Effectiveness and safety of telmisartan and telmisartan/amlodipine single-pill combination in the treatment of essential hypertension in Slovakian patients treated by general practitioners – the *TELMISTAR II* study

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Key words
arterial hypertension, telmisartan, telmisartan/amlodipine, single-pill combination, effectiveness, safety, patient satisfaction, general practitioner

Abstract

Objective: *Hypertension (HT) is the leading global contributor to premature death and disability adjusted life years. Despite a number of proven, highly effective and well-tolerated lifestyle and drug treatment strategies, blood pressure (BP) control rates remain poor. The first objective of HT treatment is to lower BP to <140/90 mmHg. Based on currently valid* 2018 ESC/ESH Clinical Practice Guidelines for the Management *of Arterial Hypertension, recommended initial pharmacological therapy in most patients is dual combination of RAS blocker (angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)) with a calcium channel blocker (CCB) or a diuretic. The present study aimed to observe the effectiveness and safety of telmisartan monotherapy and single-pill combination (SPC) of telmisartan and amlodipine in patients with uncontrolled arterial hypertension treated by general practitioners (GPs). To see if GPs deal with similar patients as specialists and if telmisartan and SPC of telmisartan and amlodipine are a suitable therapy choice also on primary care level, results were compared with the results from previous study* Telmistar I*, in which patients were treated by HT specialists (cardiologists and internists).*

Methods: *This prospective, observational clinical study enrolled 655 patients with uncontrolled hypertension, who were previously already treated by 53 GPs. Patients enrolled in this study were treated with either telmisartan (T group) or SPC of telmisartan and amlodipine (T/A group) in line with regular clinical practice and based on the investigator's decision, and were observed over the course of 6 months.*

Results: *Both T and T/A group noted similar BP reductions, with first treatment objective of BP <140/90 mmHg at the end of observational period achieved by approximately 70% of patients in both groups. BP reductions and achievement of first treatment objective were similar across different patient subgroups (smoking, dyslipidemia, obesity, diabetes mellitus, chronic kidney disease). Patients and GPs alike were very satisfied with both treatment options. Both treatments were well tolerated.*

Conclusion: *Telmisartan and SPC of telmisartan and amlodipine are effective and safe treatment choices for patients with uncontrolled hypertension, with very high rates of patient and physician satisfaction. Considering that hypertension specialists and GPs deal with similar patients and that they achieve comparable effectiveness and safety, telmisartan and SPC of telmisartan and amlodipine represent a therapy of choice for the treatment of arterial hypertension also on primary care level.*

Background

Hypertension is the leading global contributor to premature death and disability adjusted life years, mostly due to ischaemic heart disease, haemorrhagic and ischaemic stroke, and is defined as office systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg (1). According to the latest data, Slovakia is among the countries with the highest proportion of adults with hypertension (28.5%), a 3.5% above the average of ESC member countries (2).

While there are a number of proven, highly effective and well-tolerated lifestyle and drug treatment strategies, BP control rates remain poor. Only 40% of patients with hypertension are treated, and among these, only 35% have controlled BP of <140/90 mmHg. The inability to achieve better BP control rates can be attributed to several reasons, such as physician inertia (i.e. failure to uptitrate treatment), patient nonadherence to the treatment, insufficient use of combination treatment and complexity of current treatment strategy (1).

The first objective of hypertension treatment is to lower BP to <140/90 mmHg in all patients and, provided the treatment is well tolerated, to 130/80 mmHg or lower in most patients. Regarding pharmacological treatment, the recommended initial therapy is a dual combination of RAS blocker (angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)) with a calcium channel blocker (CCB) or a diuretic, preferably in the form of single-pill combination (SPC). Possible exception are patients with low risk grade 1 hypertension (SBP <150 mmHg) and frail older patients (80+ years), who are eligible for monotherapy (1).

Telmisartan is an ARB with the longest half-life, the largest volume of distribution and the highest lipophilicity in the ARB class (3–6). It was demonstrated to be highly effective in patients with all grades of hypertension and in broad spectrum of hypertensive patients, including the elderly, those with type 2 diabetes mellitus (DM), metabolic syndrome and/or renal impairment (3, 7–16). Its effectiveness in lowering BP has been documented to be at least equivalent to other frequently prescribed first-line antihypertensive agents, such as ACEi, other ARBs, β-blockers and CCB (16–27). The incidence of adverse events (AEs) with telmisartan can be compared to placebo (17). Combination of telmisartan and amlodipine, CCB of the dihydropyridine group, offers complementary action in reducing BP and synergistic cardioprotective effects. Marked reductions of BP enable up to 87.5% of patients to achieve target BP with fewer AEs, especially oedema (28–35). In a previously published study *Telmistar I*, which included patients with uncontrolled arterial hypertension, treated by HT specialists (internists and cardiologists), telmisartan (T) and single-pill combination (SPC) of telmisartan and amlodipine (T/A) led to significantly decreased BP. Similar BP reductions were observed across different patient subgroups with risk factors, including obese patients, patients with DM and patients that qualify for secondary prevention. Both T and SPC T/A treatment were well tolerated (36).

Hypertension is known to rarely occur in isolation, often clustering with other CV risk factors (1). This was also shown in study *Telmistar I*. Treated patients had on average 1.7 comorbidities, with proportion of obese patients and patients with DM by far exceeding the prevalence of these conditions in general population (obesity: 54.8% vs 20.5%; DM: 35.3% vs 6.5%, respectively) (2). Approximately 3 in 4 patients were treated for primary prevention, with almost 80% of all patients at high or very high CV risk (36).

While specialists, especially internists and cardiologists, often deal with hypertensive patients, general practitioners (GPs) mainly carry out both the diagnosis and treatment of hypertension in Slovakia (37). Therefore, the aim of the present study was to assess the effectiveness, safety and treatment satisfaction of T and SPC T/A in patients, treated by GPs. By comparing the results of the present study with those from *Telmistar I*, we wanted to see if general practitioners deal with similar patients as specialists and if T and SPC T/A are a suitable therapy choice also on primary care level.

Patients and Methods

Telmistar II study was a prospective, open-label observational study, which included 655 patients of 53 GPs from Slovakia. Eligible patients were female and male, aged 18 or more, with uncontrolled arterial hypertension, previously treated with RAS blocker (except telmisartan) or a combination of RAS blocker and amlodipine, and requiring treatment with telmisartan (T) or a single-pill combination (SPC) of telmisartan/amlodipine (T/A) at GP's discretion. Patients were excluded if there was no therapeutic reason for changing antihypertensive medication, if they had contraindication or intolerance to T or SPC T/A, or were already enrolled in another clinical study.

Patients were observed over the course of 6 months. Data were collected at three data captures: at patient's inclusion in the study (V1), at 3 months ±2 weeks from inclusion (V2) and at 6 months ±4 weeks from inclusion (V3). At each data capture, data about BP and heart rate measurement, and a blood collection test were collected. More details on blood tests are available elsewhere (*Telmistar I*). At V3, also information about patient's and physician's satisfaction with treatment were collected. During observational period also information about AE was collected.

Statistical analysis was carried out by the statistical program SPSS for Windows. A two-way unpaired Student t-test, a one-way ANOVA with post-hoc Bonferroni analysis, and a chi-square test were used to verify data differences between groups. The level of significance was at $p < 0.05$ in all statistical tests.

Results

Of 655 included patients, 336 (51.3%) were treated with T and 319 (48.7%) with SPC T/A. Demographic and baseline characteristics of study participants treated with T and SPC T/A, are summarized in Table 1.

The two groups differed significantly in age, baseline BP (SBP and DBP), SCORE value in patients, classifying for primary prevention, and CVD risk category. All of these values were higher in the T/A group. For other baseline and demographic characteristics, the differences were insignificant. Presence of risk factors was similar in both groups, as well as the distribution of patients according to type of CVD prevention.

Characteristic	T group (N = 336)	T/A group (N = 319)
Age, years, mean (SD)	60.4 (12.4)	62.3 (11.5)
Gender, n (%)*		
Female	186 (56.4%)	172 (54.6%)
Male	144 (43.6%)	143 (45.4%)
Systolic BP, mean (SD)	155.3 (14.8)	158.4 (15.5)
Diastolic BP, mean (SD)	92.4 (10.0)	94.0 (10.3)
BMI, mean (SD)	29.1 (4.8)	29.5 (5.1)
Number of antihypertensives, mean (SD)	1.8 (1.0)	1.9 (1.1)
Risk factors*,***		
Smoking	101 (31.5%)	118 (38.1%)
Dyslipidaemia	238 (73.2%)	239 (76.6%)
Obesity	158 (48.9%)	159 (51.1%)
DM	74 (22.0%)	82 (25.7%)
CKD	31 (9.6%)	35 (11.2%)
Type of CVD prevention*		
Primary prevention	240 (79.0%)	227 (82.1%)
Secondary prevention	64 (21.1%)	50 (18.0%)
SCORE value (primary prevention)	5.2 ± 5.7	6.5 ± 6.1
CVD risk category*,**		
Low	118 (38.8%)	83 (30.0%)
Moderate	37 (12.2%)	33 (11.9%)
High	75 (24.7%)	81 (29.2%)
Very high	74 (24.3%)	80 (28.9%)

BP – blood pressure, BMI – body mass index, DM – diabetes mellitus (type 1 and 2), CKD – chronic kidney disease, CVD – cardiovascular disease, SD – standard deviation, T – telmisartan, T/A – telmisartan/amlodipine;

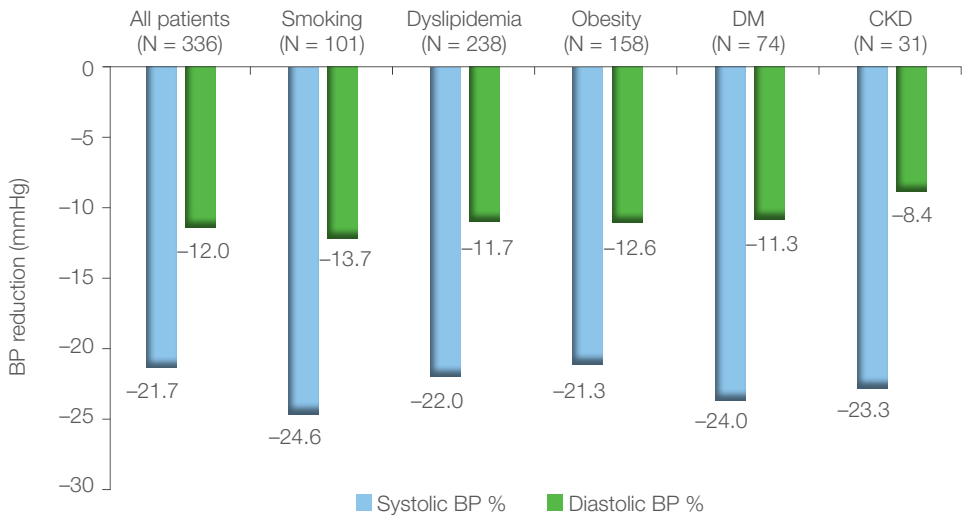
* not taking into account missing data, ** according to 2016 ESC guidelines on CVD prevention, which were valid at time of the study conclusion,*** each patient can have more than 1 risk factor

Table 1: Demographic and baseline characteristics of T and T/A group

Effectiveness results

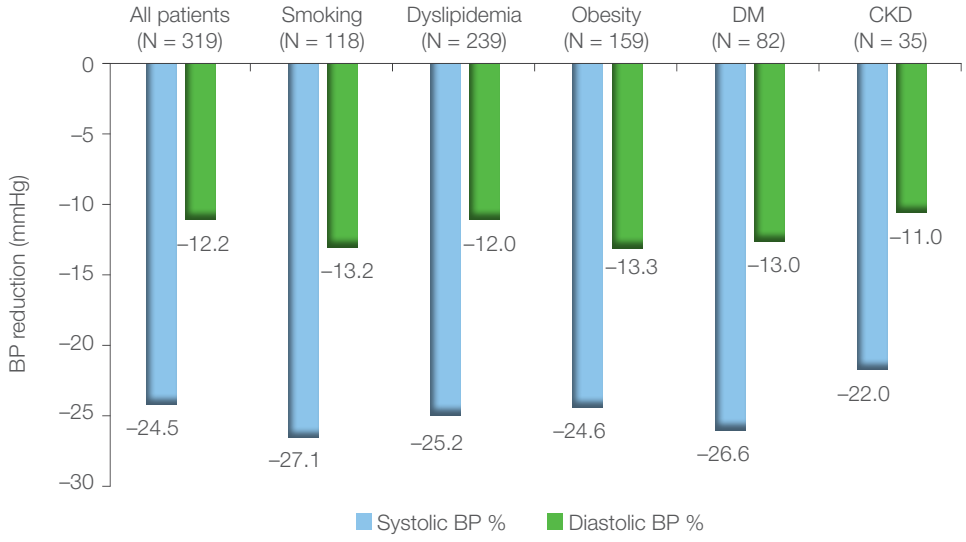
Both T and T/A group noted similar SBP and DBP reductions during the observational period, with a decreasing trend from V1 to V3. In T group, SBP was reduced by 21.7 mmHg (from 155.3 to 133.6; 14.0% reduction) and DBP by 12.0 mmHg (from 92.4 to 80.4; 13.0% reduction) from V1 to V3. In T/A group, SBP was reduced by 24.5 mmHg (from 158.4 to 133.9; 15.5% reduction) and DBP by 12.2 mmHg (from 94.0 to 81.8; 12.9% reduction) from V1 to V3. BP reductions were similar across individual patient subgroups (smoking, dyslipidemia, obesity, DM, CKD) for both T and T/A group (Figures 1 and 2).

First treatment objective (BP <140/90 mmHg) was achieved at V3 by 72.0% of patients in T group and 69.2% in T/A group. Achievement of SBP and DBP target values were very similar also across individual patient subgroups (smoking, dyslipidemia, obesity, DM, CKD) (Figure 3).



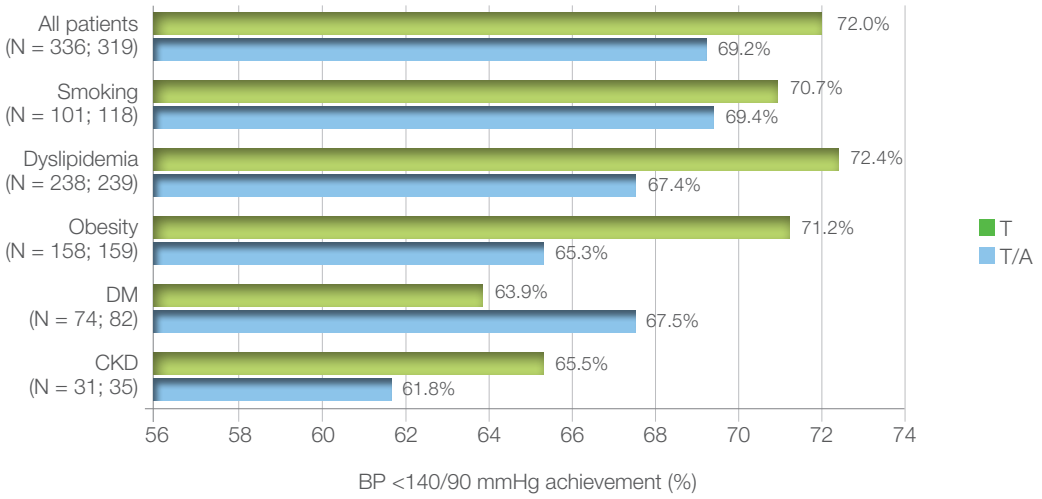
DM – diabetes mellitus (type 1 and 2), CKD – chronic kidney disease

Figure 1: Absolute BP reduction in T group from V1 to V3 (all patients and individual patient subgroups).



DM – diabetes mellitus (type 1 and 2), CKD – chronic kidney disease

Figure 2: Absolute BP reduction in T/A group from V1 to V3 (all patients and individual patient subgroups).



DM – diabetes mellitus (type 1 and 2), CKD – chronic kidney disease, T – telmisartan, T/A – SPC of telmisartan and amlodipine

Figure 3: Proportion of patients achieving BP target (<140/90 mm Hg) (all patients and individual patient subgroups).

In terms of treatment satisfaction, a vast majority (more than 80%) of patients and GPs were very satisfied with the treatment with either T or T/A, rating the chosen treatment as 'the best' on a scale 1–5 (1 – the best, 5 – the worst). More than 97% of patients were satisfied with treatment with T or T/A (Table 2).

Treatment satisfaction score* (1 – the best, 5 – the worst)	Patients	GP
1	84.6%	80.7%
2	12.9%	16.2%
3	1.5%	2.5%
4	0.2%	0.4%
5	0.8%	0.2%

* not taking into account missing data

Table 2: Satisfaction of patients and GPs with the treatment

Safety results

Concerning the tolerability, the study data indicate good tolerability of both T and T/A. AEs were reported by GPs in only 10 patients (1.6%), according to the protocol and valid local legislation about safety reporting.

Discussion

Results from the present study show that telmisartan and SPC of telmisartan and amlodipine are effective and well tolerated for the treatment of arterial hypertension in previously treated, but uncontrolled patients. First treatment objective, lowering BP to <140/90 mmHg (1), was achieved by approximately 70% of patients in both treatment groups, with no important difference between groups and individual patient subgroups with different risk factors. Furthermore, mean BP values at the end of observation period were close to target BP values of 130/80 mmHg. These values should be interpreted in the context of patient age; in the present study, an average patient was aged slightly above 60 years, which is close to the older patients group (65+ years), in which SBP values should be targeted to 130–139 mmHg (1). Effectiveness results are in line with findings from the previous observational study *Telmistar I* (36). BP reductions were similar across T and T/A group in both studies, as well as proportion of patients, achieving first treatment objective.

It was expected that SPC T/A would lower BP to a greater extent than T, since SPC T/A was previously shown to result in significantly higher BP reductions (37). In patients with grades 1 and 2 HT, T/A reduced SBP for additional 5.9 mmHg and DBP for additional 1.7 mmHg compared to T after 8 weeks of treatment (38). In patients with severe HT (SBP/DBP ≥180/95 mmHg), the difference was even greater: T/A reduced SBP for additional 10.6 mmHg (39). However, this data comes from interventional clinical studies, which include treatment groups with comparable demographic and baseline characteristics. This was not the case in the present observational study, where patients in T/A group had more unfavourable characteristics: they were significantly older, had higher baseline BP values, higher SCORE values (patients in primary prevention) and higher mean CVD risk category. This likely explains the fact that BP reductions, contrary to our expectations, were similar between T and T/A group.

The effective treatment of hypertension depends not only on treatment therapy choice, but also on patient's satisfaction with the treatment. Expectedly, patients report higher satisfaction with treatment if their BP control is improved and they experience minimal AEs. In such case, patients are also more likely to continue taking the prescribed medication. On the other hand, physician's satisfaction also matters, as this is the most common reason for switching antihypertensive therapy (40). In the present study, both patient's and physician's satisfaction was very high. More than 80% of both rated treatment satisfaction with the highest score 1 as the best (on a scale 1–5), possibly due to better BP control and low incidence of AEs.

An average patient in the present study was polymorbid, having 2.2 comorbidities, with risk factors exceeding the prevalence in general population (smokers: 34.7% vs 22.9%, obese patients: 50.0% vs 20.5%, and patients with DM 23.8% vs 6.5%) (2). To see if hypertension specialists and GPs deal with patients with similar baseline and demographic characteristics, we compared the results with results from study *Telmistar I*. There were no major differences as regards age, baseline BP values and type of CVD prevention. Risk factors were the same in both studies, with some differences (in present study, more patients were smokers, but fewer patients had DM or CKD) (36). These differences might have impacted the differences in CVD risk category, with patients in present study having on average lower CVD risk.

As regards patient approach on specialist and GP levels, a recent study by Yoshida et al. found out that there are certain differences. While specialists are more likely to provide education and are more conscious of guidance on lifestyle modifications, GPs generally care more about the patient's burden. However, regardless of a physician's status, very similar proportion of GPs and specialists achieve target BP values with their patients (41). These results are in line with the results of the present study and *Telmistar I* study, which found out that GPs and specialists achieve first treatment

objective in a very similar proportion of patients (36). When choosing the antihypertensive treatment, there seems to be little difference between specialists and GPs. A Danish study, in which specialists and GPs were sent 5 realistic cases varying in gender, age, BP and risk factors (cholesterol, DM and smoking), established no significant differences between specialists and GPs, neither in treatment decisions, nor in first-line therapy choices. However, the decision to start treatment was considered easy by a higher proportion of specialists (72%) than GPs (66%) (42).

The present study has several strengths. Being an observational study, it evaluated effectiveness and safety of telmisartan and SPC of telmisartan and amlodipine in everyday clinical practice. Moreover, the study provided insight into treatment satisfaction on both patient and physician side. The main limitation of the study is the scarcity of data on AEs. This is due to the study design (observational study), meaning that GPs are obliged to report AEs directly to local authorities in accordance with valid local legislation about safety reporting.

Conclusion

Presented results demonstrate that GPs deal with similar patients as hypertension specialists. Based on comparable effectiveness and safety results shown by the present study and *Telmistar I* study, telmisartan and SPC of telmisartan and amlodipine can be regarded as a rationale therapy for the treatment of arterial hypertension also on primary care level.

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