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META-ANALYSIS

Antihypertensive effect of telmisartan versus perindopril in hypertensive patients

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ABSTRACT

OBJECTIVE: We performed this meta-analysis determining the antihypertensive effect of telmisartan versus perindopril in patients with essential hypertension.

BACKGROUND: The comparison of antihypertensive effects between telmisartan and perindopril were controversial.

METHODS: Pubmed, Web of Science, and Cochrane Central were searched for all published studies.

RESULTS: The antihypertensive effects were assessed in 753 patients included in 7 trials with a mean follow-up of 20 ± 16 weeks. There was no significant difference between telmisartan and perindopril in reduction of systolic blood pressure (SBP, weighted mean differences (WMD) 0.02 (95% confidence interval (CI), –2.78, 2.81) mmHg, $p > 0.05$). The reduction of diastolic BP (DBP) treated with telmisartan was greater than perindopril in these patients (WMD –2.05 (95% CI, –2.60, –1.49) mm Hg, $p < 0.001$). Considering the effects of different doses on BP reduction, a sub-analysis was performed. The reduction of DBP treated with 40 mg/day telmisartan was greater than 4–5 mg/day perindopril (WMD –2.18 (95% CI, –2.83, –1.53) mmHg, $p < 0.001$). There was no difference for SBP reduction treated with 40 mg/day telmisartan or 4–5 mg/day perindopril ($p > 0.05$).

CONCLUSION: The reduction of DBP is greater treated with telmisartan than perindopril in patients with essential hypertension *(Tab. 2, Fig. 4, Ref. 34)*. Text in PDF *www.elis.sk*

KEY WORDS: essential hypertension, blood pressure, telmisartan, perindopril, meta-analysis.

Introduction

Blockade of renin-angiotensin-aldosterone system (RAAS) is an important therapeutic way to reduce blood pressure (BP) in patients with essential hypertension (EH). Both angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are the first line of antihypertensive agents. Obviously, it is a critical issue to compare the antihypertensive effects and cardiovascular protection between ACE inhibitors and ARBs in these patients. Telmisartan is a unique ARB for pharmacologic properties, including the longest half-life among all ARBs (1). Besides the strongest binding affinity with angiotensin II type 1 receptor (AT1R) (2), telmisartan partially activates peroxisome proliferator-activated receptor gamma (PPAR-γ) (3, 4). Moreover, powerful and sustained BP control, and tolerability means that telmisartan may be a preferred option for patients with EH (5). ACE inhibitors are a heterogeneous class, varying in pharmacologic properties, which include lipophilicity, tissue-ACE binding, duration of action, half-life, and increased bradykinin availability (6). Among the ACE inhibitor class, the agent perindopril, in particular, has pleiotropic effects that are not equally shared by other ACE inhibitors, including bradykinin site selectivity and subsequent enhancement of nitric oxide and inhibition of endothelial cell apoptosis (6).

The comparison of antihypertensive effects between telmisartan and perindopril were controversial in several studies. Ragot et al (7) reported that the trough effect on diastolic BP (DBP) was statistically higher with telmisartan than with perindopril. Nalbantgil et al (8) found that telmisartan and perindopril both produce significant reductions in clinic systolic BP (SBP) and DBP, but the mean reduction in ambulatory DBP during the last 8 hour of the dosing interval is greater in patients treated with telmisartan. However, Nedogoda et al (9) reported that full-dose RAAS inhibition, perindopril reduces 24-hour SBP more effectively than telmisartan. These controversial results are at least partially due to the different drug doses in different trials. At present, no large strict designed clinical trial that compares the antihypertensive

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Tab. 1. Characteristics of studies included in this meta-analysis.

Study	Country	Design (blind)	Setting	Drug	Doses	Duration (weeks)	Other Drugs (antihypertensive) (%)	BP Measurement	JADAD scale
Gilowski et al 2018	Poland	open	Single center	Telmisartan	40 mg/d	24	No	Office	0
				Perindopril	4 mg/d	24	No		
Nedogoda et al 2013	Russia	Randomized single-blind	Single center	Telmisartan	80 mg/d	24	No	ABPM	1
				Perindopril	10 mg/d		No		
Nakamura et al 2009	Japan	Randomized open	Single center	Telmisartan	44.6±2.3 mg/d	48	CCB (54%) Diuretics (15%) α/β-Blockers (38%)	Office	1
				Perindopril	4.2±0.4 mg/d		CCB (48%) Diuretics (19%) α/β-Blockers (37%)		
Remková et al 2008	Slovak	open	Single center	Telmisartan	40 mg/d	4	No	Office	0
				Perindopril	5 mg/d		No		
Nalbantgil et al 2004	Turkey	Randomized double-blind	Single center	Telmisartan	80 mg/d	6	No	Office	2
				Perindopril	4 mg/d		No		
Ghiadoni et al 2003*	Italy	Randomized open	Single center	Telmisartan	80–160 mg/d	24		Office	1
				Perindopril	2–4 mg/d				
Ragot et al 2002	France	Randomized open	Multicenter	Telmisartan	40 mg/d	12	No	Office	1
				Perindopril	4 mg/d		No		

* Patients not yet normalized by single drug administration were treated by adding a diuretic (hydrochlorothiazide 12.5 mg). ABPM – ambulatory blood pressure monitoring; BP – blood pressure; CCB – calcium channel blocker

effects head-to-head between telmisartan and perindopril is available. The choice between ACE inhibitors and ARBs in antihypertensive therapy is a clinically important issue. Therefore, we performed this meta-analysis to compare the antihypertensive effects between telmisartan and perindopril in patients with EH.

Materials and methods

Data sources

Pubmed (1966–2022), Web of Science (1986–2022), and Cochrane Central (Cochrane Central Register of Controlled Trials: Issue 9 of 12, September 2022) were searched up to September 29, 2022, for all published studies comparing the antihypertensive effects between telmisartan and perindopril in patients with EH. Searched keywords were "hypertension", "telmisartan" and "perindopril". Studies with duplicate publication of results were excluded. The clinical trials were yielded through the process of selection for this meta-analysis.

Study selection criteria

English-written studies were selected for this meta-analysis according to the following inclusion criteria: a diagnosis of EH at study entry (i.e. studies on secondary hypertension were excluded); BP assessed at office, home or with ambulatory monitor; a follow-up of at least 4 weeks; clear description of inclusion and exclusion criteria; comparable baseline characteristics between telmisartan and perindopril; clear description of outcome measures as well as of patient withdrawals and dropouts; and statistical method accurately described.

Data collection and quality assessment

Two authors (D. Zhao and H. Liu) independently collected data from each study and entered them into a structured spreadsheet.

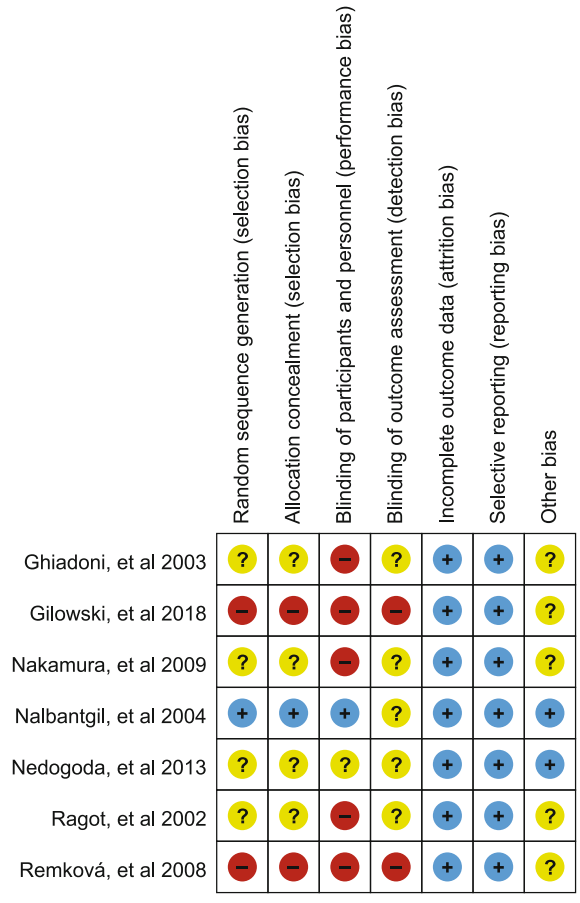


Fig. 1. Risk of bias summary for each included study. "+" circle: low risk of bias; "–" circle: high risk of bias; "?" circle: unclear risk of bias.

Tab. 2. Main Characteristics of patients included in these studies.

Study	Treatment Group	No. of pts	Age (yrs)	Gender		SBP/DBP (mm Hg)	BMI (kg/m²)	FPG (mmol/L)	HbA1c (%)
				Male	Female				
Gilowski et al 2018	Telmisartan	26	49±12	18	8	154±15/93±7	28.1±4.3	5.6±0.8	None
	Perindopril	26	45±10	17	9	149±12/90±8	27.8±3.9	5.4±0.4	None
Nedogoda et al 2013	Telmisartan	30	47.4±9.2	15	15	153±13/97±9	31.1±3.1	7.1±1.1	6.8±0.3
	Perindopril	30	49.7±8.2	16	14	156±12/99±9	31.1±2.9	7.2±1.3	6.9±0.3
Nakamura et al 2009	Telmisartan	26	66.6±2.5	12	14	157±16/87±5	24.3±0.6	6.3±0.2	5.6±0.3
	Perindopril	27	63.0±2.0	11	16	156±10/85±3	24.1±1.0	6.1±0.3	5.5±0.2
Remková et al 2008*	Telmisartan	36	55.8±14.2	11	25	148±12/92±8	27.3±2.0	5.4±0.4	None
	Perindopril								
Nalbantgil et al 2004	Telmisartan	30	51.1±7.8	18	12	167±9/102±5	None	None	None
	Perindopril	30	50.4±8.8	17	13	168±6/101±4	None	None	None
Ghiadoni et al 2003	Telmisartan	29	50±9	18	11	151±10/100±7	None	5.4±0.4	None
	Perindopril	28	51±11	18	10	153±9/100±6	None	5.3±0.4	None
Ragot et al 2002	Telmisartan	217	55.1±11.6	124	93	158±13/98±6	None	None	None
	Perindopril	218	55.5±12.0	114	104	159±13/98±6	None	None	None

* The data of baseline clinical characteristics were provided only with all hypertensive patients other than in each group. pts: patients; SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; FPG –fasting plasma glucose; HbA1c – hemoglobin A1c

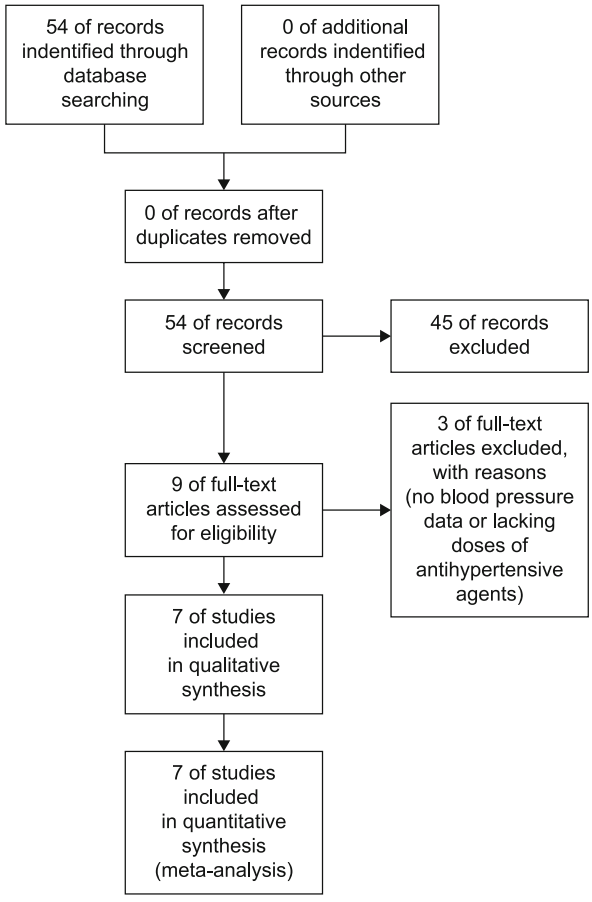


Fig. 2. Flow diagram demonstrating the selection process of included studies in this meta-analysis.

Disagreements were resolved through discussion or by a third investigator (P. Dong) as required. We extracted the following data from each trial: year of publication; demographic and methodological data; total number, mean age, gender distribution and race of enrolled patients; baseline SBP and DBP; number of patients assigned to each intervention; duration of therapy; incidence and type of adverse events; number of dropouts or withdrawals because of adverse events; and change from baseline of SBP and DBP.

The characteristics and quality of the studies included herein are shown in Table 1. Two reviewers (D. Zhao and H. Liu) independently assessed study quality using a validated scale (JADAD scale) based on the following criteria: methods used to generate the randomization sequence, methods of double blinding, and description of patient withdrawals and dropouts (10, 11). A score of 1 point was given for each criterion satisfied, and 1 additional point was given for high quality of randomization and double blinding, for a maximum of 5 points. Studies with a score > 2 were considered high quality, and studies with a score ≤ 2 were considered low quality. In addition, risk of bias summary is shown in Figure 1.

Outcome measures

The outcomes of interest were changes from baseline of both SBP and DBP during treatment periods. Incidence of any adverse event was used for safety measures. Serious adverse events were considered as withdrawal of study treatment.

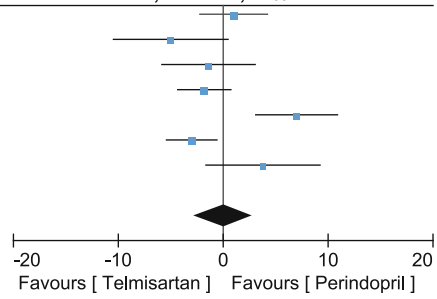
Statistical analysis

Data were combined at the study level for this meta-analysis and were analyzed utilizing the Review Manager 5.3 software (available from The Cochrane Collaboration at http//www.cochrane.org) and STATA software package (version 12.0; Stata Corp., College Station, TX), respectively. Weighted mean differences (WMD) with 95% confidence intervals (CI) were considered for comparisons of SBP and DBP reduction. Heterogeneity of the included studies was tested with Q statistics (12). We also tested the extent of inconsistency between results with I^2 statistics (12). If an $I^2 > 50$ %, heterogeneity was considered significant. A random-effect model was used for calculating summary estimates and their 95% CI if there was significant heterogeneity. Publication bias was detected with funnel plots. Significance was set at $p < 0.05$.

A. Systolic Blood Pressure Reduction

Study or Subgroup	Telmisrtan Mean	SD	Total	Perindopril Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ghiadoni, et al 2003	-18	6.3	29	-19	6.1	28	15.7%	1.00 [-2.22, 4.22]
Gilowski, et al 2018	-18	11	26	-13	9	26	11.3%	-5.00 [-10.46, 0.46]
Nakamura, et al 2009	-20.2	9.8	26	-18.8	6.26	27	13.2%	-1.40 [-5.85, 3.05]
Nalbantgil, et al 2004	-27.7	5.7	30	-25.9	4.2	30	17.0%	-1.80 [-4.33, 0.73]
Nedogoda, et al 2013	-15	8.16	30	-22	7.21	30	14.3%	7.00 [3.10, 10.90]
Ragot, et al 2002	-13.9	13.7	217	-10.9	11.9	218	17.2%	-3.00 [-5.41, -0.59]
Remková, et al 2008	-20.2	7.26	16	-24	9.39	20	11.3%	3.80 [-1.64, 9.24]
Total (95% CI)			**374**			**379**	**100.0%**	**0.02 [-2.78, 2.81]**

Heterogeneity: Tau² = 10.30; Chi² = 25.36, df = 6 (P = 0.0003); I² = 76%
Test for overall effect: Z = 0.01 (P = 0.99)



B. Diastolic Blood Pressure Reduction

Study or Subgroup	Telmisrtan Mean	SD	Total	Perindopril Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ghiadoni, et al 2003	-14	4.2	29	-14	3.8	28	7.2%	0.00 [-2.08, 2.08]
Gilowski, et al 2018	-8	7	26	-6	6	26	2.5%	-2.00 [-5.54, 1.54]
Nakamura, et al 2009	-10.2	8.2	26	-8	7.6	27	1.7%	-2.20 [-6.46, 2.06]
Nalbantgil, et al 2004	-12.4	1.7	30	-10.1	3.2	30	18.6%	-2.30 [-3.60, -1.00]
Nedogoda, et al 2013	-12	5.4	30	-13	5.4	30	4.2%	1.00 [-1.73, 3.73]
Ragot, et al 2002	-8.9	3.5	217	-6.6	4	218	62.7%	-2.30 [-3.01, -1.59]
Remková, et al 2008	-17.5	5.21	16	-13.2	4.55	20	3.0%	-4.30 [-7.54, -1.06]
Total (95% CI)			**374**			**379**	**100.0%**	**-2.05 [-2.60, -1.49]**

Heterogeneity: Chi² = 11.01, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 7.17 (P < 0.00001)

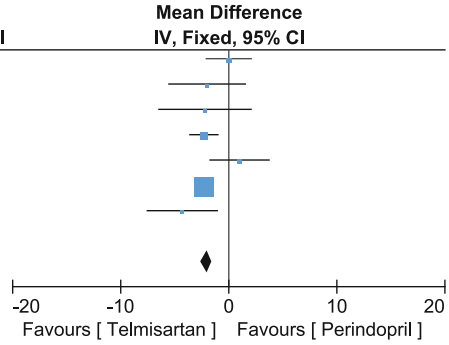


Fig. 3. Comparison of SBP and DBP reduction in patients with EH treated with telmisartan or perindopril. WMD of data with 95% CI of difference between changes in SBP and DBP were considered. The data are presented as mean ± SD. SBP – systolic blood pressure; DBP – diastolic blood pressure; WMD – weighted mean differences; CI – confidence interval; SD – standard deviation.

Results

Search strategy

A total of 131 screened articles initially met the search inclusion criteria (31 from Pubmed, 71 from Web of Science, and 29 from Cochrane databases). After excluding 0 duplicate articles, 131 articles were further evaluated. Most of these articles (n = 122) were excluded after reviewing the abstract or title, mostly due to trial design, antihypertensive agent choice or because these were reviews or reference abstract. We carefully evaluated 9 articles with full text and 2 articles were discarded due to no BP data or lacking antihypertensive agent doses. Finally, 7 articles were selected for current meta-analysis (7–9, 13–16). The selection progress of candidate article is documented as flow diagram in Figure 2.

Study participants and included studies

A total of 753 patients were included in these 7 studies. Table 1 and Table 2 show the main characteristics of included studies and study participants. All these studies investigated the antihypertensive effects of telmisartan and perindopril in patients with EH (7–9, 13–16). The duration of treatment in these studies ranged from 4 to 48 (20 ± 15) weeks.

Comparison of SBP and DBP reduction between telmisartan and perindopril

As shown in Figure 3 (A), there was not a significant difference for the reduction of SBP treated with telmisartan or perindopril (WMD 0.02 (95% CI, –2.78, 2.81) mm Hg, $p > 0.05$). As shown in Figure 3 (B), the reduction of DBP treated with telmisartan was greater than with perindopril (WMD –2.05 (95% CI, –2.60, –1.49) mm Hg, $p < 0.001$).

Considering the effects of different doses on BP reduction for ACE inhibitors and ARBs, sub-analysis was performed for comparison between 40 mg/day telmisartan and 4–5 mg/day perindopril. As shown in Figure 4 (A), there was not a significant difference for the reduction of SBP treated with telmisartan or perindopril (WMD 0.27 (95% CI, –4.16, 4.71) mm Hg, $p > 0.05$). As shown in Figure 4 (B), the reduction of DBP treated with telmisartan was greater than perindopril (WMD –2.18 (95% CI, –2.83, –1.53) mm Hg, $p < 0.001$).

Discussion

This meta-analysis provides the evidence that the reduction of DBP is greater treated with telmisartan than perindopril in patients

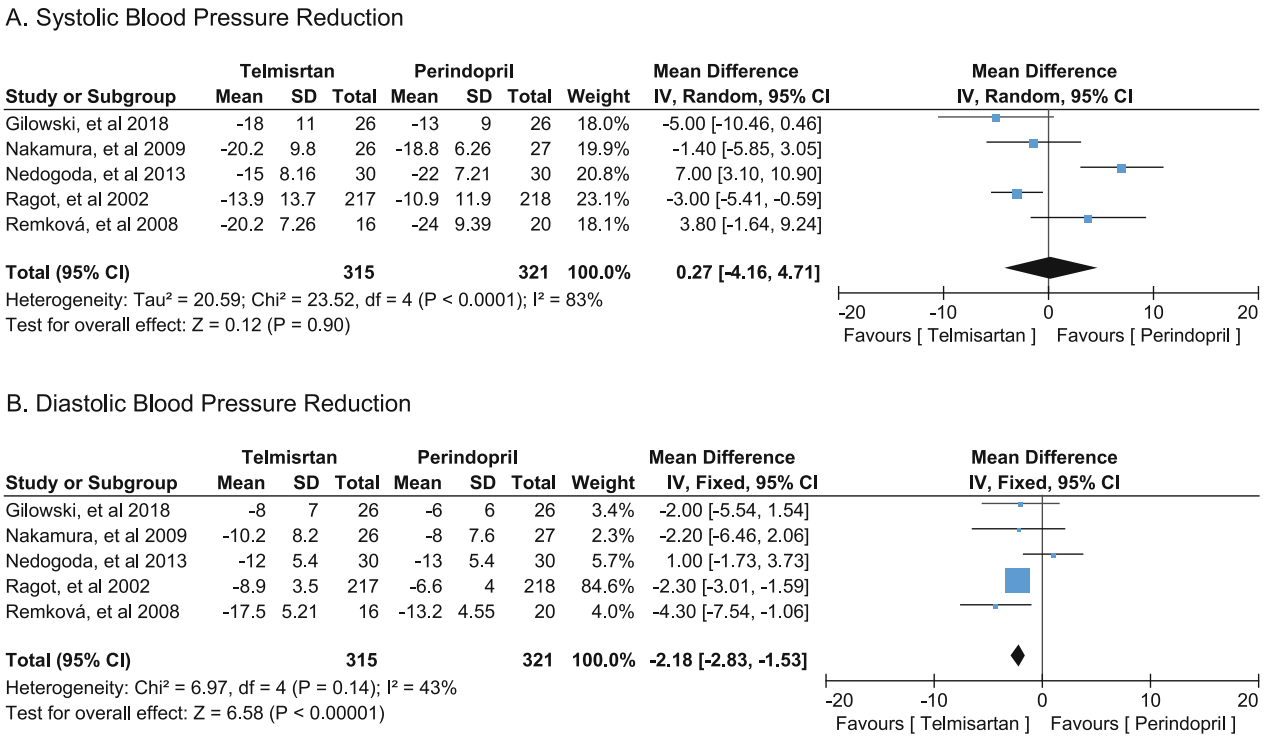


Fig. 4. Comparison of SBP and DBP reduction in patients with EH treated with 40 mg/day telmisartan or 4–5 mg/day perindopril. WMD of data with 95% CI of difference between changes in SBP and DBP were considered. The data are presented as mean ± SD. SBP – systolic blood pressure; DBP – diastolic blood pressure; WMD – weighted mean differences; CI – confidence interval; SD – standard deviation.

with EH. However, whether only near 2 mm Hg higher reduction of DBP really affects cardiovascular prognosis is an issue in clinical practice. We did not find a significant difference for SBP reduction treated with telmisartan or perindopril. In fact, the effects of telmisartan versus perindopril on reduction of SBP were inconsistent in these trials. The antihypertensive effect of telmisartan or perindopril should greatly depend on the doses of these antihypertensive agents. Therefore, we performed a sub-analysis for comparison between 40 mg/day telmisartan and 4–5 mg/day perindopril and confirmed that the reduction of DBP treated with 40 mg/day telmisartan was greater than 4–5 mg/day perindopril. However, whether this slightly stronger antihypertensive effect could provide a better cardiovascular protection and improve cardiovascular prognosis is still to be further investigated. In addition, the reduction of SBP was similar treated with 40 mg/day telmisartan or 4–5 mg/day perindopril in patients with EH.

BP control in hypertensive patients remains poor worldwide, particularly in high-risk patients with hypertension and diabetes (17). BP lowering is likely to provide a similar level of protection against major vascular events for patients with isolated diastolic hypertension as for those with isolated systolic hypertension and systolic-diastolic hypertension (18). Compared to a DBP of 70 to < 80 mm Hg, lower and higher DBP was associated with a higher risk in patients achieving a SBP of 120 to < 140 mm Hg. These findings support guidelines which take DBP at optimal SBP control into consideration (19). As the representative antihypertensive agents in ACE inhibitors and ARBs respectively, both perindopril and telmisartan have a very long half-life of 24 hours. This characteristic is very important to control BP during the last period of the dosing interval, such as the control of nocturnal BP and morning BP. Furthermore, maintaining smooth BP over the entire 24 hours dosing period may contribute to the improvement of CV outcomes, and reductions in BP variability may decrease end organ damage, and reduce CV risk (20). Parati et al (21) reported that telmisartan significantly reduced the mean morning ambulatory BP, daytime ambulatory BP, 24-hour ambulatory BP and clinic BP in previously untreated and in treated patients who switched to telmisartan. Telmisartan increased smooth 24-hour BP control in daily management of hypertension (21).

Besides the reduction of BP, antihypertensive therapy should be assessed for the possibility of improvement of cardiovascular prognosis. There is a large amount of evidence to suggest that perindopril therapy may reduce cardiovascular event rates in patients (6). Among the ACE inhibitors, perindopril appears to have the greatest effects on inhibiting the degradation of bradykinin, which stimulates local release of NO (22). This effect should contribute to the improvement of cardiovascular prognosis. Moreover, lisinopril users were significantly more likely to be admitted due to respiratory diseases, renal diseases, diabetes and all causes at 24 months than perindopril users (23, 24), suggesting different ACE inhibitors

might have a different incidence of hospital admissions (24). These intra-class differences of ACE inhibitors could be considered by clinical guidelines when the preferred first-line antihypertensive drugs are recommended (23). Notably, both baseline clinical phenotype and genotype determine the efficacy of widely prescribed ACE inhibitor in stable coronary artery disease (CAD) (25). The addition of perindopril to β-blocker in stable CAD patients was safe and resulted in reductions in cardiovascular outcomes and mortality compared with standard therapy including β-blocker (26). The beneficial cardioprotective effects of perindopril treatment are additive to the background beta-blockers use (27). The clinical trial data for ARBs are less consistent, particularly regarding cardiovascular outcomes and mortality benefit. The evidence supports the use of ACE inhibitors compared with ARBs despite current prescribing trends (28). However, in the ONTARGET trial, telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes in preventing events (29), even though BP reduction was superior with telmisartan. In a post-hoc analysis, myocardial infarction may be further reduced by telmisartan in ACE intolerant hypertensive patients with cardiovascular disease (30). These results suggest the cardiovascular protection of telmisartan in patients with antihypertensive therapy. Some of the benefits conferred by ARBs may not be class-specific effects, and instead may be molecule-specific effects. Their slightly different structures may be important for promoting molecule-specific effects (31). As the representative ARB, telmisartan has several advantages compared with other ARBs. This may be the major reason for us to compare telmisartan and perindopril, a representative ACE inhibitor. Since the target of hypertension management has shifted to reducing absolute cardiovascular risk (28), head-to-head comparison of telmisartan and perindopril with long term therapy should demonstrate the effects of these two agents on cardiovascular protection and provide more accurate evidence for a choice between them.

Telmisartan was reported to have the strongest PPAR-γ affinity among ARBs (32). It means that telmisartan provides a greater beneficial effect on glucose metabolism than other ARBs and ACE inhibitors in hypertensive patients (33) and may have beneficial effects in type 2 diabetes mellitus and the metabolic syndrome beyond its antihypertensive effect (34). However, diverse findings have been obtained in several small clinical studies (33). The incidence of diabetes in the group taking 80 mg per day telmisartan for a maximum of 5 years was not significantly different from that of the group taking the ACE inhibitor ramipril at a dose of 10 mg per day (29). Oral dosing of 80 mg telmisartan in hypertensive patients seems to be enough to inhibit the AT1 receptor, but too low to activate PPAR-γ. Therefore, its effect is too small to exert an additional benefit on glucose metabolism in clinical practice (33). Development of new ARBs with more potent PPAR-γ activating properties is needed to further improve the outcome of these patients (33).

This meta-analysis had several limitations. The major limitation may be the different doses of telmisartan and perindopril used in these studies, which definitely affect the assessment of antihypertensive efficacy, as the difference of DBP reduction is only near 2 mm Hg. The second limitation is the study design and the small samples. Strictly designed randomized controlled trials will be helpful to answer the question of antihypertensive effect of telmisartan versus perindopril.

Conclusion

The reduction of DBP is greater treated with telmisartan than perindopril in patients with EH. Future studies should investigate the effects of different ACE inhibitors and ARBs on various outcomes with long term antihypertensive therapy.

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