The Current Update on the Efficacy of Telmisartan in Patients with Hypertension: A Systematic Review

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Abstract. Hypertension is a chronic condition which is often found worldwide and becomes a major risk factor for cardiovascular disease. Initial antihypertensive therapy with Angiotensin Receptor Blocker can be used for patients who have intolerance to Angiotensin-Converting Enzyme Inhibitors, such as telmisartan. Telmisartan can be taken as monotherapy or in combination with other antihypertensive drugs. This study was designed to review the current update on the efficacy of telmisartan in patients with hypertension as single-dose or double-dose monotherapy or in combination therapy. Methods: We searched the PubMed, ScienceDirect, and Hindawi databases for terms related to telmisartan efficacy as single-dose or double-dose monotherapy, in combination with amlodipine or hydrochlorothiazide, and as therapy for hypertension with diabetes or for dyslipidemia patients with blood pressure and TGs or LDL cholesterol or post-meal blood sugar or fasting insulin or fasting plasma glucose. The articles matching the restriction criteria were then passed the PRISMA flowchart. The quality of the articles was tested using the GRADE method. Results: The article searches found 1033 journals, 12 articles were eligible for systematic review with high-grade result, 1 article with moderate-grade result, and 1 article with low-grade result based on the GRADE method. The review of articles on telmisartan single-dose monotherapy showed significantly reduced blood pressure (±5.61/5.15 mmHg) and 21.8 ± 5.592/16.00 ± 5.965 mmHg when used as double-dose therapy. The combination of telmisartan with amlodipine showed a highly significant effect to reduce blood pressure (−15.3 ± 11.2/−8.0 ± 8.6 mmHg) after 8 weeks, and with hydrochlorothiazide it was −31.1−18.1 mmHg in 8 weeks. For hypertension patients with diabetes, telmisartan has significantly reduced blood pressure (−24.9/−19.5 mmHg), post-meal blood sugar (−36.9 mg/dL) after 12 weeks, and FPG (−1.06 mg/dL) as well as fasting insulin (−0.818 μU/mL). Telmisartan has good tolerability for treatment with anti-cholesterol drugs. Conclusion: Telmisartan is favorable and effective for the treatment of patients with hypertension as single-dose and double-dose monotherapy, in combination with amlodipine or hydrochlorothiazide, and therapy for hypertension with diabetes or dyslipidemia patients.

Keywords: Telmisartan · Hypertension · Efficacy · Combination

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1 Introduction

Hypertension is one of the most common chronic conditions and is characterized by persistent elevated arterial pressure. In hypertension, there is an increasing blood pressure, where the systolic pressure is more than or equal to 130 mmHg and the diastolic pressure is more than 80 mmHg [1].

Hypertension is estimated to cause 7.5 million deaths or about 12.8% of total deaths worldwide. Hypertension also causes 57 million of Disability Adjusted Life Years (DALY). In 2011–2012, 25% of adults in the United States suffered from hypertension [2]. In Japan, more than 60% of men aged 50 years and women aged 60 had hypertension in 2016 [3].

To date, hypertension remains a major challenge in Indonesia because this condition is often found in primary health services. Based on the Basic Health Research (RISKESDAS) in 2013, the prevalence of hypertension in Indonesia was quite high, at 26.5% [4]. Uncontrolled hypertension is estimated to reach more than 50% and is the main risk of cardiovascular disease. In addition, complications that can occur due to hypertension include coronary heart disease, stroke, heart failure, chronic kidney disease, retinal damage, and peripheral vascular disease [5].

Good hypertension management is needed to control blood pressure in hypertensive patients. The Eighth Joint National Committee (JNC 8) recommends antihypertensive drugs from the class of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) as initial therapy [6]. The mechanism of action of the drugs from both groups is almost the same as they modify the renin-angiotensin-aldosterone system (RAAS) as a regulator of extracellular fluid balance and blood pressure [7]. ARB can be used for patients who have intolerance to ACEI. One example of a frequently used ARB class of antihypertensive drugs is telmisartan [8].

As a medication for hypertension, telmisartan can be taken as monotherapy or in combination with other antihypertensive drugs, such as amlodipine and hydrochlorothiazide (HCT). The combination of single-dose (SD) telmisartan and single-dose amlodipine has shown to significantly reduce systolic blood pressure (SBP) when compared with double-dose (BD) telmisartan monotherapy or double-dose amlodipine [9]. When combined with 12.5 mg HCT, telmisartan 40 mg and 80 mg were more effective than the losartan-HCT combination (50–12.5 mg). In addition, the decrease in blood pressure, both systolic blood pressure and diastolic blood pressure by the telmisartan-HCT combination (80–12.5 mg) was greater than the valsartan-HCT combination (160–12.5 mg) in obese patients with type 2 diabetes mellitus and hypertension [10].

Telmisartan can also be given as a single-dose or double-dose medication. The effect of telmisartan in lowering diastolic blood pressure is related to its long half-life. A single-dose telmisartan (40 mg) given once a day can significantly increase glucose metabolism in people with insulin resistance, making it recommended for hypertensive patients with comorbid diabetes mellitus [11]. Therefore, this study was designed to review the update on the efficacy of telmisartan therapy in patients with hypertension or other comorbidities and of telmisartan as monotherapy or combination and telmisartan as single-dose or double-dose therapy.

2 Method

2.1 Information Sources and Search Design

We used data retrieval techniques through three e-databases, which were PubMed, ScienceDirect, and Hindawi, for terms related to telmisartan efficacy as single-dose or double-dose monotherapy, in combination with amlodipine or hydrochlorothiazide, and as therapy for hypertension with diabetes or dyslipidemia patients with blood pressure and TGs or LDL cholesterol or post-meal blood sugar or fasting insulin or fasting plasma glucose. The keywords we used in the e-databases were efficacy OR "Therapeutic equivalency" AND Telmisartan OR "Angiotensin II Type 1 Receptor Agonist" AND Hypertension.

2.2 Eligibility and Selection Criteria

The study designs were randomized controlled trials (RCT), non-RCT, and observational study as the inclusion criteria, and the primary outcome was decreasing blood pressure. In addition, the journals selected in this study used Indonesian or English and were published within the last ten years. The study participants as part of the inclusion criteria were at least 18 years old. Patients who used telmisartan as monotherapy or in combination with other antihypertensives and had a history of diabetes, coronary heart disease, and chronic kidney disease were excluded.

2.3 Data Items and Data Collection

Our primary outcome was a reduction in blood pressure from the baseline to the final result. Meanwhile, our secondary outcomes that might be included in this study were decreased HbA1c, improved lipid profile, and reduced risk of complications due to hypertension calculated from the baseline to the final result. To assess the outcome efficacy, we extracted data from studies which assessed the use of telmisartan as a single drug or in combination with amlodipine or hydrochlorothiazide (HCT). In addition, data was extracted from studies which assessed the use of telmisartan as single-dose or double-dose medication.

2.4 Risk of Bias and Quality of Evidence

We used a system adopted by Cochrane's collaboration called GRADE (Grading of Recommendations, Assessment, Development, and Evaluations). It is a method used by systematic reviewers and guideline developers to assess the quality of evidence and to recommend drug intervention in certain diseases. In this study, the GRADE analysis was performed with five different steps to determine the final result of quality assessment of the articles that contained a risk of bias assessment. The first step was determining the grade value of the articles based on their study designs, such as Randomized Controlled Trials given "high" grade value and observational study given "moderate" grade value. The second step was downgrading or upgrading for each article. The articles would be downgraded if there were risk of bias, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias. Otherwise, the articles would be upgraded if there were a large magnitude of effect, all plausible confounding factors that would

reduce the demonstrated effect or increase it if no effect was observed, and dose-response gradient. The third step was determining the final grade for each article. The fourth step was considering other factors that affected the strength of the intervention recommendations, while the last step was making recommendations based on the quality of the evidence that has been found.

3 Result and Discussion

3.1 Search Results

We recorded the articles that we obtained as many as 1033 articles, consisting of 298 articles from PubMed, 718 articles from ScienceDirect, and 17 articles from Hindawi. We eliminated 51 duplicate articles. We screened titles and abstracts then eliminated irrelevant titles (n = 929) and abstracts (n = 29). Finally, we rated 24 full-text articles and found 14 articles that fitted our criteria by eliminating 10 articles because two articles used ACE-I and diuretics in previous treatment, one article was a review article, three articles involved renal disease population, one article used Chinese, two articles had no full text, and one article was a duplicate (Fig. 1).

3.2 Characteristics of the Studies

Fourteen articles with a total population of 3,753 patients consisting of 2,081 female patients and 1,579 male patients, and 93 patients were not determined. The population age contained in all articles was more than 45 years old (Table 1). There were five articles that discussed hypertension with comorbid diabetes mellitus and dyslipidemia. Two articles discussed hypertension with diabetes mellitus, and three articles discussed hypertension with dyslipidemia. There were eight articles discussing telmisartan as combination therapy, and two articles discussed telmisartan as monotherapy. All of the studies obtained provided interventions with different durations. The control interventions in each study were placebo, olmesartan, losartan, amlodipine, azilsartan, hydrochlorothiazide, rosuvastatin, and double dose telmisartan (Table 2).

3.3 Risk of Bias Assessment

We used the GRADE (Grade of Recommendations, Assessment, Development, and Evaluations) method to assess the risk of bias contained in 14 articles. There was one article that had a change in the quality of evidence from the initial grade to the final grade. The initial grade of the article was low because the article used non-RCT in the study design. Then, the final grade of the article was moderate because there was an increase in the dose-response gradient in the upgrade factor.

There was no change in the other articles in terms of the quality of evidence from the initial grade to the final grade because there was no risk of bias in the articles. In the 13 articles, there were no downgrade factors among the limitations in the study design and/or execution, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias (Table 3).

Table 1. Demographic Data

No	Autor, Years	Population	Sex		Age [(Mean; Group)]
			Male	Female	
1.	Kalikar, Mrunalini., *et al.,* 2017	57	37	20	46.2 (O20); 48.26 (T40); 49.94 (L50)
2.	Park, Chang Gyu., *et al.,* 2016	177	154	23	53.5 (A2.5/T40); 55.2 (A5/T40); 51 (T80)
3.	Ohishi, Mitsuru., *et al.,* 2013	44	23	21	67.8 ± 10.2 (A5/T40)
4.	Zhu, Dingliang., *et al.,* 2014	314	165	149	52.4 ± 9.7 (A5); 52.4 ± 8.7 (T80/A5)
5.	Neutel, Joel M., *et al.,* 2012	858	445	413	58.0 ± 10.4 (T80/A10); 58.1 ± 10.2 (T80); 58.6 ± 10.5 (A10)
6.	Gadge, Pradeep., *et al.,* 2018	132	67	65	55.3 ± 10.4 (group A) and 57.2 ± 10.7 (group B)
7.	Naruse, Miitsuhide, *et al.,* 2019	33	14	19	63.2 (Az20) and 65.3 (T40)
8.	Goyal, *et al.,* 2014	93	-	-	-
9.	Marfatia, *et al.,* 2012	725	400	325	57 (T80/H25); 56 (V160/H25); 56.4 (P)
10.	Shiga, *et al.,* 2012	44	22	22	71 ± 14 (T80/H12.5)
11.	Zhu, *et al.,* 2013	858	461	397	285 (T40/T80); 573 (T40 + H12.5/ T80 + H25)
12.	Hong, *et al.,* 2019	144	98	46	67.96 (T40/A5/R20); 66.63 (T40/A5); 65.88 (T40/R20)
13.	Oh, *et al.,* 2018	203	150	53	59.8 (T80/R20); 62.5 (R20); 62.1 (T80); 61.8 (P)
14.	Choi, *et al.,* 2021	71	45	26	62.15 (T40–80); 60.92 (T80/R10–20)

Note: O20 (Losartan 20 mg), T40 (Telmisartan 40 mg), L50 (Losartan 50 mg), A2.5 (Amlodipine 2.5 mg), A5 (Amlodipine 5 mg), T80 (Telmisartan 80 mg), A10 (Amlodipine 10 mg), Az20 (Azilsartan 20 mg), R20 (Rouvastatin 20 mg), H12.5 (Hydrochlorothiazide 12.5 mg), H25 (Hydrocholorothiazide 25 mg)

3.4 Discussion

Angiotensin Receptor Blocker therapy is appropriate and suggested as alternative therapy if there are patients who cannot tolerate Angiotensin Converting Enzymes Inhibitor therapy due to an ACE-I induced cough or angioneurotic edema [12]. Telmisartan, a highly selective angiotensin II type 1 receptor antagonist, is approved for the treatment of hypertension. Telmisartan can also be used as single-dose or double-dose monotherapy or as a combination with other antihypertensive agents [13].

Table 2. Telmisartan Efficacy Outcome Intervention

No	Author, Year	Intervention	Control	Outcome
1.	Kalikar, Mrunalini., *et al.,* 2017	Telmisartan 40 mg once a day	• Olmesartan 20 mg once a day • Losartan 50 mg mg once a day	• The decrease in SBP/DBP on telmisartan therapy was very significant with a 12th week end-point of 137.1/82.53 mmHg.telmisartan significantly reduced the FBGLs at 12 weeks which was not seen with olmesartan and losartan • Telmisartan significantly reduced serum TGs and LDL cholesterol when compared with Losartan and also significantly reduced LDL cholesterol when compared with olmesartan
2.	Park, Chang Gyu., *et al.,* 2016	• S-Amlodipine 2.5 mg/Telmisartan 40 mg • S-Amlodipine 5 mg/Telmisartan 40 mg	Telmisartan 80 mg	• The decrease in SBP/DBP was very significant in the combination group with S-Amlodipine of −10.56/−8.12 mmHg (S-AM2.5/TEL40) and −12.32/−9.88 mmHg (S-AM5/TEL40) compared to TEL80 −2.44 /−1.76 mmHg after 8 weeks of treatment
3.	Ohishi, Mitsuru., *et al.,* 2013	Telmisartan 40 mg/Amlodipine 5 mg morning administration	Telmisartan 40 mg/Amlodipine 5 mg evening administration	• There was no significant BP reduction in either the morning or afternoon treatment group after 8 weeks of treatment. However, both lowered BP −15.3 ± 11.2/−8.0 ± 8.6 mmHg (morning) and −13.5 ± 14.5/−8.0 ± 7.8 mmHg (evening)
4.	Zhu, Dingliang., *et al.,* 2014	Telmisartan 80 mg/Amlodipine 5 mg	Amlodipine 5 mg	• Patients achieving the seated through DBP goal (<90 mmHg) and seated through SBP goal (<140 mmHg) at week 8 were also significantly higher in the T80/A5 than A5. Rates for DBP (<90 mmHg and/or reduction from baseline ≥10 mmHg) and SBP (<140 mmHg and/oor reduction from baseline ≥ 15 mmHg) were significantly higher in the T80/A5 group compared with the A5 group at both week 4 and week 8.
5.	Neutel, Joel M., *et al.,* 2012	Telmisartan 80 mg/Amlodipine 10 mg	• Telmisartan 80 mg • Amlodipine 10 mg	• At 8 weeks, reductions from baseline in mean ± SD seated trough cuff DBP were observed with the T80/A10 SPC (−18.7 ± 8.0 mmHg) compared with either T80 (−13.8 ± 8.0 mmHg) or A10 monotherapy (−16.3 ± 8.1 mmHg).

(*continued*)

Table 2. (*continued*)

No	Author, Year	Intervention	Control	Outcome
6.	Gadge, Pradeep., *et al.,* 2018	Telmisartan 20–80 mg (with T2DM)	Telmisartan 20–80 mg (without T2DM)	• At 12 weeks, SBP changes from baseline in group with T2DM is −24.9 (−17.3 to −32.5) mmHg and −19.5 (−16.3 to −22.7) mmHg in gorup without T2DM. Meanwhile DBP changes from baseline after 12 weeks in group with T2DM is −9.7 (−6.4 to −13.0) mmHg and −9.9 (−8.4 to –11.4) mmHg in group without T2DM. • There was significant change from baseline in Postmeal Blood Sugar in group with T2DM after 12 weeks (−36.9 mg/dL/0.7 to −73.2 mg/dL)
7.	Naruse, Miitsuhide, *et al.,* 2019	Telmisartan 40 mg	Azilsartan 20 mg	• There was a decrease in clinical SBP/DBP of −10.6/−7.2 mmHg in the telmisartan group
8.	Goyal, *et al.,* 2014	Telmisartan 80 mg once daily Amlodipine 10 mg once daily	Telmisartan 40 mg / Amlodipine 5 mg once daily	• The highest fall in the mean SBP was observed in the group with combination therapy of Telmisartan 40 mg and Amlodipine 5 mg. • Highest reduction in mean DBP at each study visit was also observed in the group with combination therapy of Telmisartan 40 mg and Amlodipine 5 mg.
9.	Marfatia, *et al.,* 2012	Telmisartan 80 mg / Hydrochlorothiazide 25 mg once daily Valsartan 160 mg / Hydrochlorothiazide 25 mg once daily	Placebo	• Reduction in mean seated trough clinic BP with T80/H25 (−31.1/−18.3 mmHg) was significantly greater than that with placebo (−7.3/ −5.3 mm Hg; P < 0.0001 for both SBP and DBP). • Treatment with V160/H25 induced reductions in mean seated trough clinic BP of –28.4/ − 16.3 mmHg. • Treatment with T80/H25 was associated with a significantly greater mean reduction in BP compared with V160/H25 for both SBP (adjusted mean difference − 2.7 mm Hg; 95% confidence interval (CI), − 5.1, −0.3; P = 0.0265) and DBP (adjusted mean difference − 2.0 mm Hg; 95% CI, −3.4, −0.6; P = 0.0041).
10.	Shiga, *et al.,* 2012	Telmisartan 80 mg/Hydrochlorothiazide 12.5 mg	Losartan 50 mg/Hydrochlorothiazide 12.5 mg	• Systolic BP and diastolic BP significantly decreased (125 ± 15/69 ± 11 mmHg) and 85% of the patients achieved their target BP at 3 months after changeover.

(*continued*)

Table 2. (*continued*)

No	Author, Year	Intervention	Control	Outcome
11.	Zhu, *et al.,* 2013	Telmisartan 80 mg/Hydrochlorothiazide 25 mg	Telmisartan 80 mg	• Single-pill T80/ H25 combination therapy significantly reduced the adjusted mean ± standard error seated trough cuff systolic/diastolic BP from baseline (−37.0 ± 0.62/−18.6 ± 0.38 mmHg) as compared with T80 monotherapy (−28.5 ± 0.88/−15.4 ± 0.55 mmHg).
12.	Hong, *et al.,* 2019	Telmisartan 80 mg/Amlodipine 10 mg/Rosuvastatin 20 mg	Telmisartan 80 mg/Amlodipine 10 mg Telmisartan 80 mg/Rosuvastatin 20 mg	• The mean (SD) changes in msSBP from baseline after 8 weeks of double-blind treatment were −24.41 (2.38) versus − 9.31 (2.36) mm Hg in the telmisartan/ amlodipine/rosuvastatin and telmisartan/rosuvastatin groups. • The msDBP change from baseline to 8 weeks was −11.57 (8.71) and − 3.75 (9.20) mmHg in the telmisartan/amlodipine/rosuvastatin and the telmisartan/rosuvastatin groups (P < 0.0001).
13.	Oh, *et al.,* 2018	Telmisartan 80 mg/Rosuvastatin 20 mg	Telmisartan 80 mg Rosuvastatin 20 mg Placebo	• The reduction in blood pressure was significantly greater in the FDC group than in the rosuvastatin group after 8 weeks of treatment (least squares mean change from baseline, –16.1 [1.6] mm Hg vs –1.7 [2.2] mm Hg [P o 0.001] for MSSBP; –8.8 [1.0] mm Hg vs −1.6 [1.4] mm Hg [P o 0.001] for MSDBP). • Least squares mean percent change in LDL-C from baseline was also significantly greater in the FDC group compared with the telmisartan group (–49.3% [2.2%] vs 1.5% [3.0%]; P o 0.001).
14.	Choi, *et al.,* 2021	Telmisartan 80 mg/Rosuvastatin 10–20 mg	Telmisartan 40–80 mg	• The primary efficacy endpoint, change of mean central SBP at 16 weeks from baseline, significantly decreased in the telmisartan/rosuvastatin SPC group by − 5.17 ± 14.9 mmHg in (p = .045), whereas there was no significant change in the telmisartan monotherapy group (+1.94 ± 8.9 mmHg, p = 0.219)

Table 3. Final Grading of GRADE

No.	Author and Year	Downgrade faktor					Upgrade factor			Final Grade
		Limitation in study design	Inconsistency of results	Indirectness	Imprecision of results	Publication bias	Large Effect	All plausible confounding	Dose-response gradient	
1.	Kalikar, Mrunalini., *et al.,* 2017	-	-	-	-	-	-	-	-	High
2.	Park, Chang Gyu., *et al.,* 2016	-	-	-	-	-	-	-	-	High
3.	Ohishi, Mitsuru., *et al.,* 2013	-	-	-	-	-	-	-	-	High
4.	Zhu, Dingliang., *et al.,* 2014	-	-	-	-	-	-	-	-	High
5.	Neutel, Joel M., *et al.,* 2012	-	-	-	-	-	-	-	-	High
6.	Gadge, Pradeep., *et al.,* 2018	-	-	-	-	-	-	-	-	Low
7.	Naruse, Miitsuhide, *et al.,* 2019	-	-	-	-	-	-	-	-	High
8.	Goyal, *et al.,* 2014	-	-	-	-	-	-	-	-	High
9.	Marfatia, *et al.,* 2012	-	-	-	-	-	-	-	-	High
10.	Shiga, *et al.,* 2012	-	-	-	-	-	-	-	+	Moderate
11.	Zhu, *et al.,* 2013	-	-	-	-	-	-	-	-	High
12.	Hong, *et al.,* 2019	-	-	-	-	-	-	-	-	High
13.	Oh, *et al.,* 2018	-	-	-	-	-	-	-	-	High
14.	Choi, *et al.,* 2021	-	-	-	-	-	-	-	-	High

Table 4. Data Baseline to Endpoint

No.		Telmisartan 40 mg	Telmisartan 80 mg	Telmisartan in T2DM		Telmisartan in Dyslipidemia		
		Kalikar, Mrunalini., *et al.*, 2017	**Goyal *et al*. 2014**	**Naruse, Miitsuhide, *et al.*, 2019**	**Gadge, Pradeep., *et al.*, 2018**	**Hong *et al*. 2019**	**Oh *et al*. 2018**	**Choi, *et al.*, 2021**
1.	Baseline							
	• Blood Pressure (SBP/DBP)	148.8/94.53	153.8 ± 8.31/93.2 ± 6.048	145.6/89.3	142.7 ± 14.4/ 81.5 ± 6.7	147.08/83.33	151.8/91.2	135.80/82.37
	• HbA1c (%)	-	-	6.63	-	-	-	-
	• Trigliserid (mg/dl)	120.7	-	-	-	156.25	146.2	179.18
	• LDL/VLDL/HDL (mg/dl)	94.62/24.20/45.84	-	-	-	158.92/-/47.44	144.6/-/50.4	123.93/-/49.38
	• Fasting blood glucose (mg/dl)	-	-	125.44	149.1 ± 65.4	-	-	-
	• Fasting insulin (μg/ml)	-		10.808	-	-	-	-
2.	Endpoint							
	• Blood Pressure (SBP/DBP)	137.1/82.53	132 ± 7.575/77.2 ± 5.397	−10.6/−7.2	123.2 ± 9.2/ 71.6 ± 3.1	137.98/79.58	135 ± 17/82 ± 12	130.69/79.87
	• HbA1c (%)	-	-	6.73	-	-	-	-
	• Trigliserid (mg/dl)	+ 8.94	-	-	-	-	-14.7	155.28
	• LDL/VLDL/HDL (mg/dl)	+ 14.65/ + 0.18/-0.94	-	-	-	71.54/-/-	± 26.0/-/ + 13.6	65.32/-/53.83
	• Fasting blood glucose (mg/dl)	-	-	124.38	145.4 ± 53.5	-	-	-
	• Fasting insulin (μg/ml)	-	-	9.990	-	-	-	-

Table 5. Data Baseline to Endpoint

No.		Telmisartan in combination with Amlodipine (Amlodipine/Telmisartan)					Telmisartan in combination with Hydrochlorothiazide (HCT/Telmisartan)	
		Park, Chang Gyu., *et al.*, 2016		Ohishi, Mitsuru., *et al.*, 2013	Zhu, Dingliang., *et al.*, 2014	Neutel, Joel M., *et al.*, 2012	Marfatia *et al.* 2012	Zhu *et al.* 2013
		2.5 mg/40 mg	5 mg/40 mg	5 mg/40 mg	5 mg/80 mg	10 mg/80 mg	25 mg/80 mg	25 mg/80 mg
1.	Baseline							
	• Blood Pressure (SBP/DBP)	153.8/101.9	155.1/101.4	150.4 ± 9.4/ 82.5 ± 8.8	155.75 ± 1.08/ 103.32 ± 0.49	185.4 ± 4.6/ 103.4 ± 6.8	167.6/103.2	172.0 ± 9.6/ 104.7 ± 5.0
	• HbA1c (%)	-	-	5.9 ± 0.6	-	-	-	-
	• Trigliserid (mg/dl)	-	-	193.5 ± 145.1	-	-	-	-
	• LDL/VLDL/HDL (mg/dl)	-	-	113.0 ± 34.1/-/50.5 ± 34.1	-	-	-	-
	• Fasting blood glucose (mg/dl)	-	-	111.1 ± 30.0	-	-	-	-
	• Fasting insulin (μg/ml)	-	-	17.3 ± 15.2	-	-	-	-
2.	Endpoint							
	• Blood Pressure (SBP/DBP)	−10.56/−8.12	-12.32/-9.88	−15.3 ± 11.2/−8.0 ± 8.6	−16.15 ± 1.33/ −12.4	−47.5 ± 13.4/ −18.7 ± 8.0	136.6/85.1	−37.0/−18.6
	• HbA1c (%)	-	-	5.9 ± 0.9	-	-	-	-
	• Trigliserid (mg/dl)	-	-	171.6 ± 111.3	-	-	-	-
	• LDL/VLDL/HDL (mg/dl)	-	-	109.6 ± 25.0/-/49.2 ± 11.5	-	-	-	-
	• Fasting blood glucose (mg/dl)	-	-	102.3 ± 21.7	-	-	-	-
	• Fasting insulin (μg/ml)	-	-	19.1 ± 18.1	-	-	-	

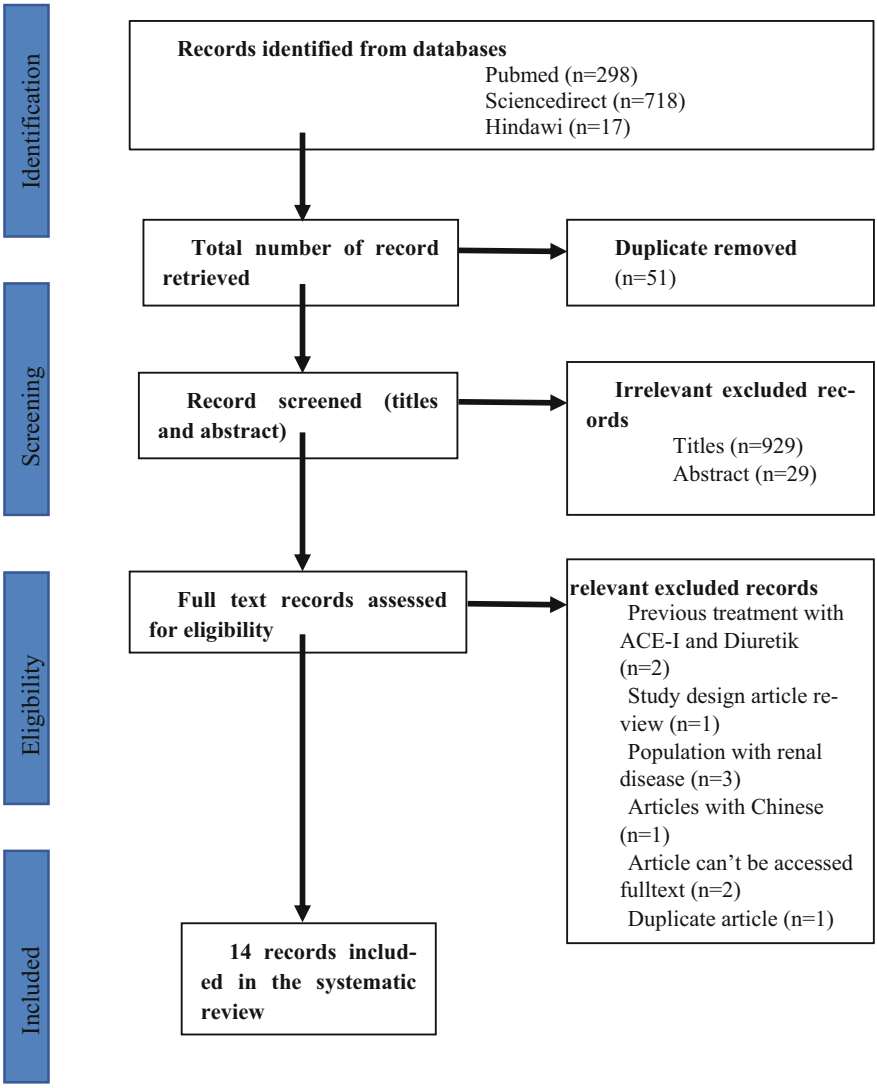

Fig. 1. Flow diagram of articles selection process

In the articles that we found, the use of telmisartan as monotherapy with a low dose (40 mg) significantly reduced SBP and DBP with a follow-up of treatment in 2 weeks, 4 weeks, 8 weeks, and 12 weeks with p value < 0.001 from 148.8/94.53 mmHg in the baseline to 137.1/82.53 mmHg in the endpoint (Table 4). This was consistent with the findings from previous studies. The study also checked the fasting blood glucose level and there was a statistically significant decrease in telmisartan treatment after 12 weeks which was not seen in the control group [11]. When compared with Losartan, single-dose telmisartan with a low-dose administration significantly reduced the serum triglyceride

and LDL cholesterol. Meanwhile, if telmisartan was compared with omesartan, there was a significant reduction only in the LDL cholesterol. Telmisartan is known to have a receptor called partial agonist of peroxisome proliferator-activated receptor-gamma (PPAR-γ) which plays an important role in the regulation of lipid metabolism [11] (Table 5).

Telmisartan used as monotherapy with a high dose (80 mg) significantly reduced SBP and DBP from the baseline (153.8 ± 8.31/93.2 ± 6.048 mmHg, p value < 0.001) to the endpoint (132 ± 7.575/77.2 ± 5/397 mmHg) with a reduction in the follow-up time of 10.00 ± 2.877 mmHg for week 0 to 2, 18.00 ± 4.756 mmHg for week 2 to 4, and 21.80 ± 5.592 for week 4 to 8. The dose of antihypertensive agent is often increased if the initial dose does not reduce blood pressure. However, some patients complain about adverse drug reactions that appear in their treatment with high-dose telmisartan, such as fatigue, nausea, headache, and dizziness [9].

Telmisartan can be used in combination such as with calcium channel blockers (amlodipine) or in combination with hydrochlorothiazide. High-dose telmisartan do not significantly reduce SBP and DBP when compared with telmisartan in combination. In the research of Goyal et al. 2014, low-dose telmisartan in combination with amlodipine led to a significantly greater reduction in SBP and DBP from the baseline 153.5 ± 10.29/94 ± 5.441 mmHg to the endpoint after 8 weeks with a follow-up of 126.4 ± 9.2/76.32 ± 5.659 mmHg (p value < 0.001). Adverse drug reactions are also low when the combination of telmisartan and amlodipine is used. In the research by Park, Chang Gyu, et al., 2016, telmisartan in combination with amlodipine significantly reduced SBP and DBP with both low-dose amlodipine (2.5 mg) and high-dose amlodipine (5 mg) compared with high-dose telmisartan (−11.78 and – 17.42 mmHg, p value < 0.0001). Besides, telmisartan in combination with amlodipine can reduce blood pressure as evidenced in a study by Ohishi, Mitsuru., et al., 2013 which found that the laboratory test showed other outcomes, such as a reduction in the fasting plasma glucose from 109.0 ± 26.2 to 101.3 ± 20.5 mg/dl (p value 0.070) and triglyceride from 150.2 ± 121.3 to 139.0 ± 91.2 mg/dl. The SBP and DBP decreased from 150.2 ± 10.4 /83.0 ± 10.2 mmHg to 135.7 ± 15.0/75.0 ± 10.0 mmHg. Meanwhile, high-dose telmisartan (80 mg) in combination with high-dose amlodipine (5 mg) significantly reduced SBP (−16.15 ± 1.33 mmHg) and DBP (−12.4) from the baseline to week 8 [14]. High-dose telmisartan in combination with amlodipine 10 mg showed a reduction in SBP from the baseline to 8 weeks by −47.5 ± 13.4 mmHg from 185.4 ± 4.6 to 137.9 ± 12.8 mmHg and in DBP by −18.7 ± 8.0 mmHg [15].

Telmisartan is also used for hypertension with diabetes mellitus. In a study by Naruse, Miitsuhide, et al., 2019, telmisartan 40 mg reduced SBP and DBP by −10.6/−7.2 mmHg, decreased the fasting blood glucose from the baseline by −1.06 mg/dl, and lowered the fasting insulin by −0.818 μg/ml. The effects of ARB on insulin resistance in patients with hypertension and type-2 diabetes mellitus are beneficially affected by unknown factors. However, the effects of ARB on insulin resistance are not always reproducible [16]. Meanwhile in non-randomized controlled trials with low GRADE quality of evidence, telmisartan in patients of hypertension and type-2 diabetes mellitus without or with complication showed significantly reduced SBP and DBP from the baseline to week 12 with p value < 0.0001. Telmisartan is also effective in retarding the progression of diabetic nephropathy [17].

Telmisartan in patients with hypertension and dyslipidemia can reduce SBP and DBP as in the research by Hong et al. 2019 which obtained a decrease from

147.08/83.33 mmHg to 137.98/79.58 mmHg, in the research by Oh et al. 2018 from 151.8/91.2 mmHg to 135 ± 17/82 ± 12 mmHg, and in the research by Choi, et al., 2021 from 135.80/82.37 mmHg to 130.69/79.87 mmHg. Telmisartan in these populations is used in combination with oral anti-dyslipidemia (rouvastatin) [18].

4 Conclusion

Telmisartan is favorable for the treatment of patients with hypertension in monotherapy when the patient is diagnosed with hypertension for the first time and cannot use ACE-Inhibitor. A higher dose medication is needed when the target blood pressure has not been achieved with low-dose telmisartan. Telmisartan also becomes a safe combination with amlodipine or hydrochlorothiazide with less adverse drug reactions than high-dose therapy. Hypertensive patients with type-2 diabetes mellitus or dyslipidemia also prefer using this drug in combination with oral anti-hyperglycemia or oral anti-dyslipidemia. The articles also indicate that telmisartan can decrease fasting blood glucose, lower LDL cholesterol, and increase HDL.

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