MEDICO RESEARCH CHRONICLES
ISSN NO. 2394-3971
DOI No. 10.26838/MEDRECH.2022.9.2.587
Contents available at www.medrech.com

TELMISARTAN'S EFFECT ON BLOOD PRESSURE IN TYPE 2 DIABETES PATIENTS WITH AND WITHOUT COMPLICATIONS

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ARTICLE INFO

Article History
Received: January 2021
Accepted: March 2022
Key Words:
Hypertension, Diabetes, ARBs, Telmisartan.

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ABSTRACT

In people with type 2 diabetes, cardiovascular disease (CVD) is the leading cause of morbidity. Hypertension (HTN) frequently coexists with diabetes, increasing the risk of end-organ damage significantly. Blockers of the RAAS, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have become a mainstay in the treatment of patients with diabetes plus hypertension. Telmisartan is the only ARB indicated for the treatment of atherothrombotic CVD (history of coronary heart disease, stroke, or peripheral arterial disease) or types 2 diabetes mellitus (T2DM) with confirmed target organ damage, therefore, reduction in the cardiovascular risk and morbidity. Trials of telmisartan have also been shown to reduce the progression of renal disease in individuals with diabetes and varying degrees of nephropathy, an effect that appears to be at least partly independent of a reduction in blood pressure. The present review article is intended to give comprehensive information about the effect of telmisartan on blood pressure in type 2 diabetes patients with and without complications.

ORIGINAL RESEARCH ARTICLE

2022, www.medrech.com

INTRODUCTION:

Hypertension (HTN) is a major cause of cardiovascular morbidity and mortality, especially in people with diabetes.[1] Patients with hypertension are two to three times more likely than those with normal blood pressure (BP) to acquire diabetes.[2] Patients with type 2 diabetes have a two- to fourfold greater risk of death from cardiovascular (CV) causes compared to those who do not have diabetes.[3] In India, there are currently 74.2 million

patients with diabetes, with the number expected to rise to 124.9 million by 2045.[4]
Hypertension and diabetes together contribute to arterial stiffness that leads to poor control of blood pressure (BP). ED caused by hyperglycemia results in vascular remodeling. Arterial stiffness, loss of elastic recoil, and decreased vasodilating capacity are caused by changes in extracellular matrix, altered functioning of endothelial cells, and vascular smooth muscle cells.[5] Arterial stiffness, in this way, not only leads to end-organ damage but also likely raises the risk of cardiovascular (CV) events.[6]

Furthermore, those with diabetes have more variability in their BP; are more likely to develop orthostatic hypotension, and have hypertension that is more resistant to treatment.[7,8] Controlling HTN in diabetes is critical for preventing the progression and development of microvascular and macrovascular complications.[5,9]

In hypertensive and diabetic conditions, both the renin-angiotensin system and insulin resistance are believed to have important roles in the pathogenesis of endothelial dysfunction and in the development of atherosclerosis.[10] According to the American Diabetes Association guideline on cardiovascular disease management in diabetes patients, angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEIs) are recommended for treatment of HTN in patients with T2DM for renal protection.[11] On the basis of their cardiovascular protective effects, pharmacological blockers of the renin–angiotensin system such as ACEIs and ARBs have been widely used to treat patients with hypertension, whereas insulin sensitizers such as peroxisome proliferator-activated receptor (PPAR)- ɣ agonists have been used to treat patients with hypertension and diabetes, respectively.[12]
Among several ARBs used clinically worldwide, telmisartan is a unique compound because it functions as a partial agonist for PPARɣ.[13] Telmisartan, a selective antagonist for angiotensin type1 receptor and a partial agonist for peroxisome proliferator-activated receptor-c, decreases blood pressure and has been shown to improve glucose and lipid metabolism, suggesting potential cardiovascular protective effects.[12]

Role of the renin-angiotensin system (RAS) in the progression of vascular disease:

Hypertension and diabetes altogether appear to increase the activity of angiotensin II, a key component and most likely the major effector peptide of the RAS, resulting in disease progression at every stage of the cardiovascular continuum **(Figure 1)**.[14,15]

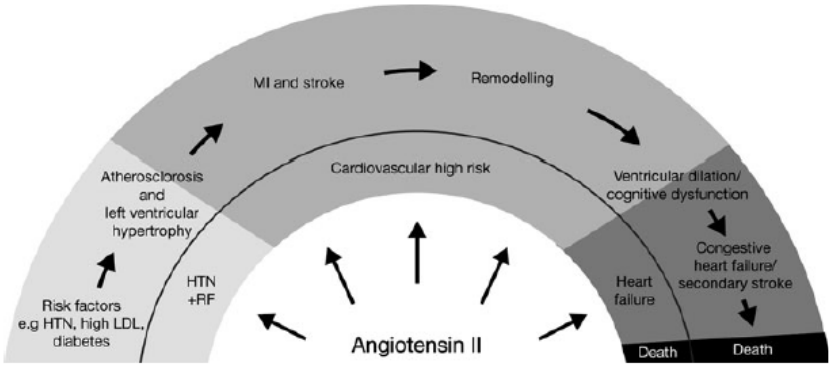

Figure 1: The cardiovascular continuum

Angiotensin II has a wide range of adverse effects, including cellular proliferation, increased oxidative stress, and diminished nitric oxide, which is mediated directly or indirectly through many signal transduction pathways, in addition to its effects on blood

pressure. Angiotensin II promotes atherosclerosis and contributes to coronary atherothrombotic disease, MI, remodelling, heart failure, and end-stage heart disease via acting through the angiotensin II type 1 receptor subtype (AT1). RAS blockers are commonly used to reduce cardiovascular risk since they not only lower blood pressure but also may slow the progression of disease. By lowering blood pressure and reducing cellular processes like inflammation that lead to atherosclerosis, blocking the RAS has the potential to minimise organ damage.[14,16]

Telmisartan's effects on hypertensive patients with diabetes mellitus and their complications:

Telmisartan is effective in lowering blood pressure in a broad range of patient populations, including those with type 2 diabetes, metabolic syndrome, diabetic nephropathy, and renal impairment.[17]

According to a study, conducted by Gadge et al., 132 patients were analyzed. Among these, 78.8% (n = 104) had no diabetes-related complications whereas 21.2% (n = 28) had one or more complications **(Figure 2)**. Most frequent complication observed was peripheral neuropathy (n = 21, 15.9%), followed by nephropathy (n = 6, 4.5%), retinopathy (n = 2, 1.5%), ischemic heart disease (n = 1, 0.8%), and cerebrovascular complication (n = 1, 0.8%).

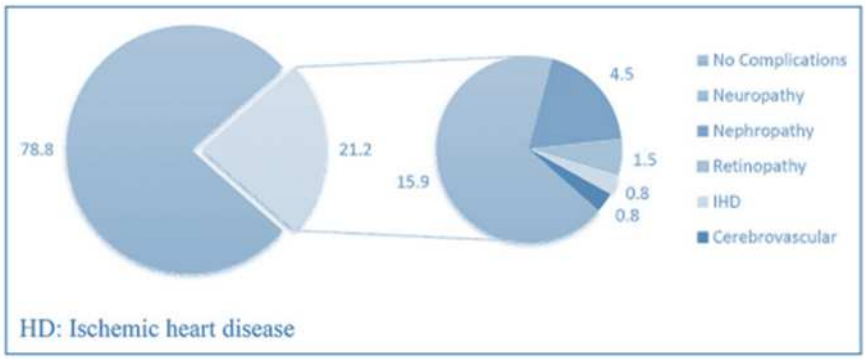

Figure 2: Complications of diabetes in the study population

Patients (adults 18 years and older with BP ≥140/80 mmHg but <160/100 mmHg) of T2DM without (Group A) or with (Group B) complications who had Stage I HTN, were prescribed telmisartan (20–80 mg/day) treatment, in this retrospective study.

Change in systolic BP from baseline were −19.5 mmHg (95% confidence interval [CI] −16.3, −22.7; P < 0.0001) and −24.9 mmHg (95% CI −17.3, −32.5; P < 0.0001) in Groups A and B respectively. In two of the groups, there was also a significant reduction in diastolic BP. **Figure 3** depicts the trend in a change of systolic and diastolic BP during a 12-weeks period. There was a change from baseline in fasting glucose levels by −3.7 mg/dL (P = 0.647) and −8.4 mg/dL (P = 0.593); postmeal glucose levels changed by −14.8 mg/dL (P = 0.280) and −36.9 mg/dL (P = 0.046), in Groups A and B, respectively.

Telmisartan is beneficial in decreasing BP and improving metabolic parameters in T2DM patients with or without complications, according to the findings of this study.[5]A number of clinical studies have shown a reduction in blood glucose and improvement in diabetic complications after treatment with telmisartan **(Table 1)**.[18]

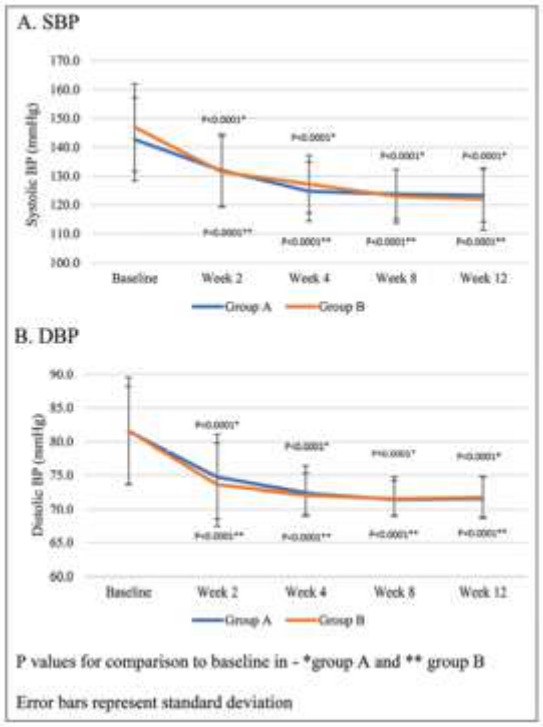

Figure 3: Changes in systolic and diastolic blood pressure in two groups over 12 weeks.

Table 1: Clinical trials evaluating the benefits of telmisartan in preventing cardiovascular and renal disease progression:

Study and Author	**Patients**	**Treatment (duration)**	**Cardiovascular and renal endpoints**	**Blood pressure levels**
ONTARGET [19, 20] Mann et al.	High-risk patients with coronary, peripheral artery disease, or cerebrovascular disease or diabetes with end-organ damage (n= 25,620).	Telmisartan, ramipril or both (median follow-up 56 months).	For the primary and secondary outcomes, Telmisartan was equal to ramipril Primary outcome: Composite of CV death, MI, stroke or heart failure hospitalization Secondary: CV death, MI or stroke; pre-specified renal endpoint (dialysis, serum creatinine doubling and death).	Baseline: All groups had the same blood pressure (142/82 mmHg). At the end of the study, telmisartan was found to have a lower mean blood pressure than ramipril (-0.9/-0.6 mmHg).

TRANSCEND [21] Yusuf et al.	High-risk patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage and intolerance to ACE inhibitors (n = 5,926).	Telmisartan or placebo on top of standard care (median follow-up 56 months).	For the primary endpoint, telmisartan was similar to placebo, while it was superior to placebo for the secondary endpoint: Primary: A composite of CV death, MI, stroke, or heart failure hospitalisation. Secondary: Cardiovascular mortality, myocardial infarction, or stroke.	Baseline: Both groups had similar blood pressure (telmisartan 141/82 mmHg, placebo 141/82 mmHg) at the start of the study. At the conclusion of the study, telmisartan reduced blood pressure more than placebo (mean weighted difference 4.0/2.2 mmHg).
INNOVATION [22, 23] Makino et al.	Hypertension, type 2 diabetes and microalbuminuria (n = 527).	Telmisartan or placebo (52 weeks).	The primary and secondary endpoints showed that telmisartan was superior than placebo: Primary: Transition rate from incipient to overt nephropathy (UACR >300 mg/g and increase ≥30% from baseline at two consecutive 4-week visits) Secondary: Microalbuminuria remission (UACR<30 mg/g).	Baseline: All three groups had identical blood pressure (telmisartan 80 mg 138/78 mmHg, telmisartan 40 mg 137/78 mmHg, placebo 137/77 mmHg). Study's conclusion: Telmisartan 80 mg 128/72 mmHg, telmisartan 40 mg 128/72 mmHg, placebo 132/74 mmHg) were similar.
DETAIL [24,25] Barnett et al.	Hypertension, type 2 diabetes and early nephropathy (n = 250).	Telmisartan or enalapril (5 years).	The primary and secondary outcomes were similar for telmisartan and enalapril: The primary concern is a change in GFR. Secondary: Annual changes in GFR, serum creatinine level, urinary albumin excretion and	Baseline: Both groups had similar blood pressure readings (telmisartan 153/85 mmHg, enalapril 152/86 mmHg). End of study: Telmisartan had a larger adjusted mean reduction in SBP than enalapril (6.9 mmHg vs. 2.9 mmHg).

			BP; end-stage renal disease and CV events; all-cause death.	
AMADEO [26] Bakris et al.	Hypertension and diabetic nephropathy (n = 860).	Telmisartan or losartan (52 weeks).	For the primary endpoint, telmisartan was superior to losartan, and the groups were similar for the secondary endpoint: Primary: UACR Secondary: Serum creatinine and aldosterone, eGFR, C-reactive protein.	Baseline: Groups were similar (telmisartan 144/80 mmHg, losartan 143/80 mmHg). Baseline: Both groups had similar blood pressures (telmisartan 144/80 mmHg and losartan 143/80 mmHg). BP reductions were similar (DBP: telmisartan -3.3 mmHg, losartan -2.9 mmHg) at the end of the study.

HTN is the most frequent accompanied comorbidity in T2DM, and it has a significant impact of development and progression of complications. In hypertensive patients with metabolic syndrome, Vitale C, et al. found that telmisartan had insulin-sensitizing activity, which could be explained by its partial PPARγ activity, and significantly reduced 24-hour mean systolic blood pressure ($p<0.05$) and diastolic blood pressure ($p<0.05$) compared to losartan.[27]

In TRENDY trial, telmisartan 40 mg was found to be as effective as ramipril 10 mg in improving ED in diabetic patients with HTN.[28] This combined with improvement in arterial stiffness contributes to favorable effects of telmisartan. Telmisartan provides end-organ protection in addition to BP control, as observed in renoprotection as seen in VIVALDI trial.[29]

A study by Sasaki et al., telmisartan showed more beneficial effects compared to olmesartan in glucose and lipid profiles.[30] In patients with diabetes, Mori et al. demonstrated benefits of telmisartan in increasing high molecular weight adiponectin levels and improving insulin resistance. Telmisartan is the treatment of choice for HTN in diabetic patients because it activates PPAR-γ, improves insulin resistance, and inhibits RAAS.[31]

CONCLUSION:

The simultaneous presence of hypertension and diabetes is devastating to the CV system. Lowering the BP in patients with diabetes is particularly beneficial. Telmisartan is a well-known anti-hypertensive drug, which is currently in clinical use. Telmisartan has been proven to have multiple clinical benefits, including anti-diabetic and cardiovascular effects, due to its partial PPARγ agonistic activity and angiotensin receptor blocking activity.

A beneficial effect on blood glucose and weight probably contributes to the improvement in vascular health. Near-equivalent BP reduction in patients with or without complications of diabetes suggests that telmisartan is the choice of therapy in these patients.

In individuals with type 2 diabetes, the main goal is to lower the risk of fatal and nonfatal cardiovascular events. A number of significant trials, including the ONTARGET trial, have found telmisartan to be effective in preventing cardiovascular events in a wide variety of high-risk cardiovascular patients, including those with type 2 diabetes.

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