systematic review

The implications of blood pressure targets from the 2018 European Society of Cardiology hypertension guidelines in Asian patients: a systematic review and meta-analysis

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BACKGROUND: The evidence for optimal blood pressure (BP) targets in Asian patients with hypertension is insufficient and controversial. Western guidelines should be used with caution in clinical practice until there is supporting evidence.

OBJECTIVE: Systematically synthesize the evidence on the efficacy of achieving the strict 2018 European Society of Cardiology (ESC) guideline BP targets versus standard BP targets in Asian patients.

DATA SOURCES: We searched PubMed, Web of Science, Scopus, the Cochrane Central Register of controlled trials, and additional databases to retrieve relevant Asian studies.

STUDY SELECTION: Randomized controlled trials (RCTs) and observational studies that reported clinical endpoints, had a minimal follow-up period of one year and included Asian patients older than 18 years with essential hypertension.

DATA EXTRACTION: Two investigators independently conducted the study selection with any discrepancies resolved between team members.

DATA SYNTHESIS: We selected 15 studies for analysis (4 RCTs, 7 observational studies, and 4 post-hoc analyses). The evidence for the strict BP targets in elderly patients was insufficient. In middle-aged patients, the meta-analysis of observational studies revealed a significant reduction in major adverse cardiac events (MACCE) (hazard ratio (HR)=0.78; 95% confidence interval (CI: 0.74-0.81). For studies that reported results for patients of any age, the tight systolic BP-lowering therapy was associated with a decrease in MACCE (HR=0.80; 95% CI: 0.69-0.92), stroke (HR=0.82; 95% CI: 0.71-0.94), but not in cardiac events (HR=0.91; 95% CI: 0.72-1.14, *P*=.41), all-cause (HR=0.80; 95% CI: 0.57-1.13) and cardiovascular mortality (HR=0.73; 95% CI: 0.40-1.33, *P*=.30). Similar findings were obtained for the strict diastolic BP targets.

CONCLUSION: Our findings provide evidence for Asian patients that support the efficacy of the strict antihypertensive treatment with BP targets proposed by the 2018 ESC hypertension guidelines for the prevention of cardiovascular events. However, these data were obtained from only observational studies and the results were not confirmed by RCTs, probably due to insufficient power. Therefore, further high-quality RCTs are crucial.

LIMITATIONS: Use of aggregated data, the subgroup and meta-regression analyses are inconclusive, limited to English language, unable to estimate summary measures for some outcomes, publication bias difficult to assess, and unclear that results could be extrapolated.
REGISTRATION: The protocol registered in PROSPERO (CRD42018115570).
CONFLICT OF INTEREST: None.

Hypertension remains the primary cardiovascular risk factor leading to increased mortality and morbidity around the world. Among patients with a systolic blood pressure (SBP) more than 140 mm Hg, the annual death rate per 100 000 rose from 97.9 to 106.3 between 1990 and 2015.[1] The burden of hypertension varies considerably depending on geographical area, with the annual death rate per 100 000 being 136.5 and 64.3 in East Asia and Western Europe, respectively, in 2015.[1]

Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) proved the superiority of strict antihypertensive treatment with a SBP target of less than 120 mm Hg over standard antihypertensive treatment with a SBP target of less than 140 mm Hg in prevention of primary composite endpoints and all-cause mortality.[2] The SPRINT study supported findings of the previous Cardio-Sis trial that also supported the benefits of tight antihypertensive treatment.[3] Then, the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) released new guidelines that lowered blood pressure (BP) targets for a general hypertensive population to a level of less than 130/80 mm Hg.[4,5] However, this tight BP-lowering therapy has not been widely investigated in Asians. The characteristics of hypertension in Asians are known to differ considerably from those in Caucasians with respect to outcomes as well as response to antihypertensive treatment.[6,7] As demonstrated in the Felodipine Event Reduction Study, Asian patients tend to benefit to a great extent even after a decrease in BP of only 4/2 mm Hg, which downsized the risk of cardiovascular mortality and stroke by 33% and 27%, respectively.[8] Asian hypertensive individuals showed a considerably stronger relationship between BP levels and stroke risk than Caucasian patients, while the association between BP levels and coronary heart disease was similar in both populations.[9-11] Taking this evidence into account, experts suggested that target BP in Asian patients should be adjusted for prevention of stroke.[6,7] Consequently, the unique features of hypertension in the Asian population suggest that physicians should not blindly follow Western guidelines in clinical practice.[12] As with antithrombotic treatment, for which a "One-Guideline-Fits-All-Races" approach was criticized by Asian experts, concerns for the safety of newly proposed BP targets in Asian countries are also growing.[6,7,12,13] While a previous meta-analysis indicated that a BP target of 140/80 mm Hg is efficacious in Asian individuals, tighter BP goals have not been investigated properly in systematic reviews.[14] We therefore intended to systematically synthesize the evidence on the efficacy of achieving the 2018 ESC guideline BP targets in Asian patients with hypertension.

PATIENTS AND METHODS

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions.[15,16] The protocol was registered in advance in PROSPERO database (CRD42018115570) (*https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=115570*). The main searched databases were PubMed (up to May 19, 2019), Web of Science (up to January 18, 2019), Scopus (up to February 19, 2019), and Cochrane Central Register of Controlled trials (up to February 27, 2019). There were no restrictions on article dates, but the majority of retrieved studies were published within the last ten-year period since the topic is a relatively new concept. As a specific search strategy for obtaining observational studies has not been validated, we did not include any filters on study design.[16] The following keywords were applied in different combinations: ''target blood pressure'', ''goal blood pressure'', ''on-treatment blood pressure'', ''achieved blood pressure'', ''Asia'', and ''hypertension''. The search was limited to English language. We also checked the international registers of trials, journal websites, references of included publications, conference materials, and grey literature. Some statistics were obtained from the authors of original

articles. The search strategy is described in detail in **Supplementary Data 1.**

Inclusion and exclusion criteria and study endpoints

We included randomized controlled trials (RCTs) and observational studies that included Asian patients older than 18 years of age with essential hypertension and that reported clinical endpoints and had a minimal follow-up period of one year. Studies that enrolled patients with secondary reasons for hypertension (chronic kidney disease (CKD), endocrine diseases, for instance) were excluded. We also excluded studies that included pregnant women, patients without on-treatment BP measurements, or studies that included patients with severe concomitant conditions (acute stroke, myocardial infarction or other acute life-threatening conditions; terminal renal insufficiency, requiring renal replacement therapy; terminal liver disease, cancer IV stage, collagen disease) that could independently affect outcomes.

The intervention group of patients was defined as participants who achieved BP targets set by the 2018 ESC guideline: 120-130/70-80 mm Hg for 18- to 65-year-old adults irrespective of the presence of diabetes mellitus or previous cardiovascular diseases, or 130-140/70-80 mm Hg for elderly patients over 65 years.[5] In the control treatment arm, the participants had on-treatment BP of 130-140/80-90 mm Hg for middle-aged adults and 140-150/80-90 mm Hg for elderly patients.

In our meta-analysis, we included studies that were initially designed to assess clinical efficacy of different BP targets. In addition, we also retrieved post-hoc analyses of RCTs and sub-analyses of observational studies that fulfilled the eligibility criteria. There were no limitations on inclusion of studies on the basis of BP measurement methods. We choose a level of home SBP at 125 mm Hg as a strict BP target according to a recent expert panel consensus.[17]

We selected the following events with definitions in the original studies as study endpoints: major adverse cardiac and cerebrovascular events (MACCEs), stroke, cardiac events, all-cause mortality, and cardiovascular mortality. Although CKD development is a crucial outcome measure, we did not estimate this because of a deficiency of reported data.

Data extraction and risk-of-bias assessment

A pre-designed Excel form was used to obtain necessary information on study and patient characteristics, follow-up period, applied statistical approaches, and main results. The risk of bias for RCTs was estimated according to the Cochrane Collaboration's tool.[18] Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool and the Newcastle-Ottawa quality assessment scale were applied to evaluate observational studies.[19-21] Two investigators conducted independently the aforementioned stages with any discrepancies resolved under discussion between team members.

Quantitative synthesis

As the included studies had different follow-up periods, we selected hazard ratios (HRs) as effect estimates in order to exclude possible bias arising from calculating dichotomous summary statistics.[16] Tierney et al's Excel spreadsheets were applied in estimation of missing data.[22] GetData Graph Digitizer (version 2.26.0.20), software for digitizing graphs, was used to minimize potential misinterpretation of graphical data. Some studies did not provide HRs for composite endpoints but reported statistics for individual endpoints or subgroup analyses. In these cases, we used a fixed-effects model to calculate statistics for the composite endpoints from the provided data before integrating them in the meta-analysis.

The meta-analysis was based on a generic inverse-variance method. As there are different BP targets for elderly and middle-aged persons, we conducted analyses for those under and over 65 years old.[5] Additionally, the majority of studies did not report summary data according to age, so we performed a separate synthesis for these studies. According to the Cochrane Handbook for Systematic Reviews of Interventions, non-randomized trials were included in the meta-analysis only in cases of unavailability or insufficiency of evidence from RCTs.[16] In order to decide whether randomized evidence is conclusive, we performed a trial sequential analysis (TSA) that could reduce possible errors from repetitive testing.[23] The information size was calculated on the basis of required sample size and accumulating number of events. For classical calculation of adequate sample size in RCTs, we chose 7% as a control group event rate considering the results from the SPRINT trial. An expected relative risk reduction was set at a level proposed by the pooled meta-analysis of low-bias trials. The maximum level for risk of type I and type II error were set at 5% and 80%, respectively. Additionally, we incorporated a heterogeneity adjustment factor in the information size as a ratio between the variance of random- and fixed-effects models. These calculations were performed in a TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, 2017).[23]

Statistical heterogeneity was considered significant if chi-squared $P \leq .05$ and I^2-statistic was more than 80%. We selected a random-effects model for evidence synthesis in order to incorporate unexplained heterogeneity.[16] Further, to reveal potential reasons for statistical heterogeneity, we performed meta-regression analyses using SPSS 20.0.0.2 (Armonk, NY: IBM Corporation, 2011) and Wilson's SPSS Macros.[24] According to the rule of thumb, independent variables in the regression analyses were selected if at least 10 studies provide necessary information.[16] Standard leave-one-out sensitivity analyses and subgroup analyses according to presence of diabetes mellitus or previous cardiovascular events were also conducted. Differences between subgroups were classified as significant if I^2-statistics was more than 80%. The Review Manager (RevMan) 5.3 (Copenhagen; the Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used as a main software package.

RESULTS

The comprehensive search identified 15 studies, out of which 4 studies were RCTs, 7 studies were observational, and the remaining 4 studies were post-hoc analyses of RCTs (**Table 1**).[25-40] The meta-analysis flow diagram is depicted in **Figure 1**. In one RCT with dual intervention, patients were randomized to follow strict or standard BP targets and to receive angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers.[25] The meta-analysis comprised 334 702 participants, who differed considerably with regard to baseline risk profile of participants. The percentage of individuals with CKD varied substantially from 0% to 23.9%. Similarly, figures for smoking, diabetes mellitus, dyslipidemia, history of cardiovascular disease and other characteristics differ markedly across investigations.

The quality assessment of investigations are presented separately in **Supplementary Figures S1-4** and **Supplementary Table 1**. Given the nature of the subject, all RCTs were open-label, but we did not consider this a source of bias because assessment of clinical endpoints was blinded. We considered all the RCTs as having an unclear risk of bias because we were unaware to what extent the design had altered the final results. Further, the majority of observational studies were regarded as having an unclear or high risk of bias given the fact that there were some flaws in study design; for instance, inadequacy in reporting of follow-up data (**Supplementary Table 1**). Moreover, observational studies are inherently associated with selection bias and confounding, which did not allow us to consider them as investigations with a low risk of bias.

Quantitative synthesis

Antihypertensive treatment with tight versus standard SBP targets in elderly patients

Three RCTs were dedicated to assessing strict SBP targets in aged persons (**Figure 2**).[27,34,37] In the analyses, the evidence for efficacy of tight antihypertensive targets was not statistically significant in prevention of MACCEs (HR=0.79; 95% confidence interval (CI): 0.52-1.19, I^2=72%, P=.26), stroke (HR=0.75; 95% CI: 0.48-1.18, I^2=59%, P=.22), cardiac events (HR=1.0; 95% CI: 0.66-1.50, I^2=0%, P=.99), all-cause mortality (HR=0.86; 95% CI: 0.54-1.36, I^2=0%, P=.51), and cardiovascular mortality (HR=0.61; 95% CI: 0.29-1.26, I^2=59%, P=.18). However, the TSA found that the cumulative Z-curve for MACCEs did not cross the monitoring O'Brien-Fleming boundaries as well as the futility boundaries (**Figure S5**). Moreover, the sample size of accumulated RCTs and related number of events were far from the required information size (37651 and 1714, respectively) that would justify further research in the field.

Antihypertensive treatment with tight versus standard SBP targets irrespective of age

In this analyses, there was only one RCT which did not find significant results (HR=1.02; 95% CI: 0.59-1.77, P=.9383).[25] Therefore, we decided to include non-randomized evidence in the meta-analysis (**Figure 3**).[16] Compared with the standard antihypertensive treatment, the intensive antihypertensive treatment appeared to decrease significantly the risk of MACCEs in Asian patients with hypertension (HR=0.80; 95% CI: 0.69-0.92, I^2=89%, P=.002). We obtained similar results after excluding studies that investigated SBP targets in combination with diastolic BP (DBP) targets (HR=0.79; 95% CI: 0.64-0.98, I^2=89%, P=.03). Tight control of SBP also reduced stroke rates to a greater extent than the standard treatment (HR=0.82; 95% CI: 0.71-0.94, I^2=66%, P=.005). When the studies that provided separate data for SBP targets were the only studies included, the results were analogous (HR=0.76; 95% CI: 0.60-0.97, I^2=77%, P=.002). As regards cardiac events, there were no statistically significant differences between BP target groups (HR=0.91; 95% CI: 0.72-1.14, I^2=82%, P=.41). Achieving lower SBP targets was also not associated with a reduction in all-cause mortality (HR=0.80; 95% CI: 0.57-1.13, I^2=95%, P=.21). Similarly, there was no significant reduction in cardiovascular mortality (HR=0.73; 95% CI: 0.40-1.33, I^2=90%, P=.30).

Antihypertensive treatment with tight versus standard DBP targets irrespective of age

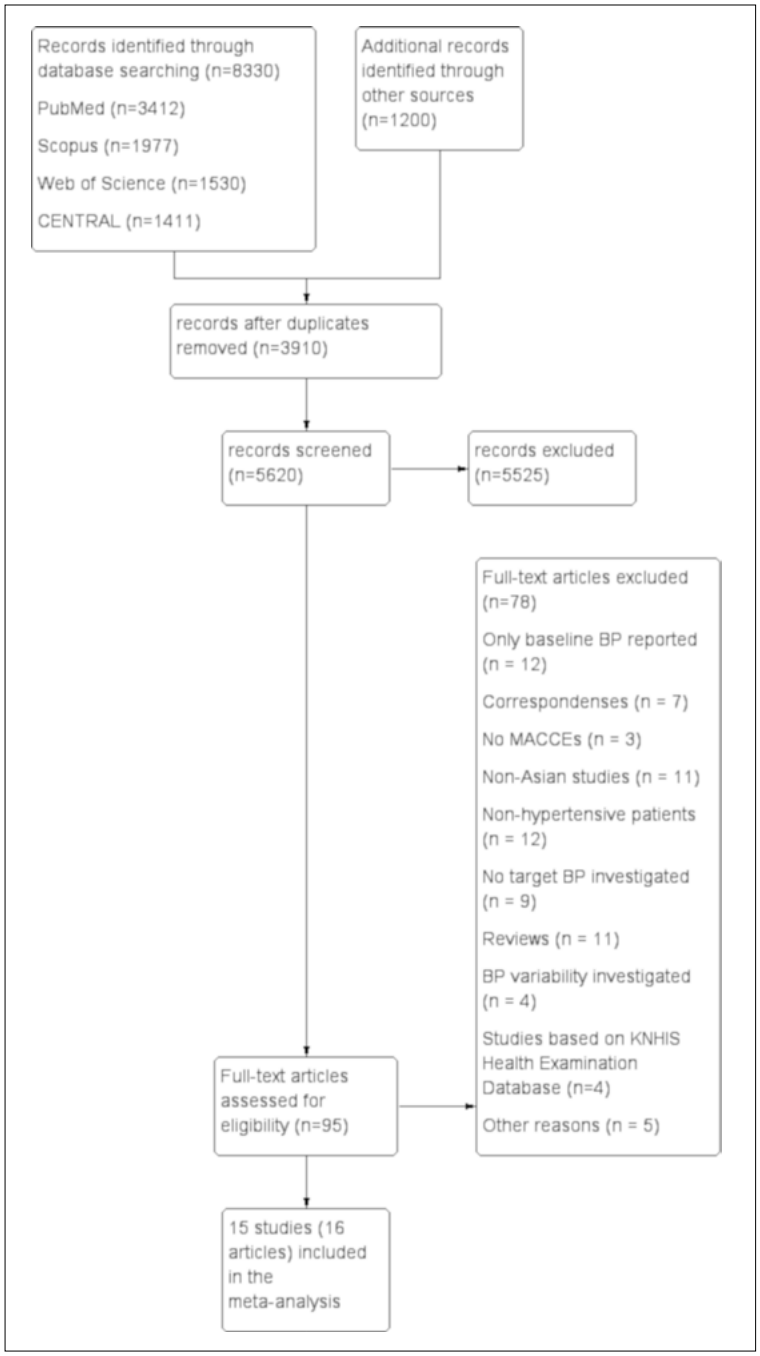

Figure 1. Flow chart of search strategy. BP: blood pressure. MACCEs: major adverse cardiac and cerebrovascular events, KHNIS: Korean National Health Insurance Service.

Unfortunately, we failed to find RCTs that specifically assessed this issue so non-randomized studies were included in the evidence synthesis (**Figure S6**).[16] Compared with the standard DBP targets, the strict DBP targets were associated with a decrease in MACCEs (HR=0.77; 95% CI: 0.65-0.90, I^2=77%, *P*=.001). After removing the studies with combined data for systolic and diastolic BP targets, we obtained comparable results (HR=0.70; 95% CI: 0.54-0.90, I^2=77%, *P*=.005).

There was also a significantly lower rate of stroke in the tight DBP target group than in the conventional DBP target group (HR=0.71; 95% CI: 0.55-0.91, I^2=84%, *P*=.006). The results corresponded with the DBP only target studies (HR=0.64; 95% CI: 0.42-0.97, I^2=88%, *P*=.04).

The risk of cardiac events was not altered to a great extent with the intensive antihypertensive treatment (HR=0.98; 95% CI: 0.85-1.13, I^2=14%, *P*=.78). Tight control of DBP reduced the risk of all-cause and cardiovascular mortality (HR=0.81; 95% CI: 0.76-0.87, I^2=0%, *P*<.0001; HR=0.75; 95% CI: 0.65-0.86, I^2=0%, *P*<.0001, respectively); however, the results came from a limited number of studies.

Antihypertensive treatment with tight versus standard DBP targets in middle-aged patients

We obtained only non-randomized evidence for this group, the synthesis of which demonstrated significant efficacy of the strict BP-lowering therapy in MACCE prevention with absence of heterogeneity (HR=0.78; 95% CI: 0.74-0,81, I^2=0%, *P*=.00001, **Figure S7**). The results were consistent after excluding each study one by one.

Subgroup analyses and publication bias assessment

Achieving the strict BP targets appeared to reduce the risk of MACCEs irrespective of diabetes mellitus status (**Figure S8**). We failed to demonstrate the efficacy of the tight BP targets in a subpopulation of patients with previous cardiovascular disease; however, these statistics were from only two studies, making it difficult to draw clear conclusions. We did not perform subgroup analyses for stroke, cardiac events, all-cause and cardiovascular mortality due to a paucity of the published data. We found no evidence of publication bias (**Figures S9 and S10**); however, the assessment of funnel plots is difficult when the majority of the included studies are of similar size.[16]

Sensitivity analyses

The results of the sensitivity analyses are shown in **Table 2**. As can be seen from the data, the strict BP targets remained beneficial for prevention of MACCEs and stroke in the standard leave-one-out sensitivity analyses.

Meta-regression analyses

There were no significant correlations between the magnitude of pooled HRs and the presence of diabetes mellitus, previous cardiovascular disease, stroke, and other factors. In univariate analyses, dyslipidemia and

Table 1. Main features of the 15 studies that compared tight versus standard blood pressure targets in Asian patient with hypertension.[a]

Study, year	Asayama et al 2012[25]	Fan et al 2017[26]	JATOS 2008[27]	Kamishima et al 2019[28]	Kario et al 2014[29]	Lee et al 2017[30]
Country	Japan	China	Japan	Japan	Japan	Korea
Study design	RCT, PROBE	Post-hoc analysis of RCT	RCT, PROBE	Post-hoc analysis of RCT	OS, prospective	OS, retrospective
Follow-up, years	5.31	4.5	2	4.2	2.02	8.3
Sample size, n	3518	9676	4418	1237	14745	1584
Mean age, years[b]	59.6	59.3	73.6	64.8	64.9	59.9
Males, %	1763 (50)	4029 (41.6)	1717 (38.9)	992 (80.2)	7225 (49)	867 (54.7)
Smoking, %	770 (22)	2241 (23.19)	595 (13.5)	777 (62.83)	1769 (12)	402 (25.4)
Drinking, %	1731 (50)	-	-	-	2359 (16)	115 (7.3)
DM, %	538 (15)	0	521 (11.8)	471 (38.1)	3096 (21)	93 (5.9)
Previous CV disease, %	106 (3)	0	134 (3)	1237 (100)	737 (5)	1584 (100)
CKD, %		0	439 (9.9)	-	2949 (20)	-
Dyslipidemia, %	1190 (34)	-	2301 (52.1)	734 (59.35)	6635 (45)	-
Previous stroke, %	-	0	192 (4.3)	-	1032 (7)	1584 (100)
BMI, kg/m^2	24.4	24.7	23.6	24.61	24.3	24.35
Baseline SBP, mmHg	154.2	160.76	171.55	135.3	153.6	133.41
Baseline DBP, mmHg	90.2	92.89	89.1	75.67	87.1	82.55
Target BP definitions, mmHg						
Lower target	<125/80	120-130 and <80	<140	120-130	<130	<130
Higher target	125-134/80-84	130-139 and 80-90	140-160	130-140	130-140	130-140
BP measurement method	Home	Clinic	Clinic	Clinic	Home and Clinic	Clinic
On-treatment BP calculation	Average BP during follow-up	Average BP during follow-up	Average BP during follow-up	Average BP during follow-up	Average BP during follow-up	Average BP during follow-up
Glucose, mmol/l	5.85	5.4	5.68	-	5.88	5.84
Cholesterol, mmol/l	5.46	5.5	5.33	-	5.24	5.35
LDL, mmol/l	-	-	-	-	3.07	-
HDL, mmol/l	-	1.4	1.46	-	1.52	-
Triglycerides, mmol/l	-	1.6	1.54	-	1.51	-
Prior antihypertensive treatment, %	-	4239 (43.8)	2475 (60)	-	7372 (50)	-
ACEI/ARB, %	-	-	1503 (34)	1081 (87.4)	3686 (25)	1102 (69.6)
Beta-blocker, %	-	-	300 (6.8)	585 (47.32)	884 (6)	423 (26.7)
Ca antagonist, %	-	-	1174 (26.5)	622 (50.31)	5308 (36)	1131 (71.4)
Diuretics, %	-	-	156 (3.5)	112 (9.02)	884 (6)	411 (25.9)
Lipid-lowering treatment, %	-	81 (0.8)	-	547 (44.26)	4128 (28)	702 (44.3)

RCT: randomized controlled trial, PROBE: prospective, randomized, open-label, blinded end-point evaluation, OS: observational study, DM: diabetes mellitus, CV: cardiovascular, CKD: chronic kidney disease, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, AHA/ACC: the American Heart Association/ American College of Cardiology, JNC8: the Eighth Joint National Committee, ACEI/ARB: angiotensin-converting enzyme inhibitor/ angiotensin-II receptor blocker.

Table 1 (cont.). Main features of the 15 studies that compared tight versus standard blood pressure targets in Asian patient with hypertension.[a]

Lee et al 2018[31]	Ogihara et al 2009[32,33]	Ogihara et al 2010[34]	Teramoto 2012[35]	Wan et al 2018[36]	Wei et al 2013[37]	Yamashita 2013[38]	Yamazaki et al 2013[39]	Zheng et al 2015[40]
Korea	Japan	Japan	Japan	China	China	Japan	Japan	China
OS, retrospective	Post-hoc analysis of RCT	RCT, PROBE	OS, prospective	OS, retrospective	RCT, PROBE	Post-hoc analysis of RCT	OS, prospective	OS, prospective
11	3.2	3.07	2.7	4.8	4	3.2	2.93	4.8
242298	2416	3079	9142	25935	724	1061	12705	2164
56.9	63.9	76.1	64.9	66.8	76.6		64.6	69.2
136606 (56.4)	1336 (55.3)	1155 (37.6)	4607 (50.4)	12111 (46.7)	480 (66.3)		6454 (50.8)	1047 (48.4)
47649 (20.46)	766 (31.7)	592 (19.2)	1673 (18.3)	2516 (9.7)	180 (24.85)		3024 (23.8)	939 (43.38)
-	1389 (57.5)	-	2386 (26.1)	-	-		-	576 (26.6)
14938 (6.2)	1039 (43)	399 (13)	2230 (24.4)	25935 (100)	169 (23.34)		2566 (20.2)	14 (0.7)
0	312 (12.9)	153 (5)	895 (9.8)	0	-		2376 (18.7)	182 (8.4)
1362 (0.6)	577 (23.9)	43 (1.4)	658 (7.2)	1659 (6.4)	-		1054 (8.3)	
46994 (19.4)	1075 (44.5)	1156 (37.5)	4406 (48.2)				4142 (32.6)	126 (5.83)
0	246 (10.2)	202 (6.5)	466 (5.1)	0	6.65		1232 (9.7)	171 (7.9)
24.06	24.5	23.5	24.75	26.27	23.35		-	22.7
136.99	162.7	169.5	157.4	151.67	159.5		161.9	158.23
85.66	91.6	81.45	88.8	80.19	84.25		91.1	90.11
2017 AHA/ ACC	<130	<140	<130/85	120-130	<140/90	<130 and <80	120-130	130-139
JNC8	130-140	140-149	130-139/85-89	130-140	140-150/90	130-139 and 80-90	130-140	140-149
Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Average BP during follow-up	BP at last visit	Average BP during follow-up	-	More 50% of follow-up records	Average BP during follow-up	Average BP during follow-up	BP at last visit	Average BP during follow-up
-	-	-	6.24	-			-	-
5.17	-	-	-	-	4.52		-	-
3.06	-	-	3.18	2.96	2.85		-	-
1.41	-	-	1.49	-	1.41		-	-
1.59	-	-	1.63	1.68	1.55		-	-
-	1645 (68.1)	1537 (49.9)	4406 (48.2)	-	-		6314 (49.7)	493 (22.8)
-	-	635 (20.6)	-	19384 (74.74)	-		3303 (26)	163 (7.5)
-	-	130 (4.2)	-	11645 (44.9)	-		1258 (9.9)	-
-	-	1001 (32.5)	-	21163 (81.6)	-		5044 (39.7)	45 (2.1)
-	-	133 (4.3)	-	4253 (16.4)	-		1219 (9.6)	7 (0.3)
-	-	706 (22.9)	-	6782 (26.15)	-		2782 (21.9)	-

[a]The table represents only the study characteristics for which data were available from the majority of reports.
[b]For this and the following study characteristics, some statistics were calculated indirectly from the available published data, so that they could be only approximations of real data.

body mass index were correlated with summary estimates; however, in the multivariate analysis, only body mass index significantly influenced the overall results, which could explain the high level of statistical heterogeneity to a certain degree (**Table 3**).

DISCUSSION

As far as we know, this is the first meta-analysis that was entirely dedicated to exploring favorable BP targets in Asian patients with hypertension. The meta-analysis appears to demonstrate the efficacy of the tight 2018 ESC guideline BP targets in prevention of cardiovascular events in an Asian population. Notably, this evidence came only from observational studies; RCTs were inconclusive, probably because of insufficient power. Notably, our analyses failed to prove the benefits of the strict BP-lowering therapy in elderly patients of Asian origin. However, the non-significant results should not be misinterpreted as intervention treatment failure. In other words, as stated by Altman and Bland: "Absence of evidence is not evidence of absence".[41] Objectively, the futility boundaries were not reached in our TSA , which implies the low statistical power of the current RCTs.[42] Moreover, the sample size of current RCTs is inadequate as compared to the required one (n=37 651). Therefore, non-significant results from RCTs could be explained by the type II errors due to small sample sizes. Hopefully, the data from the ongoing Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients trial will shed light on the optimal BP targets in this challenging population.[43] Importantly, the TSA conducted by Verdecchia et al found that only by adding SPRINT trial to the 11 previous RCTs could the efficacy of intensive BP-lowering therapy in reduction of stroke and myocardial infarction be clearly demonstrated.[44] Therefore, we underscore that our meta-analysis should be regarded as hypothesis-generating rather than hypothesis-testing, and further RCTs are needed to prove our results in Asian patients.

However, our findings are in good agreement with results from previous meta-analyses.[45-48] Some of the systematic reviews also demonstrated a more beneficial effect of the tight BP-lowering therapy on the risk of stroke than on the risk of cardiac events.[45-47] For instance, Xie et al also provided marginally significant results for myocardial infarction (relative risk reduction 13%; 95% CI: 0-24%); however, there was a significant decrease in MACCEs and stroke in the tight BP target group (MACCEs 14%, 95% CI: 4-22%;

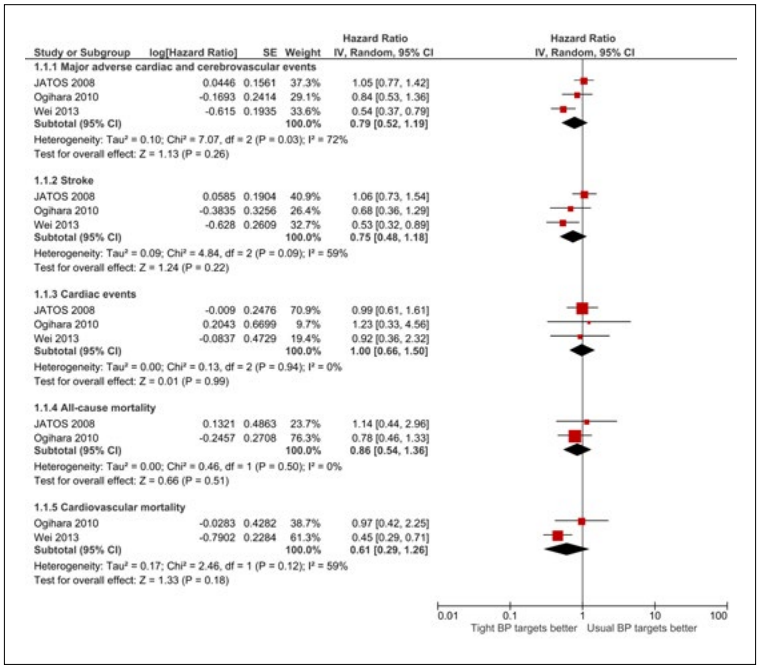

Figure 2. Forest plot of tight versus standard systolic blood pressure targets in elderly Asian patients with hypertension for the study endpoints (only RCTs). SE: standard error, IV: inverse variance, CI: confidence interval, BP: blood pressure.

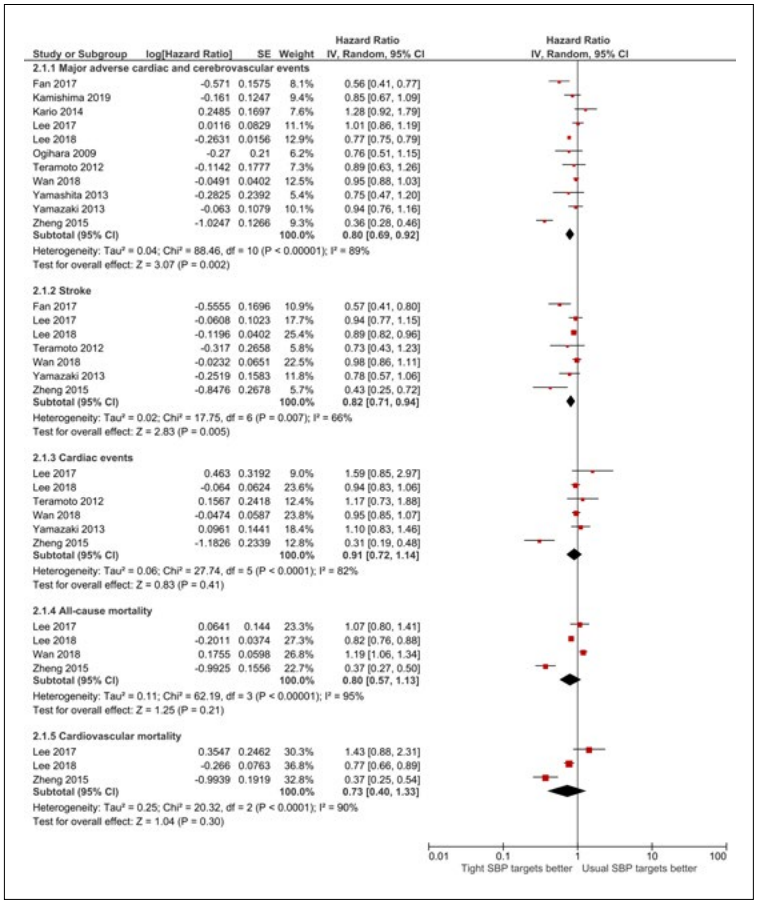

Figure 3. Forest plot of tight versus standard systolic blood pressure targets in Asian patients with hypertension irrespective of age (only observational studies). SE: standard error, IV: inverse variance, CI: confidence interval, BP: blood pressure.

Table 2. Leave-one-out sensitivity analyses for tight versus standard blood pressure targets in Asian patients with hypertension.

Study name, year	Tight versus standard SBP targets irrespective of age: HR (95% CI)		Tight versus standard DBP targets irrespective of age: HR (95% CI)		Tight versus standard DBP targets in middle-aged patients: HR (95% CI)
	MACCEs	Stroke	MACCEs	Stroke	MACCEs
Fan 2017[26]	0.82 (0.71, 0.96)	0.87 (0.77, 0.98)	0.86 (0.77, 0.97)	0.84 (0.73, 0.96)	-
Kamishima 2019[28]	0.79 (0.68, 0.93)	-	-	-	-
Kario 2014[29]	0.77 (0.67, 0.89)	-	-	-	-
Lee 2017[30]	0.78 (0.67, 0.90)	0.78 (0.66, 0.92)	0.86 (0.77, 0.97)	0.66 (0.45, 0.95)	-
Lee 2018[31]	0.80 (0.66, 0.98)	0.76 (0.61, 0.94)	0.86 (0.77, 0.97)	0.65 (0.46, 0.92)	0.80 (0.69, 0.93)
Ogihara 2009[32,33]	0.80 (0.69, 0.93)	-	0.78 (0.66, 0.92)	-	0.78 (0.74, 0.81)
Teramoto 2012[35]	0.79 (0.68, 0.92)	0.82 (0.71, 0.95)	0.75 (0.63, 0.90)	0.71 (0.54, 0.93)	-
Wan 2018[36]	0.78 (0.65, 0.93)	0.76 (0.63, 0.91)	-	-	0.77 (0.74, 0.81)
Yamashita 2013[38]	0.80 (0.69, 0.93)	-	0.77 (0.65, 0.91)	-	-
Yamazaki 2013[39]	0.79 (0.67, 0.92)	0.82 (0.70, 0.95)	0.77 (0.64, 0.92)	0.73 (0.56, 0.96)	0.78 (0.74, 0.81)
Zheng 2015[40]	0.87 (0.77, 0.98)	0.86 (0.77, 0.97)	-	-	-

MACCEs: major adverse cardiac and cerebrovascular events.

Table 3. Meta-regression analyses for tight versus standard blood pressure targets in Asian patients with hypertension.

Study characteristics	Fixed-effect univariate model		Random-effect univariate model		Random-effect univariate model	
	P value	Beta-coefficient	*P* value	Beta-coefficient	*P* value	Beta-coefficient
Sample size	.0021	-.471	.7837	-.0808		
Follow-up period	.0045	-.436	.6564	-.1311		
Male proportion	.1364	-.2289	.7267	.1064		
Diabetes mellitus	.0003	.5532	.2392	.3342		
Previous CV disease	.0655	.2830	.4161	.2385		
Baseline SBP	.2669	.1706	.4094	-.2451		
Baseline DBP	.0003	-.5555	.1696	-.3791		
Smoking	.028	-.4590	.1187	-.4286		
Dyslipidemia	.030	.6271	.0158	.6531	.8486	.0618
Previous stroke	.0364	.3216	.3525	.2844		
Body mass index	.0001	.6653	.0457	.5258	.0213	.7456

stroke 22%, 95% CI: 10-32%).[47] Notably, the previous meta-analyses mainly included trials conducted in Western populations. The cardiovascular risk pattern in Caucasian patients is different from that in Asian patients. Epidemiological studies demonstrated that the association between the rise in a BP level and the risk of stroke was significantly stronger for an Asian population than for a Western population.[9-11] In Asian patients, the burden of stroke is widely recognised to be higher than that of coronary heart disease.[9-11] Concerning a higher prevalence of stroke in Asian patients, it is not surprising that our meta-analysis demonstrated the positive effect of achieving the tight BP targets on MACCEs and stroke but not on cardiac events. As many experts stated that BP-lowering treatment in Asians should be targeted to stroke prevention, we believe that our findings will be useful in the management of hypertension in Asian countries.[6,7]

Further, the subgroup analyses highlighted the positive effect of the strict BP targets in patients with or without diabetes mellitus. In the Action to Control Cardiovascular Risk in Diabetes trial, the intensive antihypertensive treatment with a SBP target of <120 mm Hg was associated with a significantly reduced risk of stroke, although there was no significant impact on primary endpoints.[49] Considering the higher stroke risk among Asian population, a BP target of <130/80 mm Hg for patients with diabetes mellitus has been recommended by Asian experts.[6,7] Our findings could further support the importance of the tight BP-lowering therapy in this challenging group of patients.

The meta-regression analyses showed the higher impact of a tight BP-lowering therapy on MACCEs in studies of patients with a higher body mass index. The baseline risk of cardiovascular events is well-known to rise dramatically with an increasing number of cardiovascular risk factors. Consequently, in the case of the high baseline risk of study participants, any treatment intervention has a greater chance of achieving statistical significance, which could explain the results of the meta-regression analyses.

Of note, our findings are in good agreement with the recent guidelines from the Japanese Society of Hypertension that support strict BP goals in different categories of patients.[50] The Chinese guidelines also recommend tight BP-lowering therapy in both middle-aged and elderly individuals.[51,52] While suggesting intensive treatment for aged patients, the Korean and Taiwanese guidelines approve aggressive BP goals for only those middle-aged persons who have additional risk factors.[53,54]

Our analysis is not free of limitations. First, the review applied only aggregate data from the reported studies, which could bias the final results. An individual patient data meta-analysis would be the best option for this type of research. Second, due to a limited number of the included studies that enrolled participants with previous cardiovascular disease, the subgroup analyses failed to demonstrate the efficacy of the strict BP targets in this category of patients. Nevertheless, no significant correlations between the history of stroke or cardiovascular disease and MACCE rates were found in the meta-regression analyses. A meta-regression analysis is considered to be more statistically powerful than subgroup analyses,[55] but generally, subgroup and meta-regression analyses should be regarded with caution given the paucity of the obtained data. Third, our search was limited to the English language. Fourth, due to the paucity of published data, we did not manage to estimate summary measures for some important outcomes, such as CKD. Fifth, publication bias was difficult to assess because the majority of studies were of similar size. Sixth, as all the included studies were conducted in East Asian countries, whether the results can be extrapolated to other Asian countries needs further study. In this regard, different levels of traditional and non-traditional risk factors in the local population could have an independent impact on cardiovascular outcomes in different regions. Importantly, we would like to emphasize that socioeconomic factors should also be taken into account during implementation of Western guidelines in middle- or low-income countries. Social determinants of health are known to influence the distribution of risk factors (such as smoking, blood pressure level, obesity, diabetes, stress) as well as availability of preventive, diagnostic and treatment tools that inherently affect the burden of cardiovascular disease.[56-58]

In conclusion, our meta-analysis provides evidence in support of the efficacy of strict antihypertensive treatment with BP targets proposed by the 2018 ESC hypertension guidelines in Asian patients for the prevention of cardiovascular events. However, these data were obtained only from observational studies and were not confirmed by RCTs, possibly because of insufficient power. Therefore, further high-quality RCTs are of crucial importance to define the optimal BP targets for Asian patients with hypertension.

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SUPPLEMENTARY DATA 1. Search Strategy

Database: PubMed.

Last search date: 02/10/2019
#1 (((((((((((((((target* blood pressure) OR target* clinic blood pressure) OR target* bp) OR target* pressure) OR target* systolic blood pressure) OR target* diastolic blood pressure) OR target* sbp) OR target* dbp) OR target* sbp/dbp) OR blood pressur* target) OR bp target*) OR systolic blood pressur* target) OR diastolic blood pressur* target*) OR sbp target*) OR dbp target*) OR sbp/dbp target*
#2 (((((((((((((((goal* blood pressure) OR goal* clinic blood pressure) OR goal* bp) OR goal* pressure) OR goal* systolic blood pressure) OR goal* diastolic blood pressure) OR goal* sbp) OR goal* dbp) OR goal* sbp/dbp) OR blood pressur* goal*) OR bp goal*) OR systolic blood pressur* goal*) OR diastolic blood pressur* goal*) OR sbp goal*) OR dbp goal*) OR sbp/dbp goal*
#3 (((((((((((((((achiev* AND blood pressure) OR achiev* AND clinic blood pressure) OR achiev* AND bp) OR achiev* AND pressure) OR achiev* AND systolic blood pressure) OR achiev* AND diastolic blood pressure) OR achiev* AND sbp) OR achiev* AND dbp) OR achiev* AND sbp/dbp) OR blood pressur* AND achiev*) OR bp achiev*) OR systolic blood pressur* AND achiev*) OR diastolic blood pressur* AND achiev*) OR sbp achiev*) OR dbp achiev*) OR sbp/dbp achiev*
#4 (((((((on-treatment blood pressure) OR on-treatment bp) OR on-treatment pressure) OR on-treatment systolic blood pressure) OR on-treatment diastolic blood pressure) OR on-treatment sbp) OR on-treatment dbp) OR on-treatment sbp/dbp
#5 ((((((((((((intens* AND blood pressure) OR intens* AND clinic blood pressure) OR intens* AND bp) OR intens* AND pressure) OR intens* AND systolic blood pressure) OR intens* AND diastolic blood pressure) OR intens* AND sbp) OR intens* AND dbp) OR intens* AND sbp/dbp) OR intens* AND control) OR intens* AND antihypertens*) OR intens* AND anti-hypertens*) OR intens* AND lower*
#6 ((((((((((((strict* AND blood pressure) OR strict* AND clinic blood pressure) OR strict* AND bp) OR strict* AND pressure) OR strict* AND systolic blood pressure) OR strict* AND diastolic blood pressure) OR strict* AND sbp) OR strict* AND dbp) OR strict* AND sbp/dbp) OR strict* AND control) OR strict* AND antihypertens*) OR strict* AND anti-hypertens*) OR strict* AND lower*
#7 ((((((((((((tight* AND blood pressure) OR tight* AND clinic blood pressure) OR tight* AND bp) OR tight* AND pressure) OR tight* AND systolic blood pressure) OR tight* AND diastolic blood pressure) OR tight* AND sbp) OR tight* AND dbp) OR tight* AND sbp/dbp) OR tight* AND control) OR tight* AND antihypertens*) OR tight* AND anti-hypertens*) OR tight* AND lower*
#8 ((((((((((((aggressiv* AND blood pressure) OR aggressiv* AND clinic blood pressure) OR aggressiv* AND bp) OR aggressiv* AND pressure) OR aggressiv* AND systolic blood pressure) OR aggressiv* AND diastolic blood pressure) OR aggressiv* AND sbp) OR aggressiv* AND dbp) OR aggressiv* AND sbp/dbp) OR aggressiv* AND control) OR aggressiv* AND antihypertens*) OR aggressiv* AND anti-hypertens*) OR aggressiv* AND lower*
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 ((((clinic hypertension, isolated[MeSH Terms]) OR hypertension[MeSH Terms]) OR hypertens*) OR anti hypertensive drugs[MeSH Terms]) OR agents, anti hypertensive[MeSH Terms]
#11 #9 AND #10
#12 (((((((((((((((((((((((((((((((((asia*) OR asia[MeSH Terms]) OR asia, southeastern[MeSH Terms]) OR asia, central[MeSH Terms]) OR japan*) OR japan[MeSH Terms]) OR japanese[MeSH Terms]) OR china) OR chinese) OR people's republic of china[MeSH Terms]) OR chinese[MeSH Terms]) OR korea*) OR korea[MeSH Terms]) OR korea, republic of[MeSH Terms]) OR taiwan*) OR taiwan[MeSH Terms]) OR hong kong) OR hong kong[MeSH Terms]) OR malaysia) OR malaysia[MeSH Terms]) OR singapore) OR singapore[MeSH Terms]) OR thailand) OR thailand[MeSH Terms]) OR philippines) OR philippines[MeSH Terms]) OR indonesia) OR indonesia[MeSH Terms]) OR viet nam) OR viet nam[MeSH Terms]) OR kazakhstan) OR kazakhstan[MeSH Terms]) OR kyrgystan) OR kyrgyzstan[MeSH Terms]
#13 #11 AND #12

Database: Web of Science.
Last search date: 18/01/2019
#1 ((goal$ or intensiv* or strict* or target* or tight* or "on-treatment" or "in-treatment"or achiev* or aggressiv* or "J-curve" or "U-shape") NEAR/6 (antihypertensiv* or anti-hypertensiv* or bp or (blood NEAR/0 pressure) or dbp or diastolic or sbp or systolic))
#2 hypertension or antihypertensiv* or anti-hypertensiv* or hypertens*
#1 AND #2 with filters of Asian countries of origin.

Database: Scopus.
Last search date: 19/02/2019
#1 (TITLE-ABS-KEY ((goal* OR intensiv* OR strict* OR target* OR tight* OR {on-treatment} OR {in-treatment} OR achiev* OR aggressive* OR {J curve} OR {U shape} OR {J-curve} OR {U-shape}) W/6 (antihypertensiv* OR anti-hypertensiv* OR bp OR "blood pressure" OR dbp OR diastolic OR sbp OR systolic))
#2 (hypertension OR antihypertensiv* OR anti-hypertensiv* OR hypertens*)
#3 #1 AND #2 with filters of Asian countries of origin.

Database: Cochrane Central Register of Controlled trials.
Last search date: 27/02/2019
#1 ((goal* or intensiv* or strict* or target* or tight* or "on-treatment" or "in-treatment" or achiev* or aggressiv* or "J-curve" or "U-shape" or average$) NEAR (antihypertensiv* or anti-hypertensiv* or bp or "blood pressure" or dbp or diastolic or sbp or systolic))
#2 hypertension*
#3 MeSH descriptor: [Hypertension] explode all trees
#4 antihypertensiv*
#5 anti-hypertensiv*
#6 hypertens*
#7 #2 OR #3 OR #4 OR #5 OR #6
#8 #1 AND #7
#9 asia*
#10 MeSH descriptor: [Asia] explode all trees
#11 MeSH descriptor: [Asia, Southeastern] explode all trees
#12 MeSH descriptor: [Asia, Central] explode all trees
#13 japan*
#14 MeSH descriptor: [Japan] explode all trees
#15 MeSH descriptor: [Asian Continental Ancestry Group] explode all trees
#16 MeSH descriptor: [China] explode all trees
#17 MeSH descriptor: [Republic of Korea] explode all trees
#18 korea*
#19 taiwan*
#20 MeSH descriptor: [Taiwan] explode all trees
#21 hong kong
#22 MeSH descriptor: [Hong Kong] explode all trees
#23 malaysia
#24 MeSH descriptor: [Malaysia] explode all trees
#25 singapore
#26 MeSH descriptor: [Singapore] explode all trees
#27 thailand
#28 MeSH descriptor: [Thailand] explode all trees
#29 phillipines
#30 MeSH descriptor: [Philippines] explode all trees

#31 indonesia
#32 MeSH descriptor: [Indonesia] explode all trees
#33 viet nam
#34 MeSH descriptor: [Vietnam] explode all trees
#35 kazakhstan
#36 MeSH descriptor: [Kazakhstan] explode all trees
#37 MeSH descriptor: [Kyrgyzstan] explode all trees
#38 china
#39 chinese
#40 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39
#41 #8 AND #40

SUPPLEMENTARY TABLE:

Supplementary Table 1. Risk of Bias assessment of the observational studies.

Study name, year	Fan e al 2017[26]	Kamishima 2019[28]	Kario et al 2014[29]	Lee et al 2017[30]	Lee et al 2018[31]	Ogihara et al 2009[32,33]
Representativeness of the exposed cohort	*	*	*	*	*	-
Selection of the non-exposed cohort	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	-	-	*
Demonstration that outcome of interest was not present at start of study	*	*	*	*	*	*
Comparability	*	*	*	*	*	-
Assessment of outcome	*	-	*	*	*	*
Long enough follow-up[a]	*	*	*	*	*	*
Adequacy of follow-up of cohorts	-	-	-	*	*	-
General assessment of bias risk	Unclear	High	Unclear	Unclear	Unclear	High

Supplementary Table 1 (cont.). Risk of Bias assessment of the observational studies.

Study name, year	Teramoto 2012[35]	Wan et al 2018[36]	Yamashita 2013[38]	Yamazaki et al 2013[39]	Zheng et al 2015[40]
Representativeness of the exposed cohort	*	*	*	*	*
Selection of the non-exposed cohort	*	*	*	*	*
Ascertainment of exposure	-	-	-	-	*
Demonstration that outcome of interest was not present at start of study	*	*	*	*	*
Comparability	*	*	*	*	*
Assessment of outcome	-	*	*	-	*
Long enough follow-up[a]	*	*	*	*	*
Adequacy of follow-up of cohorts	*	*	-	-	-
General assessment of bias risk	High	Unclear	High	High	Unclear

Notes: * - low risk of bias; "-" - unclear or high risk of bias. [a] If 1 year or more.

SUPPLEMENTARY FIGURES:

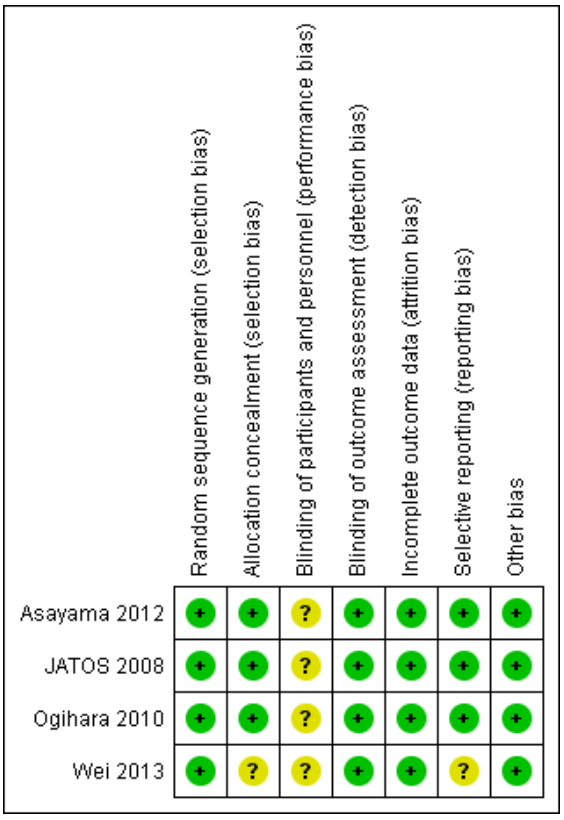

Figure S1. Risk of bias summary: judgements about each risk of bias item for each **randomized controlled trial**.

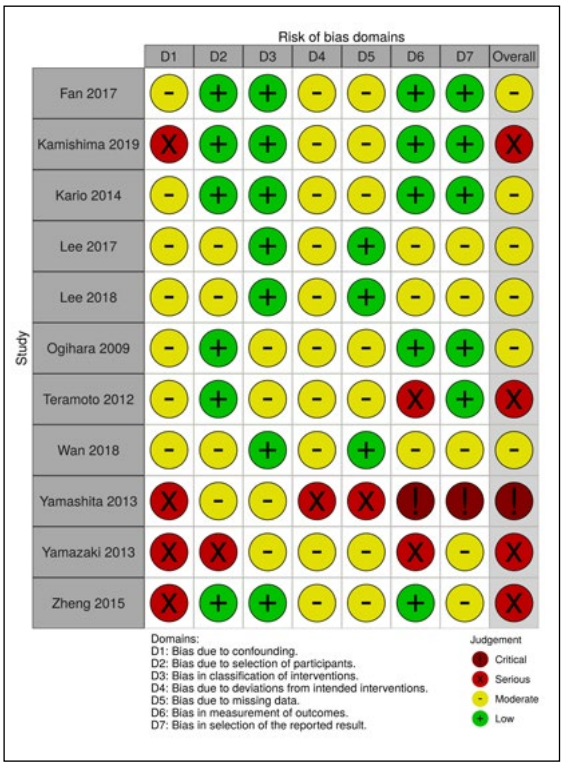

Figure S3. Risk of bias summary: judgements about each domain risk of bias item for each **observational study**.

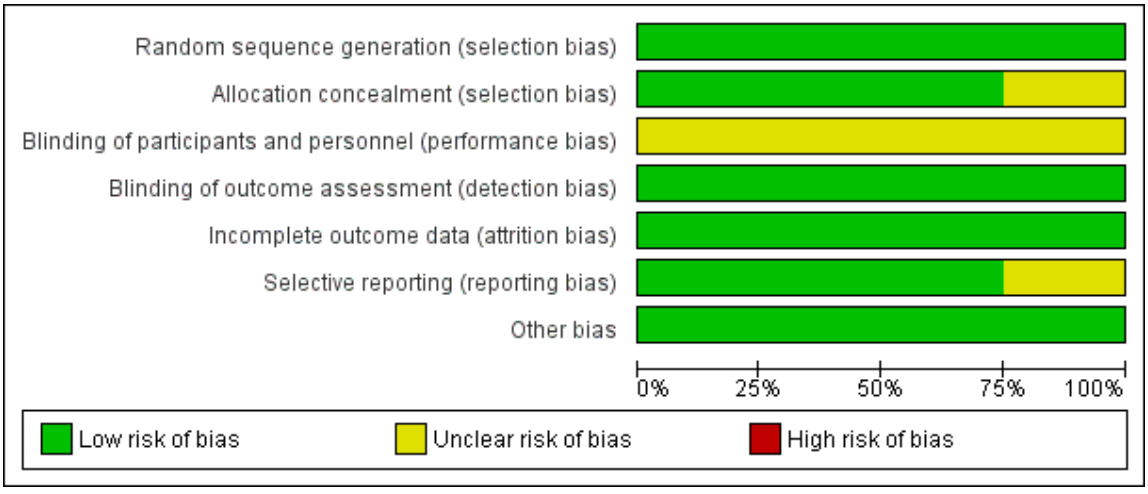

Figure S2. Risk of bias graph: judgments about each risk of bias item presented as percentages across all **randomized controlled trials**.

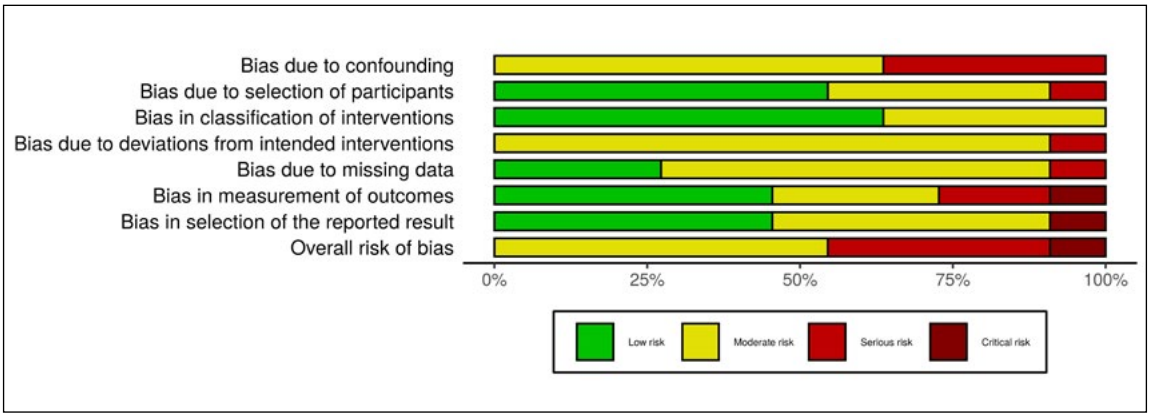

Figure S4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all **observational studies**.

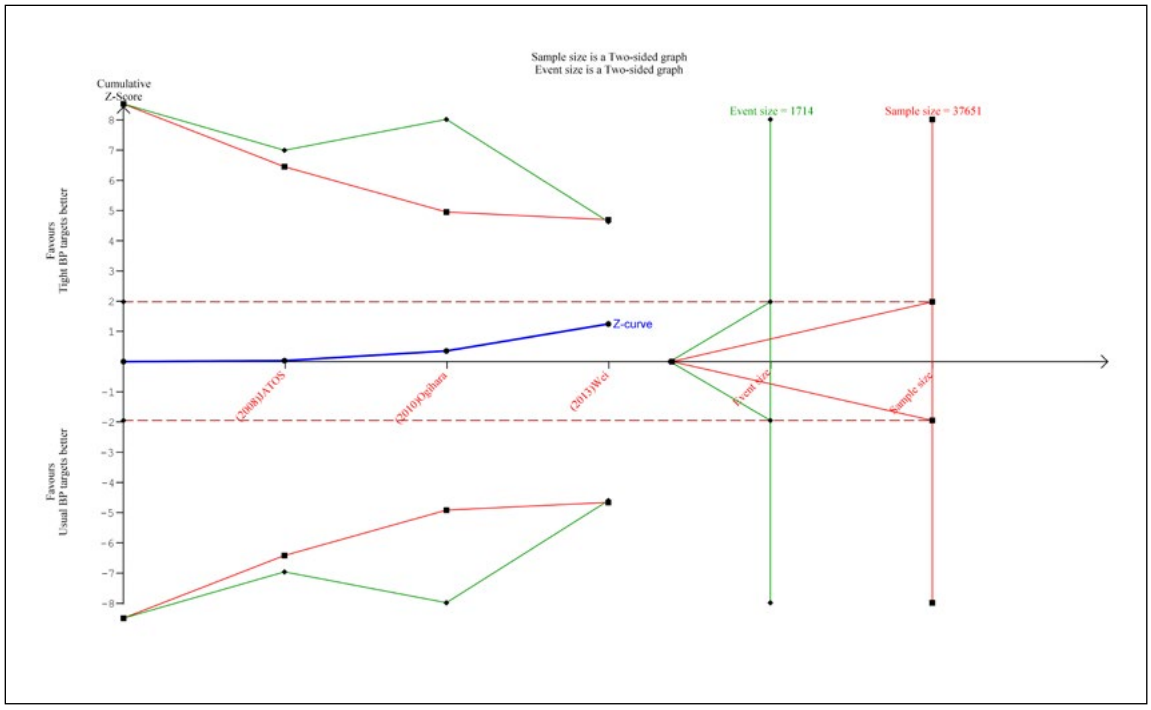

Figure S5. Trial sequential analysis of **randomized controlled studies** for tight versus standard diastolic blood pressure targets in elderly Asian patients with hypertension. The cumulative Z-curve did not cross the O'Brien-Fleming or futility boundaries. Also, the curve did not reach the required information size calculated as a required number of events (green line) or sample size (red line).

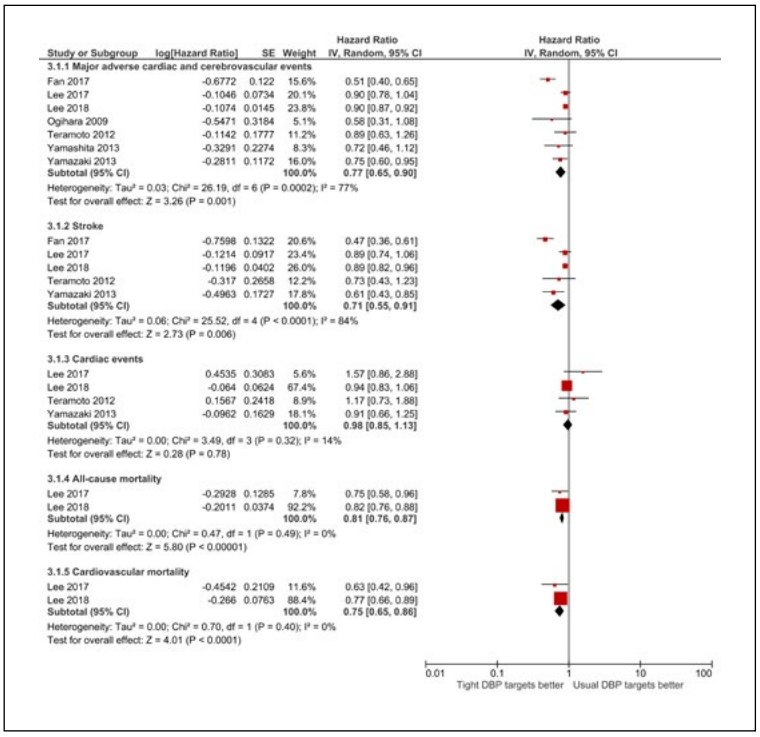

Figure S6. Forest plot of tight versus standard diastolic blood pressure targets in Asian patients with hypertension irrespective of age (**only observational studies**). SE: standard error, IV: inverse variance, CI: confidence interval, DBP: diastolic blood pressure.

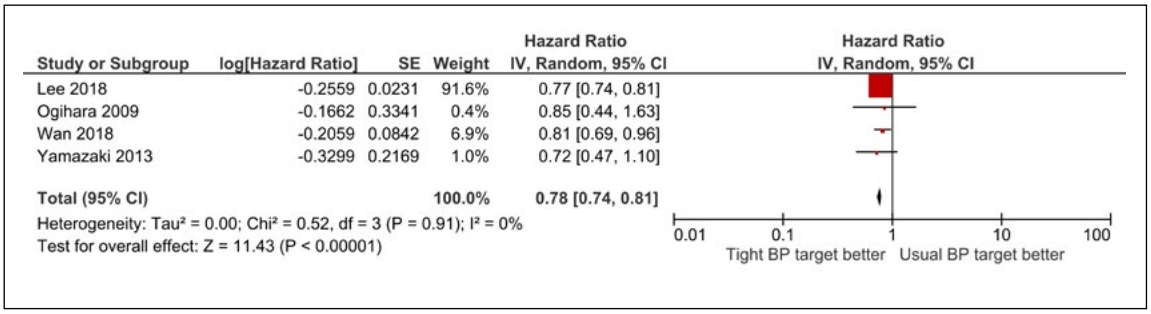

Figure S7. Forest plot of tight versus standard blood pressure targets in middle-aged Asian patients with hypertension (**only observational studies**). SE: standard error,IV inverse variance, CI: confidence interval, BP: blood pressure.

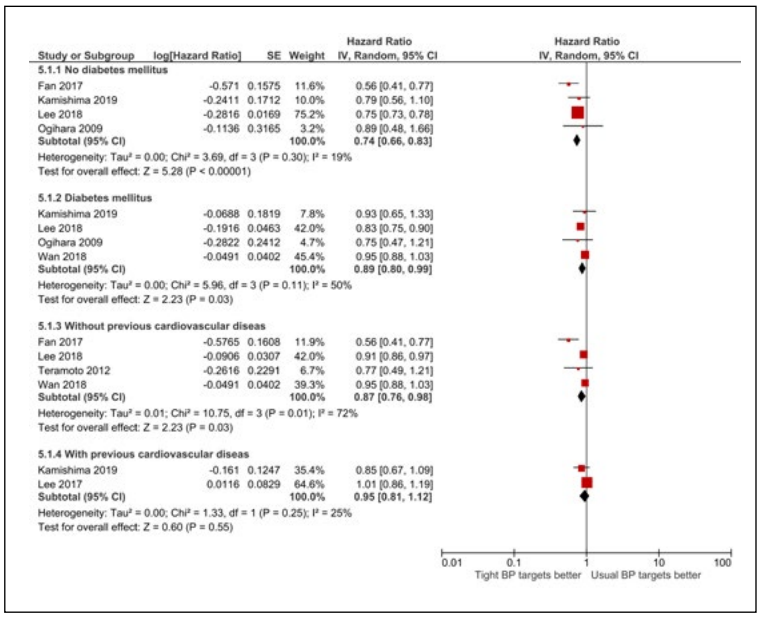

Figure S8. Subgroup analyses for tight versus standard blood pressure targets in Asian patients with hypertension for the study endpoints (**only observational studies**). SE: standard error, IV: inverse variance, CI: confidence interval, BP: blood pressure.

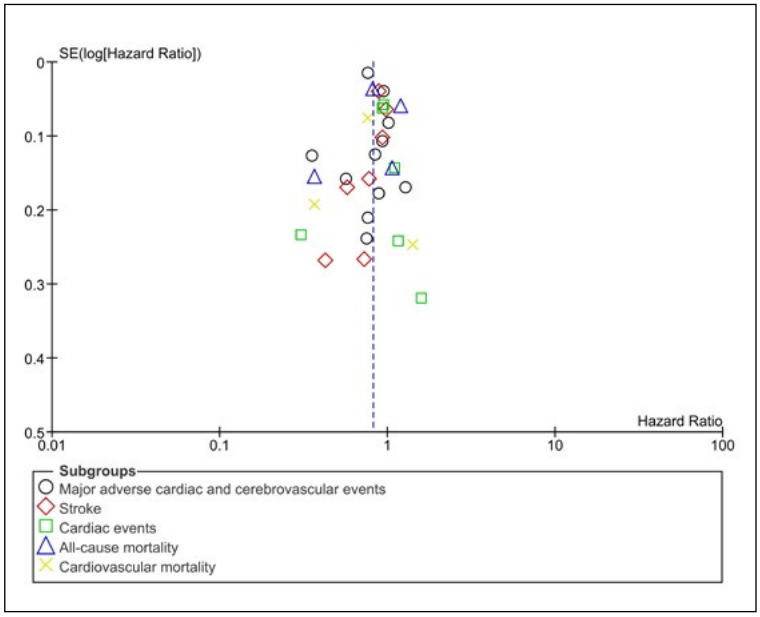

Figure S9. Funnel plots for tight versus standard systolic blood pressure targets in elderly Asian patients with hypertension for the study endpoints (**only randomized controlled studies**). SE: standard error.

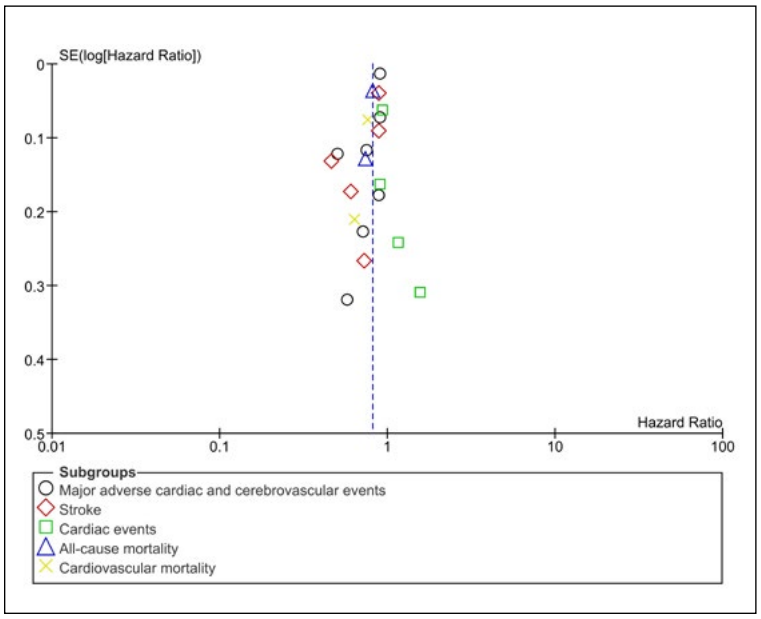

Figure S10. Funnel plots for tight versus standard systolic blood pressure targets in Asian patients with hypertension irrespective of age (**only observational studies**). SE: standard error.