simultaneously by combining all available direct and indirect evidence across the network of studies.[20–23] Placebo-controlled trials contributed directly to the hazard ratio (HR) estimates of each antihypertensive drug class on cancer risk, and all other trials contributed indirectly. We reported the proportion of direct evidence in each comparison. We used fixed-effect network meta-analysis models, and assessed inconsistency across treatment effects using Q statistics. We have presented network graphs of all pairwise treatment comparisons in the network (appendix p 5). We have also reported the results for each pairwise comparison, because the network meta-analysis estimated the treatment effect of each drug class compared with each other drug class. Network meta-analyses were not done for site-specific outcomes due to small numbers of events from placebo-controlled trials.

To assess any temporal variation in risk, we did a post-hoc analysis to estimate the HR for each drug class according to specific timepoints during follow-up, and tested for heterogeneity and linear trend in risk across the follow-up duration. In the time-stratified analysis, patients contributed to the time of exposure at each time period until they developed the outcome or were censored. For cancer and cancer death outcomes, we prespecified subgroup analyses of the stratified effects of antihypertensive drug classes by baseline age, sex, smoking status, and body-mass index (BMI). We also stratified analyses based on previous use of antihypertensive medication at baseline, to test the hypothesis that true harmful effects are masked by widespread use of non-randomised treatment before trial participation. Heterogeneity of treatment effect across drug classes and subgroups were assessed using χ^2 statistics. For the

analyses stratified by follow-up period and patient characteristics, and analyses investigating site-specific cancer outcomes, we have presented unadjusted p values for heterogeneity and adjusted p values for multiple comparisons calculated using the Bonferroni method. We did the following sensitivity analyses: competing risk analysis using Fine and Gray subdistribution models to determine whether bias was introduced into the analysis due to competing risks; two-stage meta-analysis combining estimates from individual trials using the fixed-effect inverse-variance weighting approach to ensure that the HRs from the two-stage approach were comparable with those from the one-stage approach; and a comparison of the effects of each antihypertensive drug class on any cancer between trials that explicitly excluded cancer patients at baseline, and therefore only reported incident events, and those that did not exclude cancer patients at baseline and consequently might have reported recurrent events (appendix p 3).

We reported HRs with corresponding 95% CIs for all analyses, calculated from time-to-event models, and p values for all analyses of less than 0·05 were considered to indicate significance. All statistical analyses were done using R (version 3.3). This study is registered with PROSPERO (CRD42018099283).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The systematic review identified 11 494 studies, from which 100 trials were considered potentially eligible for the BPLTTC studies. Individual patient data were obtained from 51 trials (appendix p 4). From these, 12 trials were excluded because data on cancer events during follow-up were unavailable (ie, only 39 reported on cancer outcomes). A further six trials were excluded because they did not include a drug class comparison group, therefore 33 trials[24–74] including 260 447 individuals had cancer outcome data available and included a drug

	Drug class comparison*					All trials
	ACEI *vs* other[24–28,30–32,35–37,45,46,49,50,54,55,57,62–65,70]	ARB *vs* other[29,38,39,44,53,54,58–60,62,63,68–70,72–74]	β blocker *vs* other[24,25,33,34,44,47,48,58,59]	Calcium channel blockers *vs* other[24–28,30,31,33–43,47,48,54,56,57,60,61,66,67,70,71,73,74]	Thiazide *vs* other[30–32,40,41,44,51,52,61]	
Trials	15	11	5	19	6	33
Participants	118 574	99 711	35 169	150 745	58 185	260 447
Women	44 301 (37%)	37 941 (38%)	12 589 (36%)	69 399 (46%)	27 927 (48%)	106 453 (41%)
Men	74 271 (63%)	61 769 (62%)	22 578 (64%)	81 344 (54%)	30 261 (52%)	154 489 (59%)
Participant age, years	66 (60–72)	67 (60–73)	64 (57–70)	66 (60–73)	68 (62–73)	66 (60–72)
Participant age at baseline, years						
<65	50 864/118 569 (43%)	41 441/99 673 (42%)	19 152/35 169 (54%)	65 720/150 731 (44%)	20 108/58 185 (35%)	112 373/260 393 (43%)
≥65	67 685/118 569 (57%)	58 232/ 99 673 (58%)	16 015/35 169 (46%)	85 009/150 731 (56%)	38 080/58 185 (65%)	148 517/260 393 (57%)
Ethnicity						
White	70 174/104 648 (67%)	63 770/97 377 (65%)	29 154/34 073 (86%)	84 752/138 435 (61%)	25 962/55 781 (47%)	145 853/221 293 (66%)
African American	15 799/104 648 (15%)	2746/97 377 (3%)	2096/34 073 (6%)	20 037/138 435 (14%)	13 686/55 781 (25%)	22 312/221 293 (10%)
Hispanic	9684/104 648 (9%)	4091/97 377 (4%)	116/34 073 (<1%)	16 376/138 435 (12%)	6690/55 781 (12%)	21 000/221 293 (9%)
Asian	9472/104 648 (9%)	23877/97 377 (25%)	3610/34 073 (11%)	17 096/138 435 (12%)	9443/55 781 (17%)	32 493/221 293 (15%)
Other	613/104 648 (1%)	2873/97 377 (3%)	195/34 073 (1%)	755/138 435 (1%)	NA	3440/221 293 (2%)
Pre-treatment systolic blood pressure, mm Hg	147 (21)	149 (20)	166 (17)	155 (20)	151 (17)	151 (21)
Pre-treatment diastolic blood pressure, mm Hg	84 (11)	86 (12)	95 (10)	88 (11)	86 (10)	86 (11)
Trial duration, years	4·5 (4·0–5·1)	4·4 (3·1–4·9)	5·0 (4·5–5·8)	4·0 (2·8–5·2)	4·5 (3·7–5·5)	4·3 (3·0–5·0)
Previously on blood pressure lowering medication	78 018/93 064 (83%)	77 061/95 008 (81%)	25 546/34 073 (75%)	79 058/97 810 (81%)	46 265/54 054 (86%)	167 195/210 978 (79%)
Current smoker	19 519/118 413 (16%)	16 378/99 567 (16%)	9273/35 150 (26%)	30 739/150 463 (20%)	11 132/58 185 (19%)	47 199/260 269 (18%)
BMI, kg/m^2	28 (5)	28 (5)	28 (5)	28 (5)	28 (6)	28 (5)
<25	29 830/117 465 (25%)	31 800/99 340 (32%)	8949/35 033 (25%)	30 568/111 786 (27%)	15 871/57 435 (28%)	62 862/221 135 (28%)
25–30	51 059/117 465 (43%)	41 924/99 340 (42%)	15 845/35 033 (45%)	46 248/111 786 (41%)	22 390/57 435 (39%)	95 361/221 135 (43%)
≥30	37 040/117 465 (31%)	25 616/99 340 (26%)	10 237/35 033 (29%)	34 967/111 786 (31%)	19 172/57 435 (33%)	63 409/221 135 (29%)

Data are n, n (%), median (IQR), n/N (%),or mean (SD). ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin II receptor blockers. NA=not available. BMI=body-mass index. The number of studies cited exceeds the total number of trials included in the mta-analysis because multiple references have been cited for some trials. Some percentages do not sum to 100 due to rounding. *Drug class comparison groups are not mutually exclusive; some trials contribute data to more than one drug class (appendix pp 18–19).

Table: **Characteristics of trials and participants**

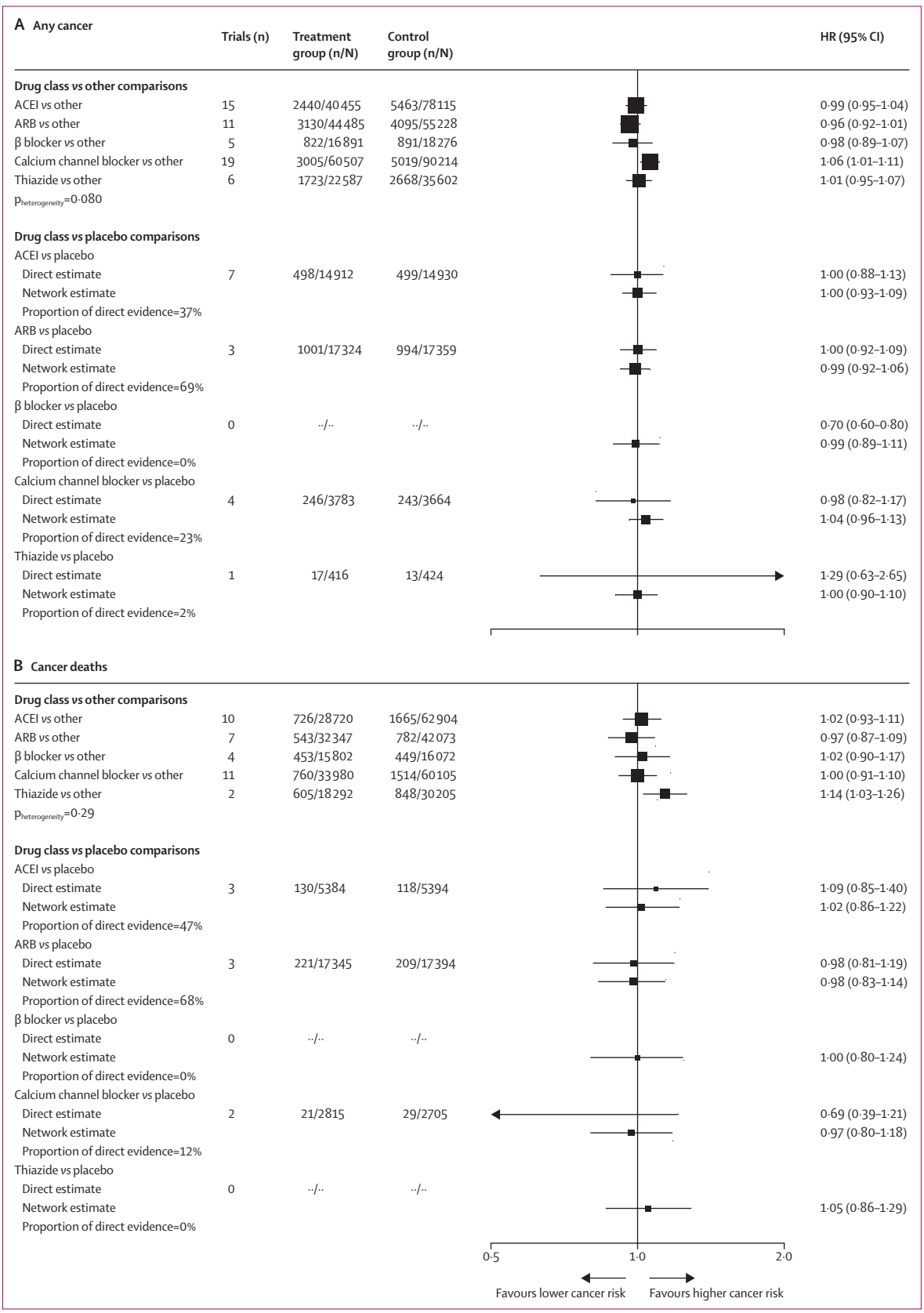


Figure 1: **Effects of antihypertensive drug classes on risk of any cancer (A) and cancer death (B)**
Estimates based on individual participant-level data meta-analysis and network meta-analysis. n/N=number of events/number of participants. HR=hazard ratio. ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin II receptor blockers. NA=not available.

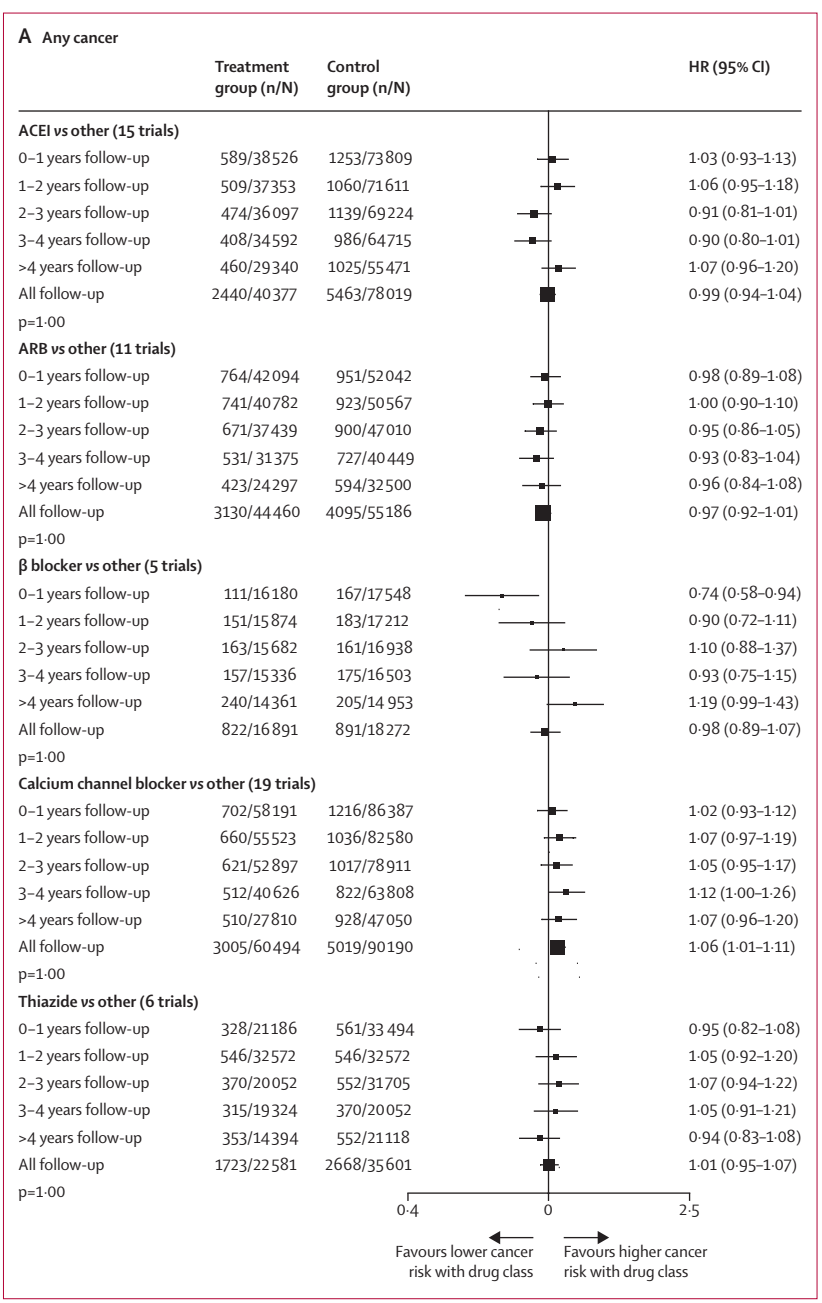
class comparison group, and thus met the inclusion criteria (table). Of the 33 trials included in the analysis, 16 (48%) trials that contributed to 11 833 (79%) of 15 012 cancer events had previously reported on cancer risk or had been included in aggregate meta-analyses of randomised controlled trials.[4,11,12] 3251 (21%) cancer events from 12 trials included were published for the first time in this study. 11 trials explicitly excluded patients with cancer at baseline (2525 [17%] events; appendix pp 13–17). Cancer was a prespecified safety outcome in 13 trials that contributed 10 119 (67%) events (appendix p 13–17). In the remaining 20 trials (4965 [33%] events), cancer was identified routinely as part of adverse event reporting. In 13 trials (6663 [44%] of 15 012 events), an endpoint committee adjudicated cancer events (appendix pp 13–17). The risk of bias assessment indicated that 29 trials were at low risk of bias, and four trials had some risk of bias (appendix p 20).

15 trials (118 574 participants) included an ACEI drug class comparison; 11 trials (99 711 participants) included ARBs; five trials (35 169 participants) included β blockers; 19 trials (150 745 participants) included calcium channel blockers; and six trials (58 185 participants) included thiazides (table). The drug class comparisons were not mutually exclusive, since some trials contributed data to more than one comparison. For the network meta-analysis comparing drug classes against placebo, individual participant data for total cancer events was available for 72 812 participants from 13 placebo-controlled trials: seven included an ACEI treatment group, three included an ARB group, four included a calcium channel blocker group, and one included a thiazide diuretic group. Individual participant data for cancer death was available for 51 038 participants included in eight placebo-controlled trials: three included ACEIs, three included ARBs, and two included calcium channel blockers. No placebo-controlled trials were identified that included a β blockers comparison group. Eight trials included more than two treatment groups: six trials included three intervention groups and two trials included four treatment groups (appendix pp 13–19).

The median age of participants across all trials was 66 years (IQR 60–72). Additional participant characteristics stratified by drug class comparison are presented in the table. Details of participant characteristics for individual trials are included in the appendix (p 21).

After a median of 4·2 years (IQR 3·0–5·0) of follow-up, 15 012 participants were diagnosed with cancer across all 33 trials. We found no evidence of an association between antihypertensive drugs and any cancer when assessing all comparison groups (hazard ratio [HR] 0·99 [95% CI 0·95–1·04] for ACEIs; 0·96 [0·92–1·01] for ARBs; 0·98 [0·89–1·07] for β blockers; 1·01 [0·95–1·07] for thiazides), with the exception of calcium channel blockers (1·06 [1·01–1·11]; figure 1A). We also did not find an increased risk of cancer with use of any hypertensive drug in the network analysis using placebo as a comparator (HR 1·00 [95% CI 0·93–1·09] for ACEIs; 0·99 [0·92–1·06] for ARBs; 0·99 [0·89–1·11] for β blockers; 1·04 [0·96–1·13] for calcium channel blockers; 1·00 [0·90–1·10] for thiazides). In the one-stage meta-analysis, no evidence of effect modification by drug class was identified ($p_{heterogeneity}$=0·080). In the network meta-analysis, no direct evidence of an effect was observed for any of the drug classes (figure 1A; appendix p 5).

In the one-stage meta-analyses comparing each drug class against all other comparators, no association was identified between antihypertensive treatments and



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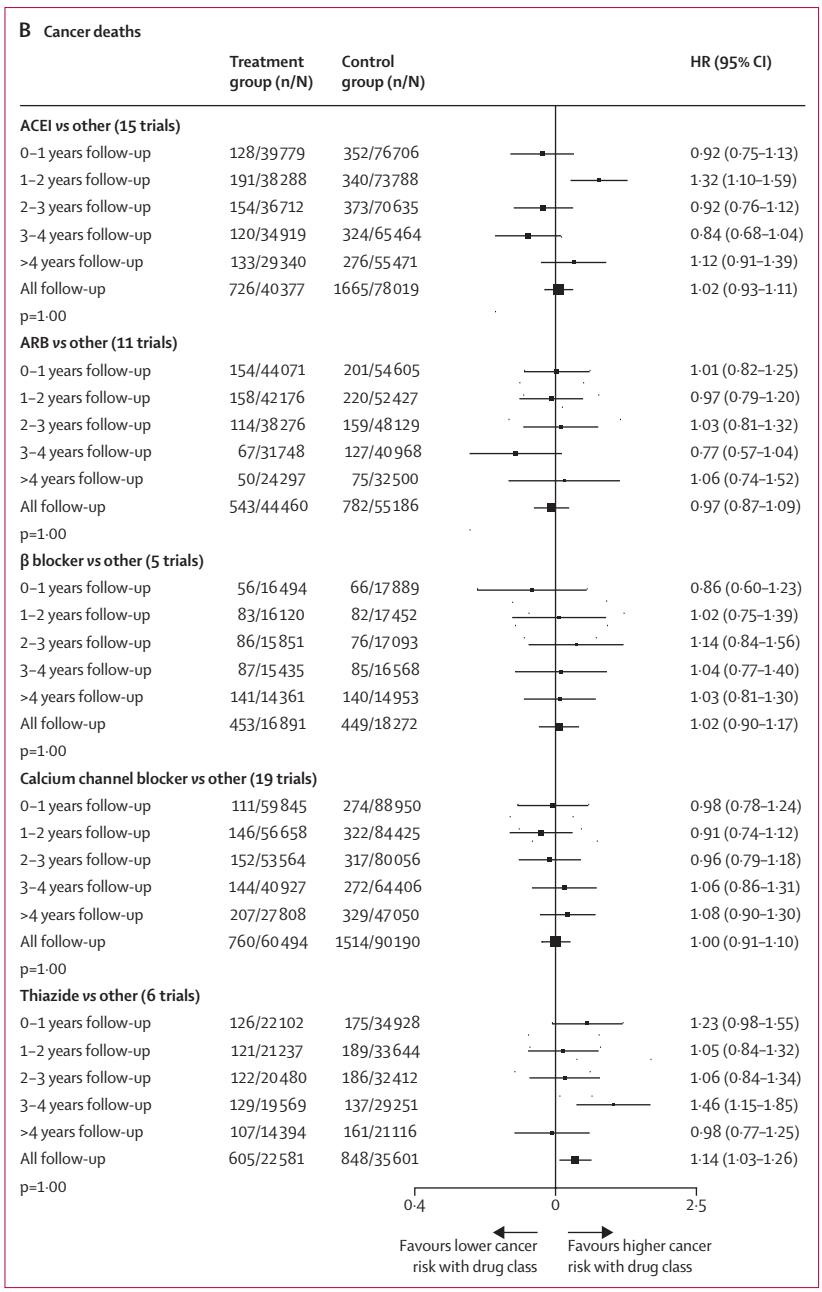

Figure 2: **Effects of antihypertensive drug classes on risk of any cancer (A) and cancer death (B), stratified by follow-up duration**

p values are for linear trend and heterogeneity adjusted for multiple testing. n/N=number of events/number of participants. HR=hazard ratio. ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin II receptor blockers.

cancer deaths, with the exception of thiazide diuretics, which were associated with an increased risk of death caused by cancer (figure 1B). In the network meta-analysis comparing each drug class against placebo, we found no associations between antihypertensive treatments and risk of cancer death. Across all associations, the network meta-analysis estimates were similar to the individual participant data meta-analysis estimates, with the exception of the effect of thiazide diuretics on the outcome of cancer death (figure 1B). Since no data were available on cancer death outcomes for any placebo-controlled trials with a thiazide diuretic drug class comparison, the network estimate was based entirely on indirect evidence from trials that included a thiazide diuretic group (two trials) or a placebo group, but not both.

In a post-hoc analysis, we also found no pattern of increasing or decreasing risk for any cancer or cancer death over time associated with any antihypertensive drug class (figure 2). Although there was some evidence of heterogeneity in treatment effect across different time periods for any cancer with ACEIs ($p_{heterogeneity}$=0·004), calcium channel blockers ($p_{heterogeneity}$=<0·0001), and thiazides ($p_{heterogeneity}$=<0·0001), and for cancer death with calcium channel blockers ($p_{heterogeneity}$=0·06) and thiazides ($p_{heterogeneity}$=<0·001), there was no indication that the risk increased consistently over time (figure 2). In prespecified subgroup analyses, we found no evidence for variation in treatment effects across different age groups, sex, BMI categories, smoking status, or previous use of antihypertensive drugs (all $p_{heterogeneity}$>0·10; appendix pp 6–8). The direct and network estimates from all pairwise comparisons of individual drug classes and placebo are presented in the appendix (p 22). We found no evidence for inconsistency in treatment effects across the network for any cancer or cancer death outcomes (p=0·60 for any cancer; p=0·88 for cancer death).

We examined the effects of antihypertensive drug classes on risks of breast, colorectal, lung, prostate, and skin cancer compared with all other comparators (figure 3). Across all drug classes and site-specific cancers, we found no evidence of any associations, with the exception of calcium channel blockers which were associated with increased risk of prostate and skin cancers. The excess risks for calcium channel blockers on prostate and skin cancers were driven by the comparison of calcium channel blockers compared with ARBs (data not shown). We also examined these effects according to duration of follow-up and found no consistent temporal pattern in the risks for all drug classes (all p=1·00; data not shown).

In the two-stage meta-analysis, the HRs were comparable in magnitude with the results of the one-stage meta-analysis (appendix p 9). We also found that the subdistribution HRs from the Fine and Gray models were comparable to the cause-specific HRs, thus there was no sign of bias due to competing risks (data not shown). In the sensitivity analysis comparing the effects of antihypertensive drug classes on any cancer between trials that explicitly excluded cancer patients at baseline and those that did not, no significant heterogeneity in treatment effects was identified for any drug class compared with all other comparators ($p_{heterogeneity}$=0·99 for ACEIs; $p_{heterogeneity}$=0·78 for ARBs; $p_{heterogeneity}$=0·55 for β blockers; $p_{heterogeneity}$=0·40 for calcium channel blockers; $p_{heterogeneity}$=0·17 for thiazides; appendix p 23).

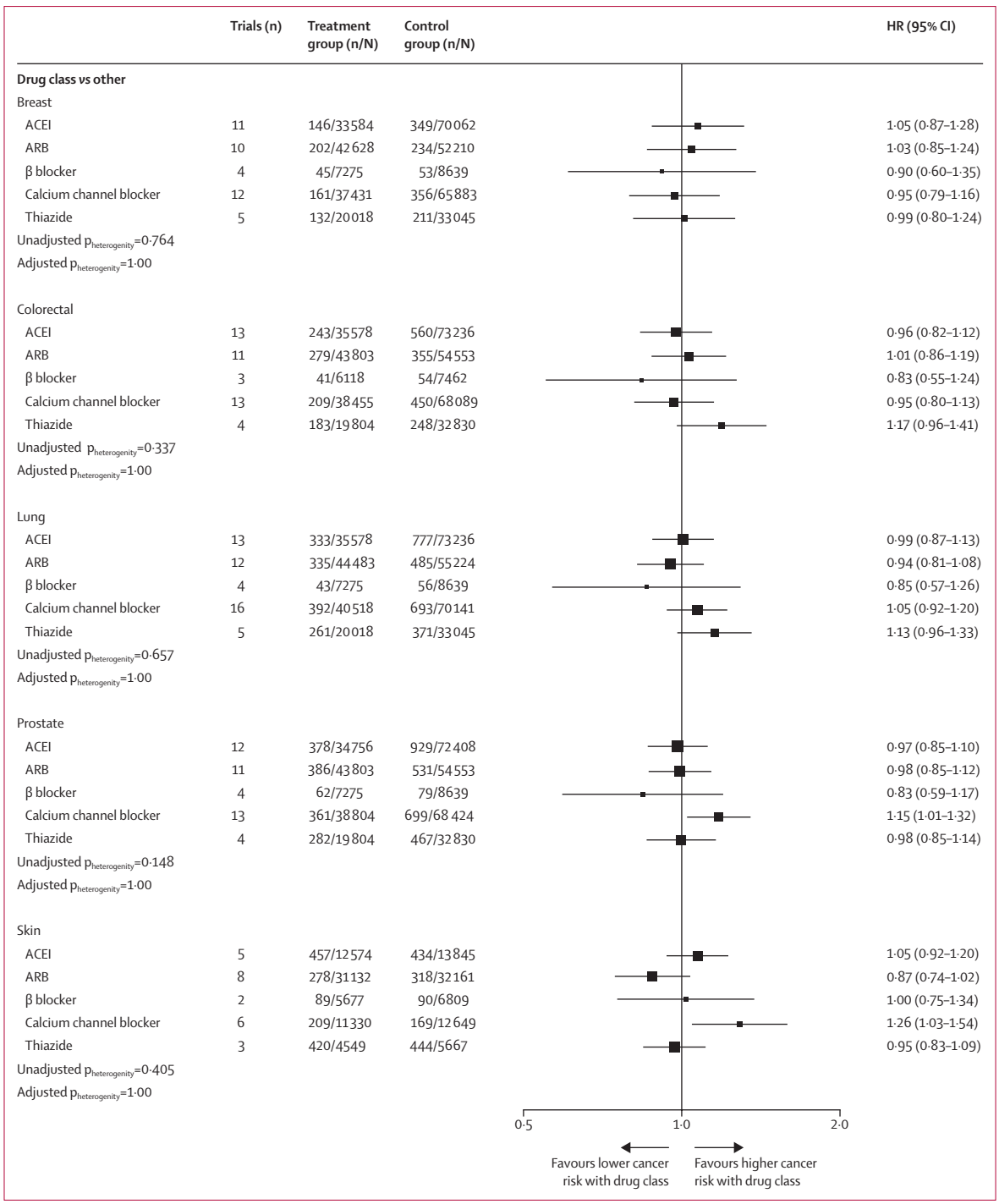

Figure 3: **Effects of antihypertensive drug classes on risk of site-specific cancers**
Unadjusted p values for heterogeneity and p values adjusted for multiple comparisons are presented. n/N=number of events/number of participants. HR=hazard ratio. ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin II receptor blockers.

Discussion

In this study, we found no consistent evidence that the use of antihypertensive medication overall increased the risk of any cancer or cancer death. We also found no strong evidence that the use of any particular antihypertensive drug class had a consistent effect on the risk of developing breast, colon, lung, prostate, or skin cancer. These findings were further corroborated in the

network meta-analyses based on the direct and indirect comparisons of drug classes with placebo, and in the time-stratified analyses, which showed no evidence of increasing or decreasing effects over time. However, the excess risks identified for calcium channel blockers on any cancer, prostate cancer, and skin cancer and for thiazide diuretics on cancer death in some analyses requires further investigation in clinical trials with a larger number of events, particularly for placebo-controlled comparisons.

Although several observational studies have previously reported an association between cancer risk and increased blood pressure or its treatment,[5,6,7,16,75,76] evidence based on randomised data is scarce, and meta-analyses of randomised evidence are mainly based on analysis of published summary statistics.[4,11,12] Such study designs cannot account for competing risks, or investigate cancer events across different durations of follow-up. Little evidence is available from meta-analyses of published findings from randomised controlled trials on the effects on site-specific cancers because it is unlikely that a single trial would have sufficient statistical power to report these effects. Due to the large number of trials included in the BPLTTC database with individual participant data available, our study also addresses the paucity of evidence on antihypertensive drug use and cancer risk among important patient subgroups, and found no significant variation in the effects on any cancer across groups defined by age, sex, BMI, smoking status, or previous antihypertensive use with any antihypertensive drug class, indicating that any cancer-related adverse effects were unlikely to have been masked by widespread use of non-randomised treatment before trial participation.

Several hypotheses have been posited linking the pathways of specific drug classes to cancer, independently of changes in blood pressure.[9,10] There has been a concern around the potential association between thiazide diuretics and skin cancer risk due to the photosensitising properties of thiazides and harmful effects identified in several observational studies;[7] however, our findings do not support an association between the use of thiazides and skin cancers. Other studies have also suggested that blockade of the renin–angiotensin system by ACEIs and ARBs might have a protective effect against a broad range of cancer types,[77] including lung, breast, and prostate cancers,[78] by affecting cell proliferation, angiogenesis, and apoptosis.[79] However, we found no significant associations between any of these drug classes and risk of any cancers. Our findings suggesting a potential increased risk of any, prostate, or skin cancers with use of calcium channel blockers and cancer death with thiazides were unexpected considering that no compelling evidence exists with regard to plausible mechanisms that would affect carcinogenesis in these parts of the body with use of these drugs.[75,80] However, our detailed analyses and the absence of plausible mechanisms suggest that calcium channel blockers or thiazides are unlikely to cause such cancers. Comparison of a single drug class against all other groups is limited by uncertainty regarding whether the apparent excess risk is a true effect of the intervention or a reflection of a potentially beneficial effect of the drug class in the comparison group (which by chance will differ for different classes). In the case of thiazide diuretics, a larger number of trials providing cancer death data is required to investigate this association further, since only two trials contributed data to this analysis. In the case of calcium channel blockers, the excess risks identified were primarily driven by the comparison of calcium channel blockers against ARBs, which in turn seems to have been driven by data from a single trial (VALUE[73,74]). Although no significant heterogeneity was identified across trials with a calcium channel blocker comparison in two-stage meta-analysis, the VALUE trial (calcium channel blocker *vs* ARB comparison), was an important driver of the excess risk for calcium channel blockers compared with all other comparators in the main analysis. To address this issue, we compared individual drug classes with placebo. Because of the relatively small number of placebo-controlled trials available for most drug classes, we did individual participant data network meta-analyses to estimate these effects. The results showed no evidence of any effects of drug classes on cancer risk when compared with placebo. This finding, together with the time-stratified analyses results, and the absence of heterogeneity in treatment effects across drug classes provide evidence against any class-specific effects on the risk of developing cancer. Consequently, it is possible that any variation around the null could be due to chance. However, these detailed and robust analyses have inadequate power to detect a statistical difference, particularly for site-specific cancers.

A key strength of this study was the use of individual participant data from the largest dataset of randomised controlled trials of antihypertensive drug treatments available to date, to our knowledge. Previously, a large meta-analysis of randomised controlled trials investigated the risk of cancer associated with antihypertensive treatment, but it was based on aggregate data[12] and one study that analysed individual participant-level data only included 28 787 participants with 1823 cancer events.[4] The number of participants included in our meta-analysis was nearly ten times higher and the number of cancer events was more than 13 000 higher than that included in the previous meta-analysis based on individual participant-level data, enabling a more detailed analysis to be done than previously possible. Another important strength of this study was that we had access to unpublished cancer event data collected during follow-up, and additional information from most trials on cancer subtypes, date of diagnosis, and information on multiple diagnoses in individual participants. Since we had access to time-to-event data, we were able to assess any trend in cancer risk over time, an analysis that has not been possible previously using randomised data.

This analysis allowed us to account for the latency period between exposure to the antihypertensive drug and occurrence of cancer, since events diagnosed early during follow-up are less likely to be linked to the study medication. The results of this analysis suggested that there was no increased risk of cancer with continued treatment during the follow-up period. Thus, our study provides the most compelling evidence to date for the safety of antihypertensive drugs with respect to cancer and cancer subtypes that we have considered.

A limitation of this study was that we did not have access to individual participant data for all trials that were eligible for inclusion in the BPLTTC database. Therefore, although we had access to a larger number of cancer events from randomly assigned participants than did previous studies, some analyses involving cancer mortality or site-specific cancer outcomes were based on relatively small numbers of events, resulting in greater uncertainty around the risk estimates. For the same reason, our pre-defined protocol excluded analyses of uncommon cancer sites. The source of cancer outcomes varied across trials. Some trials reported prespecified cancer outcomes whereas others captured cancer events through routine adverse event reporting, and less than half of the trials adjudicated cancer events. However, previous evidence[81,82] has suggested that adjudication of common outcomes does not have an impact on relative treatment effects because any misclassification is expected to be consistent across treatment groups. Because of the paucity of data on baseline cancer history, we were unable to determine whether all cancer outcomes were incident events. However, our sensitivity analysis, stratified by explicit exclusion of cancer patients at baseline, suggested that there were no differences in the relative treatment effects in trials that excluded cancer patients compared with those that did not. Investigators across many trials were also allowed to prescribe additional non-study antihypertensive treatments to participants whose blood pressure had not been controlled sufficiently with the study drug. In cases where the treatment and control groups were systemically prescribed different classes of drugs (either by design or chance), this could lead to the underestimation of each drug class effect on the outcomes. Another potential limitation was that class-specific categorisation of antihypertensive medication might have diluted the effects of individual drugs that act via different biological pathways. Additionally, our study was based on a median follow-up duration of 4 years, which might not be sufficient for some cancers to develop. Hence, it would be prudent for future trials to continue collecting outcomes, including cancer, long after the trial has ended to allow the investigation of off-target effects of antihypertensive drugs. In our analyses stratified by follow-up duration, we found no evidence of an increasing risk with more years of exposure to the treatment; however, studies with longer durations might be necessary to rule out any association with long-term antihypertensive use.

Our study has addressed an ongoing controversy about the safety of blood pressure lowering medication with respect to cancer risk, using the largest sample of individual-level randomised evidence on blood pressure lowering treatment to date, to our knowledge. In our detailed analyses, we found no evidence that the use of antihypertensive medication has any substantial effect on cancer risk, although we could not rule out potential class-specific effects for calcium channel blockers and thiazide diuretics. This finding was consistent across patients with a wide range of baseline characteristics, therefore our study addresses a gap in the evidence for the safety of antihypertensive medication. It is estimated that between 30% and 50% of individuals have poor adherence to these drugs, partly because of concerns around the harmful effects that long-term use of antihypertensive medications might cause.[2,3] The main implication of our study is that patients using antihypertensive medication should continue to take their medications because concerns about increased cancer risk seem to be unfounded.

Contributors

KR and DC acquired the funding for the study. EC, DC, and KR were responsible for the study concept and design and data curation. EC, DC, RR, JS, MW, and KR were responsible for the methods and formal analysis. EC, DC, RR, MN, ZB, MW, JC, KKT, CJP, BRD, JS, SK, and KR did the data analysis and interpreted the data. EC was responsible for data visualisation and drafted the original manuscript, which was reviewed and edited by the remaining members of the working group. All authors had full access to all the data in the study, and EC, DC, and KR verified the data. The corresponding author had the final responsibility to submit for publication.

Declaration of interests

MW reports personal fees from Amgen, Kyowa Kirin, and Freeline, outside the submitted work. JS reports ownership in companies providing services to Itrim, Amgen, Janssen, Novo Nordisk, Eli Lilly, Boehringer, Bayer, Pfizer, and AstraZeneca outside the submitted work. MN reports grants from the British Heart Foundation outside the submitted work. DC reports grants from the British Heart Foundation, during the conduct of the study. KR reports grants from the British Heart Foundation, UK Research and Innovation Global Challenges Research Fund, Oxford Martin School, and National Institute for Health Research Oxford Biomedical Research Centre, during the conduct of the study; and personal fees from BMJ Heart and PLOS Medicine, outside the submitted work. SK reports lecture honoraria from Merck GBaA and Sanofi, and study committee honoraria from Takeda. JC reports grants from National Health and Medical Research Council of Australia, outside the submitted work. EC, ZB, RR, KKT, CJP, and BRD declare no competing interests.

Data sharing

The BPLTTC is governed by the University of Oxford's policies on research integrity and codes of practice and follows the university's policy on the management of research data and records. Scientific activities based on the BPLTTC dataset are overseen by the BPLTT Steering Committee. All data shared with the BPLTTC will be considered confidential and will not be provided to any third party. Requests for data should be made directly to the data custodians of individual trials.

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obtained from the National Heart, Lung and Blood Institute Biologic Specimen and Data Repository Information Coordinating Centre and does not necessarily reflect the opinions or views of ACCORD, ALLHAT, PEACE and SHEP, or the NHLBI. The AASK trial was done by AASK Investigators and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The data reported here were supplied by the NIDDK Central Repositories. This manuscript was not prepared in collaboration with investigators of the AASK trial and does not necessarily reflect the opinions or views of AASK, the NIDDK Central Repositories, or the NIDDK. We acknowledge original depositors of the Australian National Blood Pressure Study data and the Australian Data Archive, and declare that the individuals who did the original analysis and collection of the data have no responsibility for the further analysis or interpretation of the data published in this study.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Copland E, Canoy D, Nazarzadeh M, et al. Antihypertensive treatment and risk of cancer: an individual participant data meta-analysis. *Lancet Oncol* 2021; **22:** 570–82.

Web-only supplement

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Supplementary methods

Eligibility criteria

Trials were eligible for inclusion in the Blood Pressure Lowering Trialists' Collaboration (BPLTTC) if one of the following criteria were met:

- Randomization of patients between a blood pressure-lowering agent and a placebo arm, or other inactive control
- Randomization of patients between various blood pressure-lowering intensities
- Randomization of patients between various antihypertensive drugs

A minimum of 1,000 participant years of follow-up was required in each randomly allocated arm for a trial to be eligible. There was no restriction on the publication date, setting or drug that was investigated.

The following types of trial were excluded:

- Trials exclusively conducted in patients with heart failure or short-term interventions in patients with acute myocardial infarction or other acute settings
- Trials with non-pharmacological interventions of blood pressure-lowering without a drug comparison arm
- Trials without a clearly defined randomization process
- Trials that did not provide cancer event information were further excluded from this analysis

Identifying studies

Potential eligible trials were identified through a systematic review. The search was restricted to randomised controlled trials or meta-analyses. There were no language restrictions. PubMed/MEDLINE, The Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were searched covering the periods between 1 January 1966 and 1 June 2018. The time period was extended to 1 September 2019 for the current analysis. Reference lists of eligible studies, related meta-analyses and clinical trial registries were hand-searched to identify further studies. This systematic review protocol was registered with PROSPERO[1] (CRD42018099283). The search strategy for MEDLINE is presented in Supplementary Table 1 (p 10). The overall search strategy underlying the BPLTTC is summarized in Supplementary Figure 1 (p 4). 100 eligible trials were identified.

Study selection

Two investigators conducted independent searches and screened the publication titles and abstracts to assess their eligibility (DC, MN). Full manuscripts of potential eligible studies were requested and assessed based on the eligibility criteria. Disagreements were resolved through discussion with a third investigator (KR).

Data collection, transfer and storage

Individual participant-level data (IPD) was requested from investigators of newly identified trials as well as existing BPLTT collaborators. The full list of variables that were sought is presented in Supplementary Table 2 (p 11). As of December 2020, the collaboration had acquired data from 51 trials comprising 352,744 participants. Data are still being sought for the remaining 49 trials, however, many of these trials were published many years ago and the identification of a data guardian or electronic trial database has proven challenging.

Trial data were transferred using a secure file transfer system and stored on a secure server at the University of Oxford, to comply with data protection regulations and data sharing agreements. Access to the data is restricted to investigators directly involved in the research and can only be used for the exclusive purpose of the study that has been pre-approved by the BPLTTC Steering Committee.

Data cleaning and harmonization

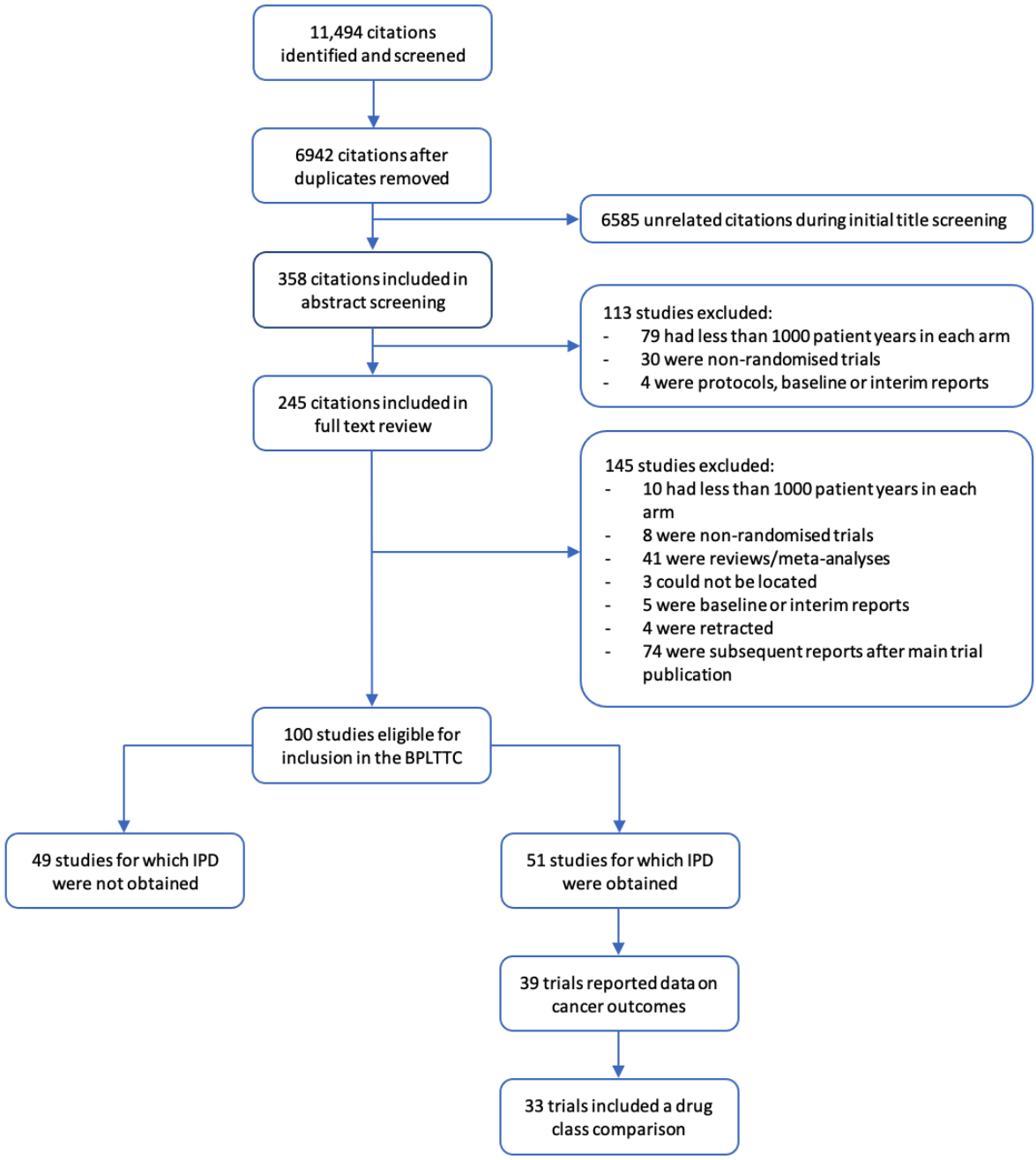
The process of data cleaning and harmonization involved creating a database with all information obtained from investigators using the data dictionaries provided. Individual trial data, including number of participants, baseline characteristic variables, follow-up and outcome data, were checked and verified by comparing against published data. Prepared data were also checked for consistency and completeness. Investigators were contacted if any inconsistencies or missing data was identified.

Sensitivity analysis

In our sensitivity analyses, we repeated the primary analysis using Fine-Gray models and compared the subdistribution hazard ratios from these models to the cause-specific hazard ratios to determine whether bias was introduced into the analysis due to the competing risk of non-cancer death. Fine and Gray subdistribution models were not selected as the models for the primary analysis as they are less appropriate for addressing aetiological questions, such as the association between an exposure and the risk of an outcome, than cause-specific hazard models.[2] We also conducted a two-stage meta-analysis and compared the results against those from the one-stage meta-analysis investigating the effect of each antihypertensive drug class on cancer risk. In the two-stage meta-analysis, the estimates for each trial were combined using the fixed-effect inverse-variance weighting approach. We also compared the class-specific effects of antihypertensive drug classes on any cancer between trials that explicitly excluded cancer patients at baseline and those that did not.

Supplementary figures

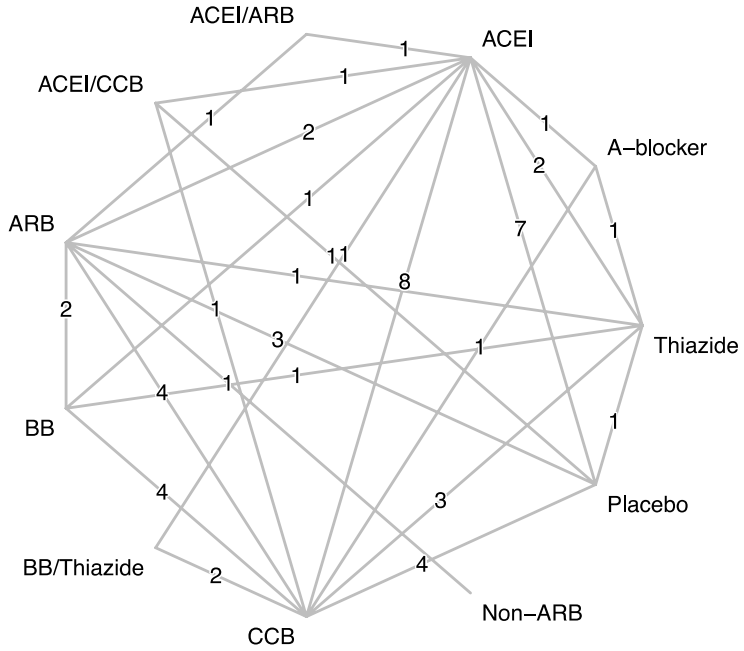
Supplementary Figure 1. PRISMA diagram for included trials.



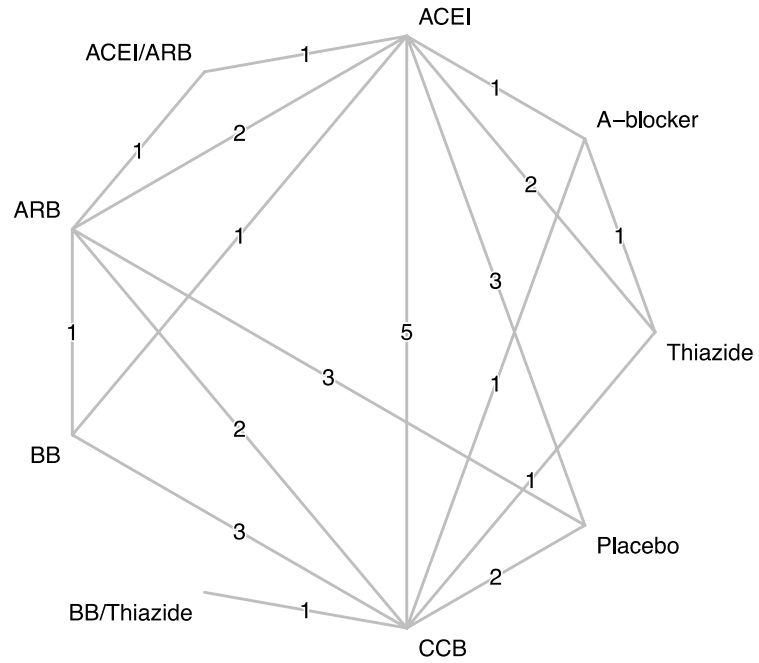
BPLTTC=Blood Pressure Lowering Treatment Trialists' Collaboration. IPD=individual participant-level data.

Supplementary Figure 2. Network of treatment comparisons for a) any cancer and b) cancer death. The number associated with each line represents the number of trials providing a direct comparison between the drug classes connected by the line.

A) Any cancer



B) Cancer death

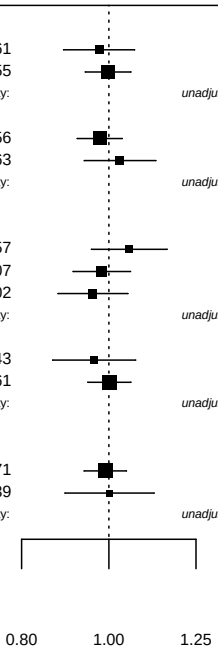


A-blocker=α-blocker. ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin-II receptor blockers. BB=ß-blockers. CCB=calcium channel blockers.

Supplementary Figure 3. Class-specific effects of antihypertensive drugs on any cancer compared against all other comparators and placebo, stratified by baseline characteristics of participants.
Adjusted P values for heterogeneity indicate adjustment for multiple comparisons.

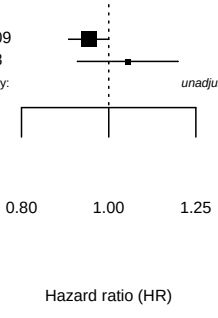
A. ACEI vs all other comparators

By baseline characteristic	N trials	Number of events / participants: Treatment	Control	HR (95% CI)
Age				
Less than 65	13	701 / 17503	1613 / 33361	0.98 (0.89, 1.07)
65 and over	15	1749 / 22950	3862 / 44755	1.00 (0.94, 1.06)
		Heterogeneity:		*unadjusted P=0.263, adjusted P=1*
Gender				
Male	15	1756 / 26415	3862 / 47856	0.98 (0.92, 1.03)
Female	15	694 / 14038	1613 / 30263	1.03 (0.94, 1.13)
		Heterogeneity:		*unadjusted P=0.426, adjusted P=1*
Body mass index (kg/m^2)				
Less than 25	15	641 / 10532	1318 / 19257	1.05 (0.96, 1.16)
25−30	14	1094 / 17899	2364 / 33007	0.98 (0.91, 1.06)
30 and over	14	704 / 11668	1761 / 25102	0.96 (0.88, 1.05)
		Heterogeneity:		*unadjusted P=0.713, adjusted P=1*
Smoking status				
Current smoker	15	497 / 6455	1261 / 13643	0.96 (0.87, 1.07)
Ex or never smoker	15	1953 / 33954	4213 / 64361	1.00 (0.95, 1.06)
		Heterogeneity:		*unadjusted P=0.154, adjusted P=1*
Antihypertensive drug use				
Yes	13	1962 / 29247	4599 / 59971	0.99 (0.94, 1.05)
No	14	392 / 9001	665 / 13739	1.00 (0.89, 1.12)
		Heterogeneity:		*unadjusted P=0.263, adjusted P=1*



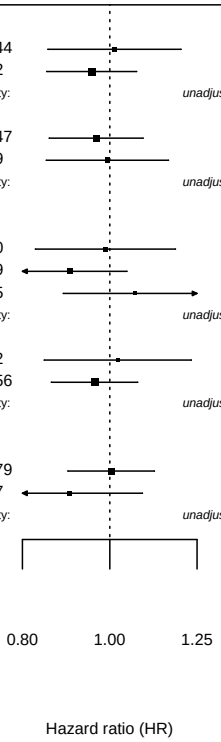
B. ARB vs all other comparators

By baseline characteristic	N trials	Number of events / participants: Treatment	Control	HR (95% CI)
Age				
Less than 65	11	848 / 18284	1138 / 23157	0.97 (0.89, 1.06)
65 and over	11	2306 / 26189	2994 / 32043	0.96 (0.91, 1.02)
		Heterogeneity:		*unadjusted P=0.908, adjusted P=1*
Gender				
Male	11	2174 / 27231	2912 / 34538	0.97 (0.92, 1.03)
Female	11	980 / 17253	1223 / 20688	0.94 (0.87, 1.03)
		Heterogeneity:		*unadjusted P=0.911, adjusted P=1*
Body mass index (kg/m^2)				
Less than 25	11	867 / 14036	1153 / 17764	0.96 (0.88, 1.05)
25−30	11	1414 / 18796	1800 / 23128	0.99 (0.92, 1.06)
30 and over	11	866 / 11506	1168 / 14110	0.93 (0.85, 1.02)
		Heterogeneity:		*unadjusted P=0.593, adjusted P=1*
Smoking status				
Current smoker	11	573 / 7648	727 / 9307	1.02 (0.92, 1.14)
Ex or never smoker	11	2581 / 36781	3408 / 45830	0.95 (0.90, 1.00)
		Heterogeneity:		*unadjusted P=0.665, adjusted P=1*
Antihypertensive drug use				
Yes	9	2646 / 34052	3589 / 43009	0.95 (0.90, 1.00)
No	10	459 / 8078	500 / 9868	1.05 (0.92, 1.19)
		Heterogeneity:		*unadjusted P=0.380, adjusted P=1*



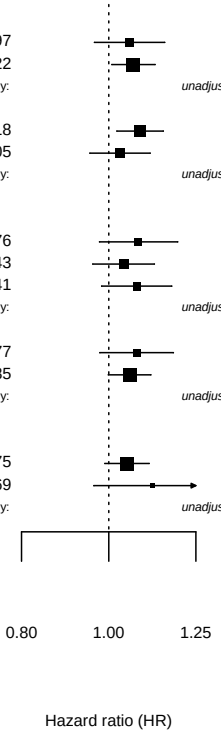
C. BBs vs all other comparators

By baseline characteristic	N trials	Number of events / participants: Treatment	Control	HR (95% CI)
Age				
Less than 65	6	260 / 9108	280 / 10044	1.01 (0.85, 1.20)
65 and over	6	562 / 7783	615 / 8232	0.95 (0.85, 1.07)
		Heterogeneity:		*unadjusted P=0.541, adjusted P=1*
Gender				
Male	6	515 / 10931	566 / 11647	0.97 (0.86, 1.09)
Female	6	307 / 5960	329 / 6629	0.99 (0.85, 1.16)
		Heterogeneity:		*unadjusted P=0.683, adjusted P=1*
Body mass index (kg/m^2)				
Less than 25	6	226 / 4099	265 / 4850	0.99 (0.83, 1.18)
25−30	6	351 / 7706	397 / 8139	0.90 (0.78, 1.04)
30 and over	6	236 / 5012	228 / 5225	1.07 (0.89, 1.28)
		Heterogeneity:		*unadjusted P=0.346, adjusted P=1*
Smoking status				
Current smoker	6	216 / 4461	222 / 4812	1.02 (0.85, 1.23)
Ex or never smoker	6	606 / 12419	673 / 13456	0.96 (0.86, 1.07)
		Heterogeneity:		*unadjusted P=0.598, adjusted P=1*
Antihypertensive drug use				
Yes	6	615 / 12730	659 / 13879	1.00 (0.90, 1.12)
No	5	207 / 4161	236 / 4397	0.90 (0.75, 1.09)
		Heterogeneity:		*unadjusted P=0.344, adjusted P=1*

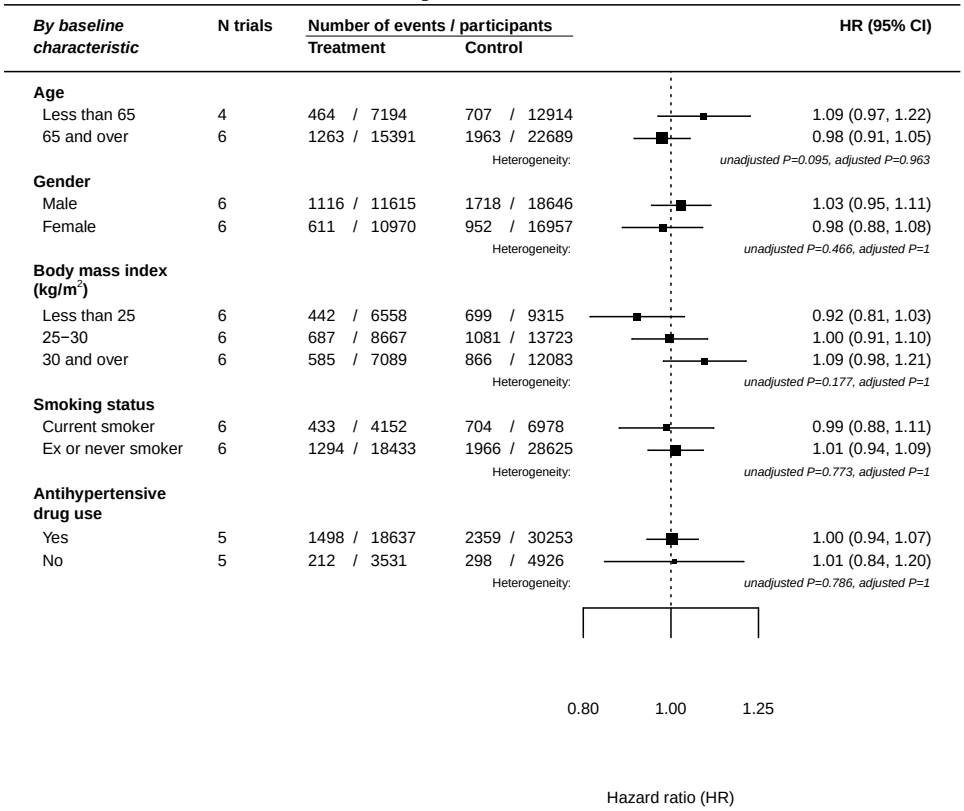


D. CCB vs all other comparators

By baseline characteristic	N trials	Number of events / participants: Treatment	Control	HR (95% CI)
Age				
Less than 65	17	819 / 26623	1428 / 39097	1.05 (0.96, 1.15)
65 and over	19	2189 / 33887	3592 / 51122	1.06 (1.01, 1.13)
		Heterogeneity:		*unadjusted P=0.269, adjusted P=1*
Gender				
Male	19	1897 / 32926	3165 / 48418	1.08 (1.02, 1.15)
Female	19	1111 / 27594	1855 / 41805	1.03 (0.95, 1.11)
		Heterogeneity:		*unadjusted P=0.990, adjusted P=1*
Body mass index (kg/m^2)				
Less than 25	17	674 / 11992	1129 / 18576	1.08 (0.98, 1.19)
25−30	16	1039 / 17305	1896 / 28943	1.04 (0.96, 1.12)
30 and over	16	788 / 12027	1494 / 22941	1.07 (0.98, 1.18)
		Heterogeneity:		*unadjusted P=0.700, adjusted P=1*
Smoking status				
Current smoker	19	755 / 12739	1290 / 18577	1.07 (0.98, 1.18)
Ex or never smoker	19	2249 / 47660	3729 / 71485	1.05 (1.00, 1.11)
		Heterogeneity:		*unadjusted P=0.260, adjusted P=1*
Antihypertensive drug use				
Yes	12	1995 / 28697	3748 / 51275	1.05 (0.99, 1.11)
No	12	317 / 7483	470 / 10969	1.12 (0.96, 1.30)
		Heterogeneity:		*unadjusted P=0.947, adjusted P=1*

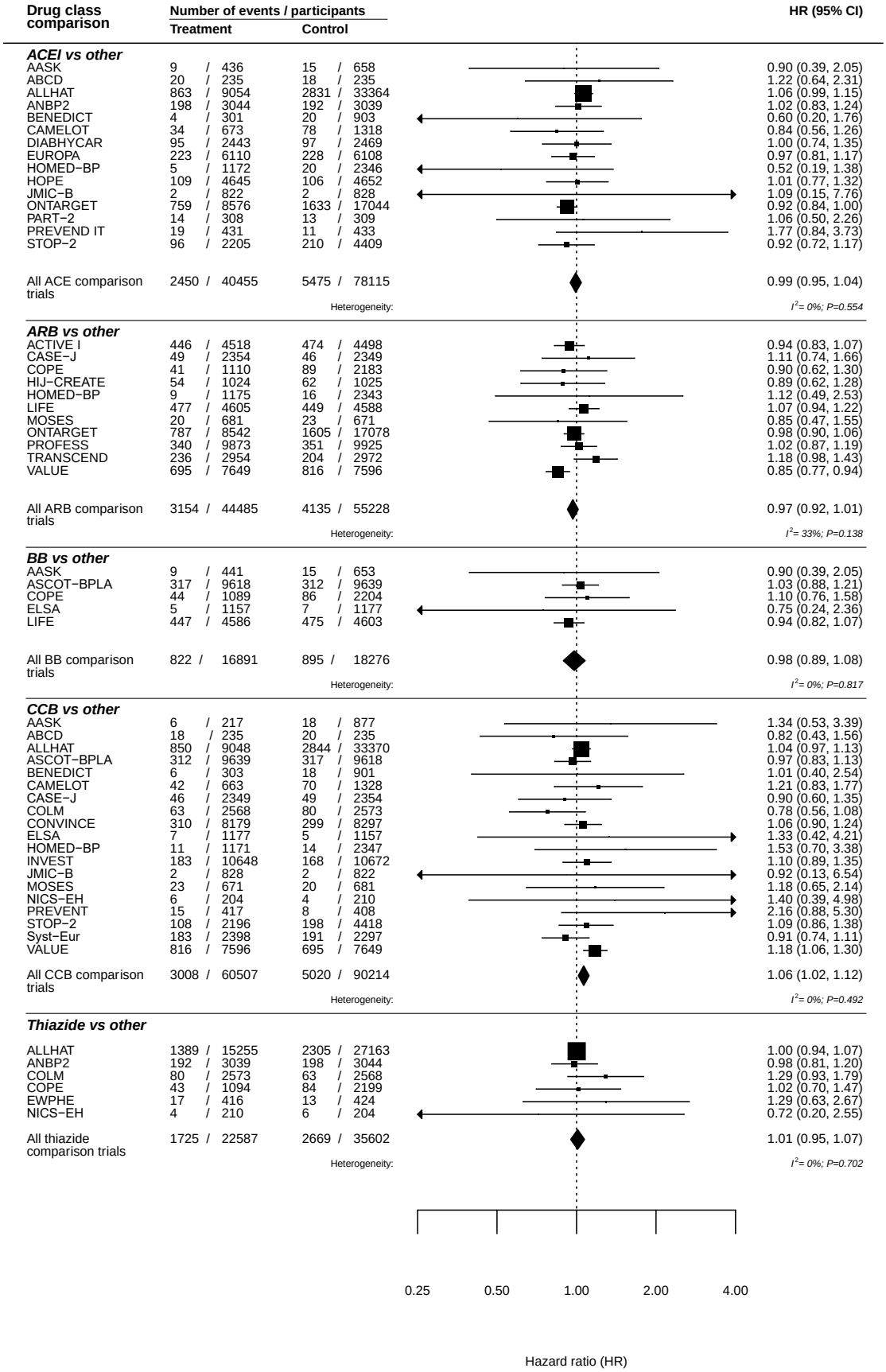


E. Thiazide diuretics vs all other comparators



ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin-II receptor blockers. BB=ß-blockers. CCB=calcium channel blockers. CI=confidence interval. HR=hazard ratio.

Supplementary Figure 4. Two-stage individual participant-level data meta-analysis for any cancer.



ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin-II receptor blockers. BB=ß-blockers. CCB=calcium channel blockers. CI=confidence interval. HR=hazard ratio. Trial name acronyms are described in full in the footnote of **Supplementary Table 3.**

Supplementary tables

Supplementary Table 1. MEDLINE search strategy for BPLTTC.

Search ((((("Hypertension/drug effects"[Mesh] OR "Hypertension/drug therapy"[Mesh]))) AND (("Blood Pressure/drug effects"[Mesh] OR "Blood Pressure/therapy"[Mesh]))) AND ((Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase III[ptyp]) AND Humans[Mesh] AND adult[MeSH]))) AND ((((((((((("Antihypertensive Agents" [Pharmacological Action]) OR "Antihypertensive Agents/therapeutic use"[Mesh])) OR (((("Vasodilator Agents" [Pharmacological Action])) OR ("Vasodilator Agents/therapeutic use"[Mesh] OR "Vasodilator Agents/therapy"[Mesh]))) OR (("Adrenergic alpha-Antagonists/therapeutic use"[Mesh]) OR "Adrenergic alpha-Antagonists" [Pharmacological Action])) OR (("Adrenergic beta-Antagonists" [Pharmacological Action]) OR "Adrenergic beta-Antagonists/therapeutic use"[Mesh])) OR (("Sodium Chloride Symporter Inhibitors" [Pharmacological Action]) OR "Sodium Chloride Symporter Inhibitors/therapeutic use"[Mesh])) OR "Angiotensin-Converting Enzyme Inhibitors/therapeutic use"[Mesh]) OR (("Angiotensin II Type 1 Receptor Blockers" [Pharmacological Action]) OR "Angiotensin II Type 1 Receptor Blockers/therapeutic use"[Mesh])) OR (("Calcium Channel Blockers" [Pharmacological Action]) OR "Calcium Channel Blockers/therapeutic use"[Mesh])) AND ((Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase III[ptyp]) AND Humans[Mesh] AND adult[MeSH])) Filters: Clinical Trial; Controlled Clinical Trial; Randomized Controlled Trial; Clinical Trial, Phase III; Meta-Analysis; Systematic Reviews; Humans; Adult: 19+ years

BPLTTC=Blood Pressure Lowering Treatment Trialists' Collaboration.

Supplementary Table 2. Full list of variables requested from participating trials.

Type of data	Variables
Study-level	Region
	Treatment and comparator groups
	Study period/duration of follow-up
	Randomization method
	Outcome ascertainment
	Early stopping and reasons
	Funding source
Participant-level	
Baseline information	Patient Identifier
	Sex
	Date of birth *or* age at randomization
	Ethnicity
	History of diabetes mellitus
	Currently treated hypertension
	History of chronic kidney disease
	History of cardiovascular disease (coronary heart and cerebrovascular disease)
	History of peripheral vascular disease
	History of atrial fibrillation
	Height
	Weight
	Systolic blood pressure
	Diastolic blood pressure
	Smoking status
	Estimated alcohol intake
	Baseline drug therapy:
	Lipid lowering therapy at baseline
	Antiplatelet or anticoagulant therapy
	Antihypertensives (ACEIs, ARBs, BBs, CCBs, diuretics, α-blockers)
	Randomization blood and urine measurements:
	Haemoglobin concentration
	Fasting blood glucose
	C-reactive protein
	Serum albumin
	Baseline total cholesterol
	Baseline HDL cholesterol
	Serum/plasma creatinine
	Urinary albumin/protein excretion or concentration
	Albuminuria/proteinuria (if quantitative measure for excretion/concentration not available)
Randomization data and scheduled follow-up	Date of randomization
	Randomized treatment allocation code
	Scheduled end-date of trial treatment
	Date of last follow-up
Outcomes (diagnosed after randomization)	Stroke (date, outcome (i.e. fatal/non-fatal), confirmation)
	Myocardial infarction (date, outcome)
	Coronary revascularization (date)
	Heart failure leading to hospitalization or death (date, outcome)
	Need for renal replacement therapy (dialysis or transplant) (date)
	Primary site of first cancer diagnosed after randomization (date, outcome)
	First fracture after randomization (date)
	Study treatment stopped early (date, reason)
	Death (date, cause)
	Diabetes diagnosed after randomization (date)
	Retinopathy diagnosed after randomization (date)
	Dementia diagnosed after randomization (date)
	Peripheral vascular disease diagnosed after randomization (date)

Follow-up measurements (repeated for each follow-up visit)	Visit number (n)
	Date of visit
	Weight
	Systolic blood pressure
	Diastolic blood pressure
	Serum/plasma creatinine
	Urinary albumin/protein excretion or concentration
	Visit number (n)
Safety and less common efficacy outcomes after randomization	Name of serious adverse event(s) recorded
	Date of diagnosis of serious adverse event
	Discontinuation of medication
	Date of discontinuation
	Discontinuation due to adverse event (y/n)
	Date of discontinuation
	Acute kidney injury/renal failure recorded
	Date of acute kidney injury/renal failure
	Atrial fibrillation event recorded
	Date of atrial fibrillation event
	Albuminuria/microalbuminuria (new or worsening) event recorded
	Date of albuminuria/microalbuminuria event
	Name of any other adverse event/outcome reported
	Date of adverse event/outcome

ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin-II receptor blockers. BB=ß-blockers. CCB=calcium channel blockers. HDL=high-density lipoprotein.

Supplementary Table 3. Characteristics of individual trials included in study.

Trial	Country	Recruitment period	Randomisation groups	Number of participants (% women)	Additional (open-label) treatment	Follow-up duration (year)	Explicit exclusion of cancer patients at baseline	Source of cancer outcomes	Adjudication	Level of detail of cancer outcomes provided
AASK [3,4]	USA	Feb 1995 to Sept 1998	All	1094 (39)	Furosemide, doxazosin, clonidine, hydralazine and minoxidil (sequentially)	4.8	No	Routine adverse event	No	Site of cancer diagnosis (lung, colon, breast, prostate, skin, other types)
			Drug class comparison							
			ACEI (Ramipril)	436 (39)						
			CCB (Amlodipine)	217 (39)						
			β-blocker (Metoprolol)	441 (39)						
			BP-lowering intensity comparison							
			More intense BP-lowering	540 (38)						
			Less intense BP-lowering	554 (40)						
ABCD [5–7]	USA	Mar 1991 to May 1993	All	950 (33)	β-blocker (Metoprolol), diuretic (HCTZ), or others but not CCB or ACEI	4.7	Yes (patients with active cancer)	Routine adverse event	No	Cancer diagnosis yes/no (no information on site of cancer)
			Drug class comparison							
			CCB (Nisoldipine)	235 (32)						
			ACEI (Enalapril)	235 (33)						
			BP-lowering intensity comparison							
			More intense BP-lowering	474 (40)						
			Less intense BP-lowering	476 (38)						
ACTIVE I [8]	Multi-country	Jun 2003 to May 2006	All	9016 (39)	None	4.1	No	Routine adverse event	No	Site of cancer diagnosis (lung, colon, breast, prostate, skin, other types)
			ARB (Irbesartan)	4518 (39)						
			Placebo	4498 (39)						
ALLHAT [9,10]	Multi-country	Feb 1994 to Jan 1998	All	42,418 (47)	Atenolol, clonidine or reserpine	4.8	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, colon, breast, prostate, bladder, other)
			Diuretic (Chlorthalidone)	15,255 (47)						
			CCB (Amlodipine)	9048 (47)						
			ACEI (Lisinopril)	9054 (46)						
			α-blocker (Doxazosin)	9061 (46)						
ANBP2 [11]	Australia	April 1995 to Jun 1998	All	6083 (51)	β-blocker, CCB and α-blocker	4.1	No	Pre-specified safety outcome	Yes	ICD-9 codes for site of cancer
			ACEI (Enalapril)	3044 (50)						
			Diuretic (HCTZ)	3039 (52)						
ASCOT-BPLA [12,13]	Multi-country	Feb 1998 to May 2000	All	19,257 (23)	For CCB arm: plus ACEI (Perindopril); For β-blocker arm: plus diuretic (Bendroflumethiazide) and potassium	5.3	No	Routine adverse event	No	Fatal cancer yes/ no (no information on site of cancer)
			CCB (Amlodipine-based)	9639 (23)						
			β-blocker (Atenolol-based)	9618 (23)						

BENEDICT [14,15]	Italy	Around 2000 to 2003	All	1204 (47)	Diuretic (HCTZ or furosemide), then doxazosin, prazosin, clonidine, methyldopa or β-blocker, then minoxidil, or CCB	3.1	Yes	Routine adverse event	No	Site of cancer diagnosis (lung, colon, breast, prostate, other)
			ACEI (Trandolapril)	301 (48)						
			CCB (Verapamil)	303 (46)						
			ACEI (Trandolapril) and CCB (Verapamil)	300 (45)						
			Placebo	300 (50)						
CAMELOT [16]	Multi-country	Apr 1999 to Apr 2002	All	1991 (26)	Allowed to continue β-blocker, α-blocker, diuretic	1.6	No	Routine adverse event	No	Site of cancer diagnosis (text description)
			CCB (Amlodipine)	663 (24)						
			ACEI (Enalapril)	673 (28)						
			Placebo	655 (27)						
CASE-J [17,18]	Japan	Sep 2001 to Jan 2003	All	4703 (45)	Allowed to continue background treatment (diuretic, α-blocker, β-blocker); Can add other except ARB, CCB, ACEI	3.1	Yes (patients with history of malignant tumour (confirmed or suspected) within 5 years of enrolment)	Routine adverse event	No	Site of cancer diagnosis (text description)
			ARB (Candesartan)	2354 (46)						
			CCB (Amlodipine)	2349 (43)						
COLM [19,20]	Japan	Apr 2007 to Sep 2008	All	5141 (48)	β-blocker, α-blocker, ACEI	3.0	Yes (patients with malignant tumours)	Routine adverse event	Yes	Cancer diagnosis yes/no (no information on site of cancer)
			CCB (Amlodipine or azelnidipine) and ARB (Olmesartan)	2568 (48)						
			Diuretic (HCTZ, Trichlormethiazide, or indapamide) and ARB (Olmesartan)	2573 (48)						
CONVINCE [21,22]	Multi-country	Sep 1996 to Dec 1998	All	16476 (55)	Additional treatment if necessary	2.8	Yes (disease likely to cause death within 5 years of enrolment, e.g. untreated malignancy)	Pre-specified safety outcome	Yes	Cancer diagnosis yes/no (no information on site of cancer)
			CCB (Verapamil)	8179 (56)						
			β-blocker (Atenolol) or diuretic (HCTZ)	8297 (56)						
COPE [23]	Japan	Jun 2003 to Nov 2006	All	3293 (49)	Additional treatment if necessary	3.6	Yes (history of malignancy 5 years prior to study entry)	Routine adverse event	No	MedDRA codes for site of cancer
			ARB/CCB (ARB/Benidipine)	1110 (49)						
			β-blocker/CCB (β-blocker/Benidipine)	1089 (49)						
			Diuretic/CCB (Thiazide/Benidipine)	1094 (49)						
DIABHYCAR [24,25]	The Nether-lands	Oct 1997 to Jun 2000	All	4912 (30)	Usual treatment	3.9	Yes (patients with poor life expectancy, e.g. due to cancer)	Routine adverse event	No	Site of cancer diagnosis (text description)
			ACEI (Ramipril)	2443 (30)						
			Placebo	2469 (30)						

ELSA [26,27]	Multi-country	Possibly between 1994 to 1998	All	2334 (45)	Diuretic (HCTZ)	3.4	No	Routine adverse event	No	ICD-9 codes for site of fatal cancer
			CCB (Lacidipine)	1177 (46)						
			β-blocker (Atenolol)	1157 (45)						
EUROPA [28,29]	Multi-country (Europe)	Oct 1997 to Jun 2000	All	12,218 (15)	None specified	4.2	No	Routine adverse event	No	Site of cancer diagnosis (text description)
			ACEI (Perindopril)	6110 (14)						
			Placebo	6108 (15)						
EWPHE [30,31]	Multi-country	From 1972	All	840 (70)	Methyldopa	4.6	Yes (malignancy)	Routine adverse event	No	ICD-8 codes for site of cancer
			Diuretic (HCTZ or triamterene)	416 (69)						
			Placebo	424 (71)						
HIJ-CREATE [32]	Japan	Jun 2001 to Apr 2004	All	2049 (20)	None	4.0	Yes (known malignant neoplasm)	Routine adverse event	Yes	Site of cancer diagnosis (text description)
			ARB (Candesartan)	1024 (18)						
			Non-ARB (including ACEI)	1025 (21)						
HOMED-BP [33]	Japan	May 2001 to Oct 2009	All	3518 (50)	Diuretic; β-blocker; then other drugs (avoid reaching BP <110/65 mmHg)	4.9	No	Routine adverse event	No	ICD-10 codes for site of fatal cancer
			Drug class comparison							
			ACEI	1172 (50)						
			ARB	1175 (50)						
			CCB	1171 (50)						
			BP-lowering intensity comparison							
			More intense BP-lowering	1759 (50)						
			Less intense BP-lowering	1759 (50)						
HOPE [34]	Multi-country	Dec 1993 to Jun 1995	All	9297 (27)	None specified	4.5	No	Pre-specified safety outcome	Yes	Cancer diagnosis yes/no (no information on site of cancer)
			ACEI (Ramipril)	4656 (28)						
			Placebo	4652 (26)						
INVEST [35]	Multi-country	From Jan 1998	All	21,230 (52)	ACEI (Trandolapril) and/or diuretic (HCTZ)	2.8	Yes (but patients with history of skin, prostate and other cancer with long survival expectancy were not necessarily excluded)	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, colon, breast, prostate, bladder, other)
			CCB (Verapamil)	10,648 (52)						
			Non-CCB (Atenolol)	10,672 (52)						
JMIC-B [36]	Japan	Jan 1994 to Jul 1997	All	1650 (31)	α-blocker (doxazosin, bunazosin or prazosin); nitrates or β-blocker for angina if needed	2.3	No	Pre-specified safety outcome	Yes	ICD-9 codes for site of fatal cancer
			CCB (Nifedipine)	828 (32)						
			ACEI (Enalapril, imidapril or lisinopril)	822 (30)						
LIFE [37,38]	Multi-country	June 1995 to May 1997	All	9193 (54)	Diuretic (HCTZ) and other except ACEI, ARB and β-blocker	4.9	No	Pre-specified safety outcome	No	Site of cancer diagnosis (text description)
			ARB (Losartan)	4605 (54)						
			β-blocker (Atenolol)	4588 (54)						

MOSES [39]	Germany and Austria	Oct 1998 to Feb 2002	All	1352 (46)	Diuretic, β-blocker, α-blocker or centrally-acting drugs; ACEI, ARB or CCB only if clinically necessary	3.3	No	Routine adverse event	Yes	ICD-10 codes for site of cancer
			ARB (Eprosartan)	681 (46)						
			CCB (Nitrendipine)	671 (45)						
NICS-EH [40]	Japan	Oct 1989 to Apr 1992	All	414 (67)	Titration but no additional treatment	3.2	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, bowel, breast, other)
			CCB (Nicardipine)	204 (60)						
			Diuretic (Trichlormethiazide)	210 (74)						
ONTARGET [41,42]	Multi-country	Jan 2002 to Aug 2003	All	25,620 (27)	None	4.8	No	Pre-specified safety outcome	No	Site of cancer diagnosis (lung, colon, breast, prostate, other)
			ACEI (Ramipril)	8576 (27)						
			ARB (Telmisartan)	8542 (26)						
			ACEI (Ramipril) and ARB (Telmisartan)	8502 (26)						
PART-2 [43]	New Zealand	Not specified; Publicat-ion in 2000	All	617 (18)	None	4.6	No	Routine adverse event	No	Site of cancer diagnosis (lung, colon, breast, other)
			ACEI (Ramipril)	308 (18)						
			Placebo	309 (18)						
PREVEND IT [44]	The Nether-lands	Apr 1998 to Jun 1999	All	864 (35)	None	3.8	No	Routine adverse event	No	ICD-10 codes for site of fatal cancer
			ACEI (Fosinopril)	433 (36)						
			Placebo	431 (34)						
PREVENT [45,46]	USA and Canada	Nov 1992 to Sep 1994	All	825 (20)	None	3.0	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (text description)
			CCB (Amlodipine)	417 (20)						
			Placebo	408 (20)						
PROFESS [47,48]	Multi-country	Sep 2003 to Jul 2006	All	19,798 (36)	At physician's discretion to control blood pressure: diuretic, then β-blocker or CCB, then ACEI but not ARB	2.5	Yes	Pre-specified safety outcome	Yes	Site of cancer diagnosis (text description)
			ARB (Telmisartan)	9873 (35)						
			Placebo	9925(36)						
STOP Hyper-tension-2 [49]	Sweden	Sep 1992 to Dec 1994 1987 to 1991	All	6614 (67)		4.5	No	Routine adverse event	No	Site of cancer diagnosis (text description)
			Conventional: β-blocker (Atenolol or metoprolol), diuretic (HCTZ) or both	2213 (68)						
			ACEI (Enalapril or lisinopril	2205 (66)						
			CCB (Felodipine or isradipine)	2196 (66)						
Syst-Eur [50]	Multi-country	Dec 1988 to Jan 1997	All	4695 (67)	ACEI (Enalapril) and/or diuretic (HCTZ)	2.6	No	Pre-specified safety outcome	Yes	Site of cancer diagnosis (lung, colon, breast, prostate, other)
			CCB (Nitrendipine)	2398 (67)						
			Placebo	2297 (66)						

TRANSCEND [41,51]	Multi-country	Nov 2001 to May 2004	All ARB (Telmisartan) Placebo	5926 (43) 2954 (43) 2972 (43)	None	4.9	No	Pre-specified safety outcome	No	Site of cancer diagnosis (lung, colon, breast, prostate, other)
VALUE [52,53]	Multi-country	Sept 1997 to Dec 1999	All ARB (Valsartan-based) CCB (Amlodipine-based)	15,245 (42) 7649 (42) 7596 (42)	Diuretic (HCTZ, then other antihypertensive drugs except ARB (ACEI or CCB if clinically indicated other than for hypertension)	4.2	No	Routine adverse event	No	MedDRA codes for site of cancer

AASK=African American Study of Kidney Disease and Hypertension. ABCD=Appropriate Blood Pressure Control in Diabetes. ACEI=angiotensin-converting enzyme inhibitors. ACTIVE I=Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events. ALLHAT=Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial. ANBP2=Second Australian National Blood Pressure Study. ARB=angiotensin-II receptor blockers. ASCOT-BPLA=Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm. BB=ß-blockers. BENEDICT=BErgamo NEphrologic DIabetes Complications Trial. CAMELOT=Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis. CASE-J=Candesartan Antihypertensive Survival Evaluation in Japan Trial. CCB=calcium channel blockers. COLM=Combination of OLMesartan study. CONVINCE=Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints trial. COPE=Combination Therapy of Hypertension to Prevent Cardiovascular Events. DIABHYCAR=Noninsulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril. ELSA=European Lacidipine Study on Atherosclerosis. EUROPA=EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease. EWPHE=European Working Party on High Blood Pressure in the Elderly. HCTZ=hydrochlorothiazide. HIJ-CREATE=Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease. HOMED-BP=Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure. HOPE=Heart Outcomes Prevention Evaluation. ICD=International Classification of Diseases. INVEST=International Verapamil-Trandolapril Study. JMIC-B=Japan Multicenter Investigation for Cardiovascular Diseases-B. LIFE=Losartan Intervention For Endpoint reduction. MedDRA=Medical Dictionary for Regulatory Activities. MOSES=Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention. NICS-EH=National Intervention Cooperative Study in Elderly Hypertensives. ONTARGET=Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial. PART-2=Prevention of Atherosclerosis with Ramipril Trial. PREVEND IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial. PREVENT=Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial. PROFESS=Prevention Regimen for Effectively Avoiding Second Strokes. STOP Hypertension 2=Swedish Trial in Old Patients with Hypertension-2. Syst-Eur=Systolic Hypertension in Europe. TRANSCEND=Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease. VALUE=Valsartan Antihypertensive Long-term Use Evaluation.

Supplementary Table 4. List of trials and interventions assigned to the trial arms.

Trial	Active group	Control group(s)
ACEI vs other comparisons (15 trials)		
AASK [3,4]	ACEI	ß-blocker, CCB
ABCD [5–7]	ACEI	CCB
ALLHAT [9,10]	ACEI	CCB, thiazide, α-blocker
ANBP2 [11]	ACEI	Thiazide
BENEDICT [14,15]	ACEI	ACEI/CCB, CCB, placebo
CAMELOT [16]	ACEI	CCB, placebo
DIABHYCAR [24,25]	ACEI	Placebo
EUROPA [28,29]	ACEI	Placebo
HOMED-BP [33]	ACEI	ARB, CCB
HOPE [34]	ACEI	Placebo
JMIC-B [36]	ACEI	CCB
ONTARGET [41,42]	ACEI	ACEI/ARB, ARB
PART-2 [43]	ACEI	Placebo
PREVEND IT [44]	ACEI	Placebo
STOP Hypertension-2 [49]	ACEI	ß-blocker and/or thiazide, CCB
ARB vs other comparisons (11 trials)		
ACTIVE I [8]	ARB	Placebo
CASE-J [17,18]	ARB	CCB
COPE [23]	ARB (/CCB)	CCB/ß-blocker, CCB/thiazide
HIJ-CREATE [32]	ARB	Non-ARB
HOMED-BP [33]	ARB	ACEI, CCB
LIFE [37,38]	ARB	ß-blocker
MOSES [39]	ARB	CCB
ONTARGET [41,42]	ARB	ACEI, ACEI/ARB
PROFESS [47,48]	ARB	Placebo
TRANSCEND [41,51]	ARB	Placebo
VALUE [52,53]	ARB-based	CCB-based
BB vs other comparisons (5 trials)		
AASK [3,4]	ß-blocker	ACEI, CCB
ASCOT-BPLA [12,13]	ß-blocker-based	CCB-based
COPE [23]	ß-blocker (/CCB)	CCB/ARB, CCB/thiazide
ELSA [26,27]	ß-blocker	CCB
LIFE [37,38]	ß-blocker	ARB
CCB vs other comparisons (19 trials)		
AASK [3,4]	CCB	ACEI, ß-blocker
ABCD [5–7]	CCB	ACEI
ALLHAT [9,10]	CCB	ACEI, thiazide, α-blocker
ASCOT-BPLA [12,13]	CCB-based	ß-blocker-based
BENEDICT [14,15]	CCB	ACEI, ACEI/CCB, placebo
CAMELOT [16]	CCB	ACEI, placebo
CASE-J [17,18]	CCB	ARB
COLM [19,20]	CCB (/ARB)	ARB/thiazide
CONVINCE [21,22]	CCB	ß-blocker/thiazide
ELSA [26,27]	CCB	ß-blocker
HOMED-BP [33]	CCB	ACEI, ARB
INVEST [35]	CCB	Non-CCB
JMIC-B [36]	CCB	ACEI
MOSES [39]	CCB	ARB
NICS-EH [40]	CCB	Thiazide
PREVENT [45,46]	CCB	Placebo
STOP Hypertension-2 [49]	CCB	ACEI, ß-blocker and/or thiazide
Syst-Eur [50]	CCB	Placebo
VALUE [52,53]	CCB-based	ARB-based

Thiazide diuretic vs other comparisons (6 trials)		
ALLHAT [9,10]	Thiazide	ACEI, CCB, α-blocker
ANBP2 [11]	Thiazide	ACEI
COLM [19,20]	Thiazide (/ARB)	ARB/CCB
COPE [23]	Thiazide (/CCB)	CCB/ARB and CCB/ß-blocker
EWPHE [30,31]	Thiazide	Placebo
NICS-EH [40]	Thiazide	CCB

ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin-II receptor blockers. BB=ß-blockers. CCB=calcium channel blockers. Trial name acronyms are described in full in the footnote of **Supplementary Table 3.**

Supplementary Table 5. Risk of bias assessment for individual trials.

Trial	Risk of bias arising from randomization	Risk of bias due to effect of assignment to intervention	Risk of bias due to missing outcome data	Risk of bias due to measurement of outcome	Risk of bias due to reporting of result	Overall risk of bias
AASK [3,4]	Low	Low	Low	Low	Low	Low
ABCD [5–7]	Low	Low	Some	Low	Low	Low
ACTIVE I [8]	Low	Low	Some	Low	Low	Low
ALLHAT [9,10]	Low	Low	Low	Low	Low	Low
ANBP2 [11]	Low	Some	Some	Low	Low	Some
ASCOT-BPLA [12,13]	Low	Some	Low	Low	Low	Low
BENEDICT [14,15]	Low	Low	Low	Low	Low	Low
CAMELOT [16]	Low	Low	Low	Low	Low	Low
CASE-J [17,18]	Low	Some	Low	Low	Low	Low
COLM [19,20]	Low	Some	Low	Low	Low	Low
CONVINCE [21,22]	Low	Low	Low	Low	Low	Low
COPE [23]	Low	Some	Some	Low	Low	Some
DIABHYCAR [24,25]	Low	Low	Low	Low	Low	Low
ELSA [26,27]	Low	Low	Low	Low	Low	Low
EUROPA [28,29]	Low	Low	Low	Low	Low	Low
EWPHE [30,31]	Low	Low	Low	Low	Low	Low
HIJ-CREATE [32]	Low	Some	Low	Low	Low	Low
HOMED-BP [33]	Low	Some	Some	Low	Low	Some
HOPE [34]	Low	Some	Low	Low	Low	Low
INVEST [35]	Low	Some	Some	Low	Low	Some
JMIC-B [36]	Low	Some	Low	Low	Low	Low
LIFE [37,38]	Low	Low	Low	Low	Low	Low
MOSES [39]	Low	Some	Low	Low	Low	Low
NICS-EH [40]	Low	Some	Low	Low	Low	Low
ONTARGET [41,42]	Low	Some	Low	Low	Low	Low
PART-2 [43]	Low	Low	Low	Low	Low	Low
PREVEND IT [44]	Low	Low	Some	Low	Low	Low
PREVENT [45,46]	Low	Low	Low	Low	Low	Low
PROFESS [47,48]	Low	Low	Low	Low	Low	Low
STOP Hypertension-2 [49]	Low	Some	Low	Low	Low	Low
Syst-Eur [50]	Low	Some	Low	Low	Low	Low
TRANSCEND [41,51]	Low	Low	Low	Low	Low	Low
VALUE [52,53]	Low	Low	Low	Low	Low	Low

Trial name acronyms are described in full in the footnote of **Supplementary Table 3.**

Supplementary Table 6. Characteristics of participants at baseline for each trial.

Trial	Participants, N (% women)	Age (years), mean (SD)	Body mass index (kg/m^2), mean (SD)	% Current smokers (N)
AASK [3,4]	1094 (39)	54 (11)	30.6 (6.6)	29 (321)
ABCD [5–7]	470 (39)	58 (8)	31.7 (5.7)	14 (128)
ACTIVE I [8]	9016 (39)	70 (10)	29.1 (5.8)	8 (698)
ALLHAT [9,10]	42,418 (47)	67 (8)	29.6 (5.9)	22 (9269)
ANBP2 [11]	6083 (51)	73 (5)	27.1 (4.2)	7 (431)
ASCOT-BPLA [12,13]	19,257 (23)	63 (9)	28.7 (4.6)	33 (6277)
BENEDICT [14,15]	1204 (47)	62 (8)	29.1 (4.7)	12 (146)
CAMELOT [16]	1991 (26)	58 (10)	29.8 (5.3)	26 (528)
CASE-J [17,18]	4703 (45)	64 (11)	24.5 (3.7)	22 (1025)
COLM [19,20]	5141 (48)	74 (5)	24.3 (3.4)	11 (551)
CONVINCE [21,22]	16,476 (56)	66 (7)	-	23 (3795)
COPE [23]	3293 (49)	64 (11)	24.5 (3.4)	21 (700)
DIABHYCAR [24,25]	4912 (30)	65 (8)	29.2 (4.6)	15 (756)
ELSA [26,27]	2334 (46)	57 (7)	27.2 (3.8)	20 (478)
EUROPA [28,29]	12,218 (15)	61 (9)	27.4 (3.5)	15 (1862)
EWPHE [30,31]	840 (70)	71 (8)	26.4 (4.5)	17 (143)
HIJ-CREATE [32]	2049 (20)	65 (9)	24.6 (3)	25 (509)
HOMED-BP [33]	3518 (50)	60 (10)	24.4 (3.5)	21 (743)
HOPE [34]	9297 (27)	66 (7)	27.7 (4.4)	14 (1319)
INVEST [35]	21,320 (51)	66 (10)	29.2 (7.1)	12 (2809)
JMIC-B [36]	1650 (31)	65 (85)	24 (2.9)	34 (563)
LIFE [37,38]	9193 (54)	67 (7)	28 (4.8)	16 (1499)
MOSES [39]	1352 (46)	68 (10)	27.5 (4.3)	18 (247)
NICS-EH [40]	414 (67)	70 (7)	23.4 (3.1)	9 (38)
ONTARGET [41,42]	25,620 (27)	67 (7)	28.2 (4.8)	13 (3225)
PART-2 [43]	617 (18)	60 (8)	26.8 (3.6)	16 (100)
PREVEND IT [44]	864 (35)	51 (12)	26.4 (4.4)	40 (345)
PREVENT [45,46]	825 (20)	57 (10)	28 (4.8)	25 (204)
PROFESS [47,48]	19,798 (36)	66 (8)	26.8 (5)	21 (4231)
STOP Hypertension-2 [49]	6614 (67)	76 (4)	26.7 (4)	9 (594)
Syst-Eur [50]	4695 (67)	70 (7)	27 (4.1)	7 (343)
TRANSCEND [41,51]	5926 (43)	68 (7)	28.2 (4.8)	10 (582)
VALUE [52,53]	15,245 (42)	67 (8)	28.6 (5)	24 (3664)

SD=standard deviation. Trial name acronyms are described in full in the footnote of **Supplementary Table 3.**

Supplementary Table 7. Effects of antihypertensive drug classes on the risk of any cancer and cancer death, based on direct comparison and network meta-analysis estimates.

	Any cancer		Cancer death	
	Direct comparison	**Network estimate**	**Direct comparison**	**Network estimate**
Placebo	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
ACEI	1.00 (0.88 – 1.13)	1.00 (0.93 – 1.09)	1.09 (0.85 – 1.40)	1.02 (0.86 – 1.22)
ARB	1.00 (0.92 – 1.09)	0.99 (0.92 – 1.06)	0.98 (0.81 – 1.19)	0.98 (0.83 – 1.14)
BB		0.99 (0.89 – 1.11)		1.00 (0.80 – 1.24)
CCB	0.98 (0.82 – 1.17)	1.04 (0.96 – 1.13)	0.69 (0.39 – 1.21)	0.97 (0.80 – 1.18)
Thiazide	1.29 (0.63 – 2.65)	1.00 (0.90 – 1.10)		1.05 (0.86 – 1.29)
ACEI	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
ARB	1.05 (0.95 – 1.16)	0.99 (0.92 – 1.05)	0.99 (0.82 – 1.20)	0.95 (0.82 – 1.10)
BB	1.00 (0.40 – 2.50)	0.99 (0.89 – 1.09)	0.88 (0.32 – 2.42)	0.97 (0.82 – 1.16)
CCB	1.01 (0.93 – 1.10)	1.04 (0.97 – 1.11)	0.96 (0.83 – 1.12)	0.95 (0.83 – 1.09)
Thiazide	0.95 (0.88 – 1.03)	0.99 (0.92 – 1.07)	1.03 (0.90 – 1.16)	1.02 (0.90 – 1.16)
ARB	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
BB	0.95 (0.84 – 1.08)	1.00 (0.91 – 1.10)	1.04 (0.81 – 1.35)	1.02 (0.85 – 1.22)
CCB	1.16 (1.06 – 1.28)	1.05 (0.99 – 1.12)	1.37 (0.67 – 2.78)	1.00 (0.84 – 1.18)
Thiazide	1.10 (0.71 – 1.69)	1.01 (0.92 – 1.10)		1.08 (0.90 – 1.29)
BB	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
CCB	1.01 (0.89 – 1.14)	1.05 (0.96 – 1.15)	0.98 (0.84 – 1.15)	0.98 (0.85 – 1.12)
Thiazide	0.96 (0.63 – 1.47)	1.01 (0.90 – 1.13)		1.05 (0.88 – 1.26)
CCB	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Thiazide	0.99 (0.90 – 1.08)	0.96 (0.89 – 1.03)	1.07 (0.93 – 1.23)	1.08 (0.94 – 1.23)

ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin-II receptor blockers. BB=ß-blockers. CCB=calcium channel blockers.

Supplementary Table 8. Effects of antihypertensive drug classes compared against all other comparators on any cancer stratified by explicit exclusion of cancer patients at baseline.

	Exclusion of cancer patients at baseline			**No explicit exclusion of cancer patients at baseline**			
	N trials	N events (treatment/ comparison)	HR (95% CI)	N trials	N events (treatment/ comparison)	HR (95% CI)	Heterogeneity
ACEI	3	119 / 135	0.99 (0.76 – 1.28)	12	2331 / 5340	0.99 (0.94 – 1.04)	P = 0.99
ARB	4	484 / 548	0.98 (0.86 – 1.11)	7	2670 / 3587	0.96 (0.91 – 1.01)	P = 0.78
BB	1	44 / 86	1.09 (0.76 – 1.57)	4	778 / 809	0.97 (0.88 – 1.07)	P = 0.55
CCB	6	626 / 634	1.02 (0.91 – 1.14)	13	2382 / 4386	1.07 (1.02 – 1.13)	P = 0.40
Thiazide	3	142 / 161	1.18 (0.94 – 1.48)	3	1585 / 2509	0.99 (0.93 – 1.06)	P = 0.17

ACEI=angiotensin-converting enzyme inhibitors. ARB=angiotensin-II receptor blockers. BB=ß-blockers. CCB=calcium channel blockers. CI=confidence interval. HR=hazard ratio.

Collaborating Trialists

A Adler (UKPDS [54] [UK Prospective Diabetes Study]),
L Agodoa (AASK [3,4] [African-American Study of Kidney Disease and Hypertension]),
A Algra (Dutch TIA Trial [55] [Dutch Transient Ischemic Attack Trial]),
F W Asselbergs (PREVEND IT [44] [Prevention of Renal and Vascular End- stage Disease Intervention Trial]),
N Beckett (HYVET [56] [Hypertension in the Very Elderly Trial]),
E Berge (deceased) (VALUE [52,53] trial [Valsartan Antihypertensive Long-term Use Evaluation trial]),
H Black (CONVINCE [21,22] [Controlled Onset Verapamil Investigation of Cardiovascular End Points]),
F P J Brouwers (PREVEND IT [44]),
M Brown (INSIGHT [57] [International Nifedipine GITS Study: Intervention as a Goal in Hypertension]),
C J Bulpitt (EWPHE [30,31] [European Working Party on High Blood Pressure in the Elderly], HYVET [56]),
B Byington (PREVENT [45,46] [Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial]),
J Chalmers (ADVANCE [58] [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], PROGRESS [59] [Perindopril protection against recurrent stroke]),
J Cutler (ALLHAT [9,10] [Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial]),
B R Davis (ALLHAT [9,10]),
R B Devereaux (LIFE [37,38] [Losartan Intervention For Endpoint reduction in hypertension]),
J Dwyer (IDNT [60] [Irbesartan Diabetic Nephropathy Trial]),
R Estacio (ABCD [5–7] [Appropriate Blood Pressure Control in Diabetes]),
R Fagard (Syst-Eur [50] [SYSTolic Hypertension in EURope]),
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S E Kjeldsen (VALUE, [52,53] LIFE [37,38]),
J Kostis (SHEP [62] [Systolic Hypertension in the Elderly Program]),
K Kuramoto (NICS-EH [40] [National Intervention Cooperative Study in Elderly Hypertensives]),
J Lanke (STOP Hypertension-2 [49] [Swedish Trial in Old Patients with Hypertension-2], NORDIL [63] [Nordic Diltiazem]),
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L H Lindholm (CAPPP [49] [Captopril Prevention Project], STOP Hypertension-2,[49] NORDIL [63]),
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S MacMahon (ADVANCE [58]),
M Matsuzaki (COPE [23] [The Combination Therapy of Hypertension to Prevent Cardiovascular Events]),
M H Mehlum (VALUE [52,53]),
S Nissen (CAMELOT [16] [Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis]),
H Ogawa (HIJ-CREATE [32] [Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Heart Disease]),
T Ogihara (CASE-J,[17,18] COLM [19,20] [Combinations of OLMesartan], COPE [23])
T Ohkubo (HOMED-BP [33]),
C Palmer (INSIGHT [57]),
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BPLTTC Research Protocol

Project: Cancer in BPLTTC
Date: 28 Aug 2019
Version: 082019_05

Protocol title:
Effects of antihypertensive use on the risk of cancer, stratified by drug class

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Background

Hypertension is one of the most prevalent chronic conditions, affecting over one billion people globally (1). The prevalence and incidence of hypertension is increasing further due to population ageing and growth, as well as an increase in the prevalence of cardiometabolic risk factors, including high BMI and lack of physical activity. Hypertension is an important risk factor for cardiovascular disease, therefore, the World Health Organisation has pledged to reduce the prevalence of hypertension by 25% between 2010 and 2025. Antihypertensive medication is an important tool for controlling blood pressure, and although less than one in five hypertensive individuals have their blood pressure controlled, millions of individuals are prescribed antihypertensive drugs globally. While the evidence for the benefits of antihypertensive medication in the reduction of cardiovascular disease is well-established (2), there have been some concerns about possible unintended consequences in the use of these drugs, including increasing the risk of developing cancer (3–6). In the absence of any evidence for an association between blood pressure and cancer risk (7), it seems unlikely that blood pressure reduction per se increases the risk of cancer. However, several hypotheses have been posited linking the pathways of specific drug classes to cancer, independently of a change in blood pressure. For example, the blockade of angiotensin II receptors by angiotensin II receptor blockers (ARBs) has been implicated in increased cell proliferation, angiogenesis and tumour progression (8). Additionally, several antihypertensive drugs across different classes, particularly thiazide diuretics, have photosensitising properties that could increase susceptibility to skin cancer (9). Nevertheless, the evidence for an increased risk of cancer overall or by specific type with the use of different antihypertensive classes has been inconsistent and even conflicting. Meta-analyses of observational studies have suggested that ARBs are not associated with skin (5), prostate (10) or breast cancer (11). Conflicting meta-analyses of observational studies have been reported, with some suggesting that thiazide diuretics are associated with an increased risk of skin cancer (4,5) but others suggesting there is no association (6). Calcium channel blockers (CCBs) and beta-blockers have also been linked to an increased risk of skin cancer (6) and there is some evidence that angiotensin-converting-enzyme inhibitors (ACEis) have a protective effect on breast (11) and skin cancer (5). However, observational studies suffer from inherent biases and residual confounding. Evidence from a meta-analysis of nine randomised controlled trials (RCTs) suggested that participants using ARBs had an increased risk of cancer compared to control groups (3), but two subsequent meta-analyses of RCTs did not find any association between ARBs and cancer risk (12,13). While one meta-analysis of RCTs did not find a link between any drug class and the incidence of cancer overall (13), it could not rule out an increased risk of cancer overall with the use of ACEis in combination with ARBs; this meta-analysis also did not investigate specifically the association between thiazide diuretics and skin cancer risk. Findings from existing trials and their meta-analyses are currently limited as it is possible that such investigations lacked statistical power to investigate cancer incidence due to small numbers of events.

The third cycle of the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) provides the largest individual patient-level data (IPD) on blood pressure-lowering trials currently available. Cancer outcomes were requested from all trials when invited to join the collaboration, providing a large number of cancer events that were not published and therefore not available for most aggregate patient-data level meta-analyses. The availability of IPD also offers an opportunity to investigate the effect of antihypertensive drug classes on cancer risk across a number of important patient groups.

Objectives

In this proposed IPD meta-analysis, we aim to investigate the effect of use of specific antihypertensive drug classes on the risk of cancer. More specifically, we aim to:

1) Investigate the effect of each antihypertensive drug class (ACEis, ARBs, beta-blockers, CCBs and diuretics) on the risk of any cancer and cancer mortality
2) Investigate the effect of specific antihypertensive drug classes on specific cancer types (colon, lung, breast, prostate, skin cancers), particularly where associations have been identified in the literature, depending on power:
    a. ARBs and all common cancer types
    b. Diuretics and skin cancers
    c. CCBs and skin cancers
    d. Beta-blockers and skin cancers
    e. ACEis and breast and skin cancers
3) Investigate the effect of antihypertensive drug classes on the risk of developing cancer in patient subgroups, defined by age at baseline and sex-specific analyses for breast and prostate cancer, as well as other cancer types depending on statistical power

Methods

Study design
This study is an IPD meta-analysis of blood pressure-lowering trials which examines the effects of antihypertensive drug classes on the incidence of cancer.

Eligibility criteria
All trials that met criteria described previously and have contributed IPD to the collaboration will be considered (14). The search criteria was extended to include the period between 1st June 2018 and 1st September 2019. Eligible trials are those that have provided data on cancer outcomes and have a study design that compares at least one drug class (or drug class combination) with a control group (Appendix table).

Study population
All participants from the eligible trials will be included in the analysis.

Interventions
In this meta-analysis, the intervention is pharmacologic lowering of blood pressure using various antihypertensive drug classes. Both placebo-controlled trials and trials of drug class (or drug class combination) comparisons are included.

Outcome variables
The primary outcome is any cancer event, defined as the first cancer event diagnosed after randomisation in participants. These cancer events include those pre-specified as outcomes as well as those reported as adverse events in each trial. Some trials reported both non-fatal and fatal cancer events while others only reported cancer mortality. Cancer events were reported using ICD codes, MedDRA classifications, by cancer grouping or as any cancer or cancer death. The primary outcome comprises first cancer event recorded through at least one of these methods. The secondary outcomes comprise cancer mortality and cancer incidence by major cancer grouping (lung, prostate, breast, colon, skin, other). The type of outcome data provided by each trial will be described (illustrative table 2).

Comparison groups
Analyses will be conducted for comparisons between each antihypertensive drug class (ACEis, ARBs, beta-blockers, CCBs and diuretics) and all other comparator groups, including placebo, standard treatments or other drug classes (or drug class combinations). We will also conduct separate analyses on placebo-controlled trials for drug classes where we have sufficient data.

In the stratified analyses according to patient subgroups, we will categorise patients according to:

1. Age (<60, 60 to 69, 70 to 79 and ≥80 years)
2. Sex (men and women)
3. Use of blood pressure-lowering treatment at baseline (yes vs no) [this could be either a pre-specified subgroup or part of sensitivity analyses – might depend on numbers]
4. Smoking status (current smokers and past or never smokers)
5. BMI (normal weight: 18.5 to 25kg/m^2 and overweight/obese: >25kg/m^2)

Age categories may be combined to ensure that there are sufficient numbers of patients within each of the category.

Sample size considerations
The exact numbers of cancer events in each comparison group are not known at this stage, therefore we estimate the number of cancer events required to achieve 80% power for a range of effect sizes based on published cancer data for individual trials included in the analysis (Table 1). The R package 'powerSurvEpi' was used for the sample size estimations.

The proportions of participants with cancer events in the two largest trials for ACEi *vs* other (ALLHAT and ONTARGET) range from 7.7% to 9.1% (13). If the number of events in our dataset is within this range we expect to have enough events to detect a HR of 1.07 with 80% power.

The two largest trials in the ARB *vs* other group (ONTARGET and VALUE) report the overall proportion of participants with cancer events as 7.2% and 9.1% (13). Assuming that the proportion of participants in our dataset with cancer events is 9% overall, we expect to have 80% power to detect a HR as low as 1.065. Two other trials (LIFE and TRANSCEND) report proportions of 7.3% and 7.4% (13). If the proportion of participants with cancer events in our dataset overall is 7% we expect to have enough events to detect a HR of 1.08 with 80% power in the ARB *vs* other group.

The largest trial in the BB *vs* other comparison group (ASCOT-BPLA) reports that 9.8% of participants developed cancer during the trial (13). Assuming that the proportion of participants with cancer events in our dataset is 9.8%, we expect to have 80% power to detect a HR of 1.10. Another trial (LIFE) reported the overall the proportion of participants with

cancer events as 7.3% (13). If the proportion of participants with cancer events in our dataset overall is 7.3% we expect to have enough events to detect a HR of 1.15 with 80% power.

The proportions of participants with cancer events in the largest trials for CCB *vs* other (ALLHAT, ASCOT-BPLA and VALUE) range from 7.2% to 9.8% (13). If the number of events in our dataset is at the lower end of this range we expect to have enough events to detect a HR of 1.06 with 80% power, at the higher end we expect to have enough events to detect a HR of 1.05 with 80% power. Two other large trials (CONVINCE and INVEST) report that between 1.7% and 3.7% of participants developed cancer (13). Assuming that the proportion of participants with cancer events in our dataset is 2%, we expect to have 80% power to detect a HR of 1.15.

The only trial with published cancer data included in the diuretic *vs* comparison group (ALLHAT) reports that 7.7% of participants developed cancer during follow-up (13). Assuming that the proportion of participants with cancer events in our dataset is 7.7%, we expect to have 80% power to detect a HR of 1.09.

Assessment of trials

The trials included in the analysis will be assessed for risk of bias using the Cochrane risk-of-bias tool (15).

Statistical analysis

The IPD meta-analyses will be conducted using the one-stage approach (16,17). The baseline characteristics of the participants in each drug class comparison group will be described (illustrative table 3). For continuous variables mean values and standard deviations will be reported; for categorical variables, the frequencies and proportions will be reported. The analyses will be based on intention-to-treat principle – we will included all eligible participants regardless of whether they received the allocated treatment. Time-to-event analyses will be conducted using clustered Cox proportional hazards models. These mixed effects models will include a random effects term for trial to take into account clustering at the trial level. The start time of the analysis is defined as the date of randomisation for each participant. Individuals are censored at their last follow-up date or the date of a competing risk event such as death that is not cancer-related. Methods that account for informative censoring will be used to take into account the presence of competing risks (18).

The effects of antihypertensive drugs on total cancer events will also be investigated in different patient subgroups. The pre-specified subgroups will be defined by age, sex, baseline use of antihypertensive drugs. Table 4 is an illustrative table to summarise the effects of antihypertensive use on the risk of cancer by drug class. Heterogeneity at the trial-level or across subgroups will be assessed through χ^2 tests, including χ^2 tests for trend where appropriate. Results for all analyses will be presented using forest plots.

Sensitivity analysis

A number of sensitivity analyses will be undertaken. We will compare results separately for trials that reported adjudicated cancer events to those that recorded unadjudicated cancer events to determine whether the difference in adjudication of events impacts the results of the analysis. In the main analysis, trials reporting both non-fatal and fatal cancer events and those only reporting cancer mortality will be pooled together to maximise statistical power. In a sensitivity analysis, we will perform separate analyses on these two types of trials and compare the results. We will also conduct a sensitivity analysis where any individuals with pre-existing cancer at baseline will be excluded.

The main analyses will be limited to trials for which we have IPD; however, excluding trials where IPD is not available could introduce bias. To investigate this possibility, published results or aggregate data from eligible trials for which we do not have IPD will be combined with the IPD available in a sensitivity analysis. We will extract hazard ratios (HRs) and 95% confidence intervals (CIs) from published papers where available, and tabular data will be extracted from trials where HR estimates are not reported. IPD, published HR estimates (and 95% CIs) and tabular data will be pooled in a meta-analysis using random effects. This method will account for information on censoring where available. Relative risks (RRs) will be reported for these analyses. Through this approach, the consistency of the findings with and without inclusion of eligible trials for which we do not have IPD will be evaluated. Meta-regression will be used if considerable residual heterogeneity remains after controlling for all possible variables and recognized effect modifiers, with P-value adjusted for false positive findings based on Monte Carlo simulation. Funnel plots could also be generated to assess potential selection bias associated with inclusion of trials based on availability of IPD.

We will investigate the application of network meta-analysis models to our analysis. These models allow the synthesis of individual trials with different treatment comparisons, thereby combining both direct and indirect evidence of relative treatment effects (19). This method may be useful where simple pairwise comparisons between drug classes are not possible due to small numbers of trials or where there is no direct comparison. Recently, methods for conducting network meta-analysis using individual patient-level information have been developed, although the adoption of this method remains limited (20,21). If assessed to be informative, we will use this method to indirectly estimate relative treatment effects from RCTs with different treatment comparisons. Novel network meta-analysis methods incorporate both IPD and Bayesian/mixed effects frameworks (22,23).

For the main analyses we will report summary HRs with their 95% CIs with P values tested at 5% significance level (two-tailed). To account for the increased possibility of obtaining a chance finding due to multiple testing in the subgroup analyses, tests will be conducted at the more stringent significance level of 1% (two-tailed) and estimates will be reported with 99% CIs (24).

Table 1. Number of events needed for an 80% power to detect a statistically significant difference in risk over a range of risk estimates. HR = hazard ratio.

Drug class comparison	**N of trials**	**Treatment: control ratio**	**Number of events needed overall to detect HR with 80% power**							
			1.05	***1.06***	***1.07***	***1.08***	***1.09***	***1.10***	***1.15***	***1.20***
ACEi *vs* other	13	0.47	14,715	10,285	7605	5860	4660	3795	1740	1010
ARB *vs* other	10	0.76	13,190	9235	6845	5285	4210	3440	1595	935
BB *vs* other	4	0.93	13,025	9130	6770	5235	4175	3415	1590	935
CCB *vs* other	18	0.63	13,585	9505	7040	5430	4325	3530	1630	950
Diuretic *vs* other	6	0.63	13,585	9505	7040	5430	4325	3530	1630	950

TABLES AND FIGURES FOR ILLUSTRATIVE PURPOSES ONLY

Table 2. Definition and quality of cancer outcomes in each trial. Type of cancer outcome recorded in each trial (any cancer, cancer deaths, first cancer whether or not it is fatal, cancer subtype), details on whether the cancer events where adjudicated (pre-specified outcomes) or not (adverse events) and whether the date of diagnosis was provided. [*Illustrative purpose only*.]

Trial	Type of cancer outcome reported in trial	Adjudicated outcome	Date of event provided
AASK			
ABCD			
ACTIVE I			
ALLHAT			
ANBP2			
ASCOT-BPLA			
BENEDICT			
CAMELOT			
CASE-J			
COLM			
CONVINCE			
COPE			
DIABHYCAR			
ELSA			
EUROPA			
EWPHE			
HIJ-CREATE			
HOMED-BP			
HOPE			
INVEST			
JMIC-B			
LIFE			
MOSES			
NICS-EH			
ONTARGET			
PART-2			
PREVEND IT			
PREVENT			
PROFESS			
STOP-Hypertension-2			
Syst-Eur			
TRANSCEND			
VALUE			

Table 3. Summary details of trials included in the BPLTTC individual patient-level data meta-analysis. [*Illustrative purpose only*.]

Characteristics	**ACEi vs other**	**ARB vs other**	**BB vs other**	**CCB vs other**	**Diuretic vs other**
N of trials					
N of participants (% women)					
% Caucasian/European ethnicity (N)					
% current smoker (N)					
Mean (SD) pre-treatment SBP/DBP					
Mean (SD) achieved SBP/DBP					
Mean (SD) age (years)					
N of participants by age (years) at baseline					
<50					
50 to 59					
60 to 69					
70 to 79					
≥80					
Mean (SD) trial duration (years)					
% with condition at baseline (N)					
Cardiovascular disease					
Diabetes					
Chronic kidney disease					
% previously on blood pressure-lowering medication (N)					
No. of participants by year of end of trial (N of trials)					
<1990					
1990 to 1999					
2000 to 2009					
≥2010					
N of participants/trials with alcohol intake data					
Mean (SD) alcohol intake (g/day)					
N of participants/trials with BMI data					
Mean (SD) BMI (kg/m^2)					

Table 4. Effects of antihypertensive use on overall cancer incidence by drug class, overall and in pre-specified patient subgroups. [*Illustrative purpose only*.]

	Hazard ratio (95% confidence interval) for cancer incidence				
	ACEi vs other	ARB vs other	BB vs other	CCB vs other	Diuretic vs other
All					
By age (years)					
<60					
60-69					
70-79					
≥80					
By sex					
Women					
Men					
By baseline BP medication					
Yes					
No					
By smoking status					
Current smoker					
Ex- or never smoker					
Body mass index					
18.5 to 25kg/m^2 (normal weight)					
>25kg/m^2 (overweight/obese)					

Appendix Table. Summary of blood pressure-lowering treatment randomised trials included in the analysis.

Study name or author	Publication year	Drug class comparisons	N
AASK (African American Study of Kidney Disease and Hypertension)	2002	ACEi *vs* CCB *vs* BB and more vs less intense BP-lowering	1094
ABCD (Appropriate Blood Pressure Control in Diabetes Trial)	1998	CCB *vs* ACEi	950
ACTIVE I (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events)	2011	ARB *vs* placebo	9016
ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attacks Trial)	2002	ACEi *vs* CCB *vs* Diuretic	42,418
ANBP2 (Second Australian National Blood Pressure Study)	2003	ACEi *vs* Diuretic	6083
ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm)	2005	CCB(+ACEi) *vs* BB(+Diuretic)	19,257
BENEDICT (Bergamo Nephrologic Diabetes Complications Trial)	2004	ACEi *vs* CCB *vs* ACEi+CCB *vs* placebo	1209
CAMELOT (The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis)	2004	ACEi *vs* CCB *vs* placebo	1997
CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)	2008	ARB *vs* CCB	4703
COLM (Combination of OLMesartan and calcium channel blocker or diuretic)	2014	CCB+ARB *vs* Diuretic+ARB	5141
CONVINCE (Controlled Onset Verapamil Investigation of Cardiovascular End Points)	2003	CCB *vs* BB/Diuretic	16,476
COPE (Combination Therapy of Hypertension to Prevent Cardiovascular Events)	2011	ARB+CCB *vs* BB+CCB *vs* Diuretic+CCB	3293
DIABHYCAR (Noninsulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril)	2004	ACEi *vs* placebo	4912
ELSA (European Lacidipine Study on Atherosclerosis)	2002	CCB *vs* BB	2334
EUROPA (European trial on reduction of cardiac events with perindopril in stable coronary artery)	2003	ACEi *vs* placebo	12,218
EWPHE (European Working Party on High Blood Pressure in the Elderly)	1985	Diuretic *vs* placebo	840
HIJ-CREATE (Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Heart Disease)	2009	ARB *vs* non-ARB	2049
HOMED-BP (Hypertension Objective Treatment based on Measurement by Electrical Devices of Blood Pressure Study)	2012	ACEi *vs* ARB *vs* CCB	3518
HOPE (Heart Outcomes Prevention Evaluation Study)	2000	ACEi *vs* placebo	9297
INVEST (International Verapamil-Trandolapril Study)	2003	CCB *vs* non-CCB	22,576
JMIC-B (Japan Multicenter Investigation for Cardiovascular Diseases-B)	2004	CCB *vs* ACEi	1650
LIFE (Losartan Intervention for Endpoint Reduction in Hypertension Study)	2002	ARB *vs* BB	9193
MOSES (Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention)	2005	ARB *vs* CCB	1352
NICS-EH (National Intervention Cooperative Study in Elderly Hypertensives)	1999	CCB *vs* Diuretic	429
ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial)	2008	ACEi *vs* ARB *vs* ACEi+ARB	25,620
PART-2 (Prevention of Atherosclerosis with Ramipril Trial)	2000	ACEi *vs* placebo	617
PREVEND IT (Prevention of Renal and Vascular Endstage Disease)	2004	ACEi *vs* placebo	864
PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial)	2000	CCB *vs* placebo	825
PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes)	2003	ARB *vs* placebo	19,798
STOP Hypertension-2 (Swedish Trial in Old Patients with Hypertension-2)	1999	ACEi *vs* CCB *vs* BB+Diuretic	6614
Syst-Eur (Systolic Hypertension in Europe)	1997	CCB *vs* placebo	4695
TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease)	2008	ARB *vs* placebo	5926
VALUE (Valsartan Antihypertensive Long-Term Use Evaluation)	2004	ARB *vs* CCB	15,245
Total participants			**260,447**

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