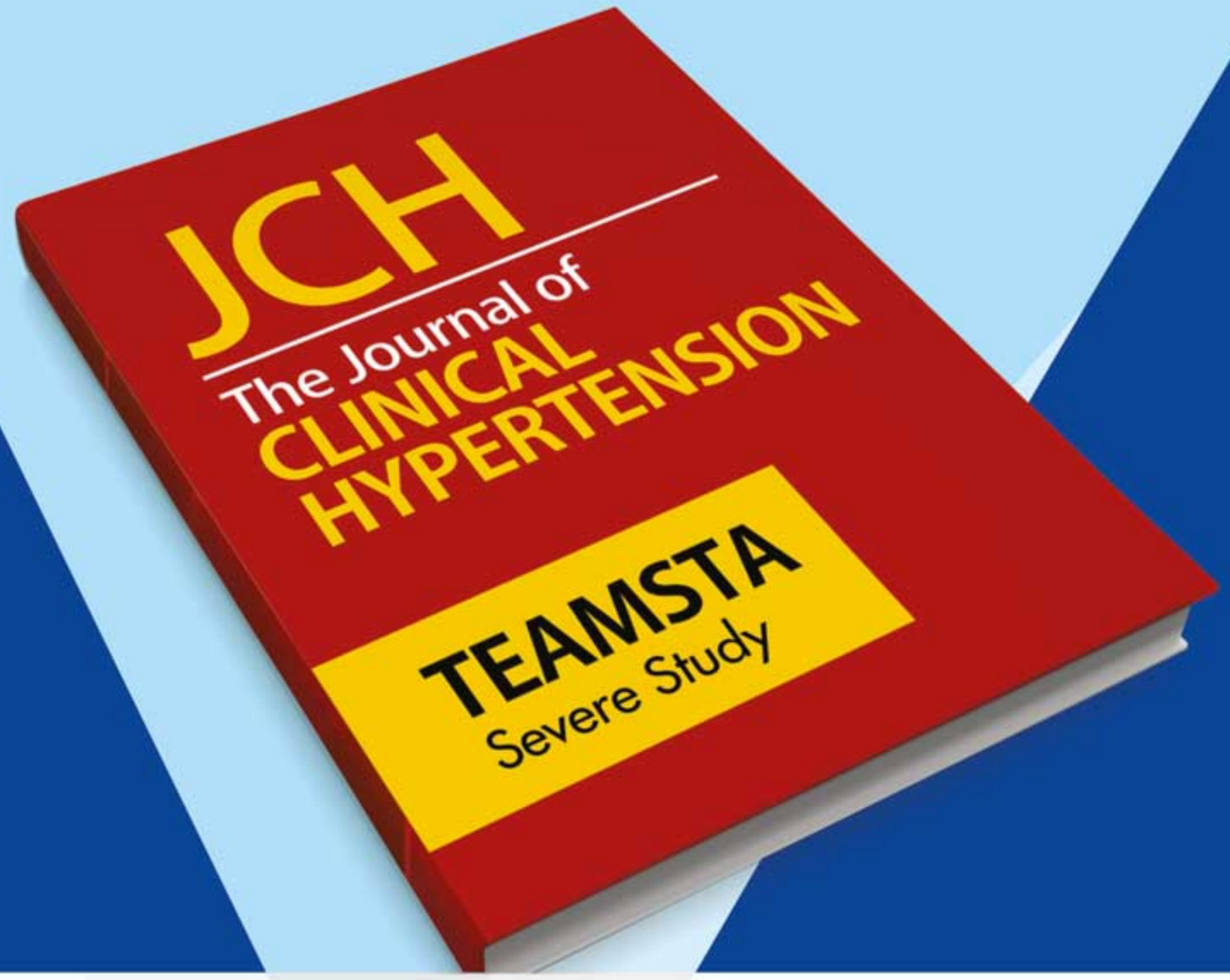
Dr.Reddy's

5 Times more effective

BP lowering with combination therapy **than uptitration**[1]



TEAMSTA-Severe

8 week multicenter, multinational, randomized, double-blind, parallel-group study[2]

Treatment of severe HTN patients with **Amlodipine** + **Telmisartan** SPC

resulted in significantly greater BP reductions than the respective monotherapies[2]

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

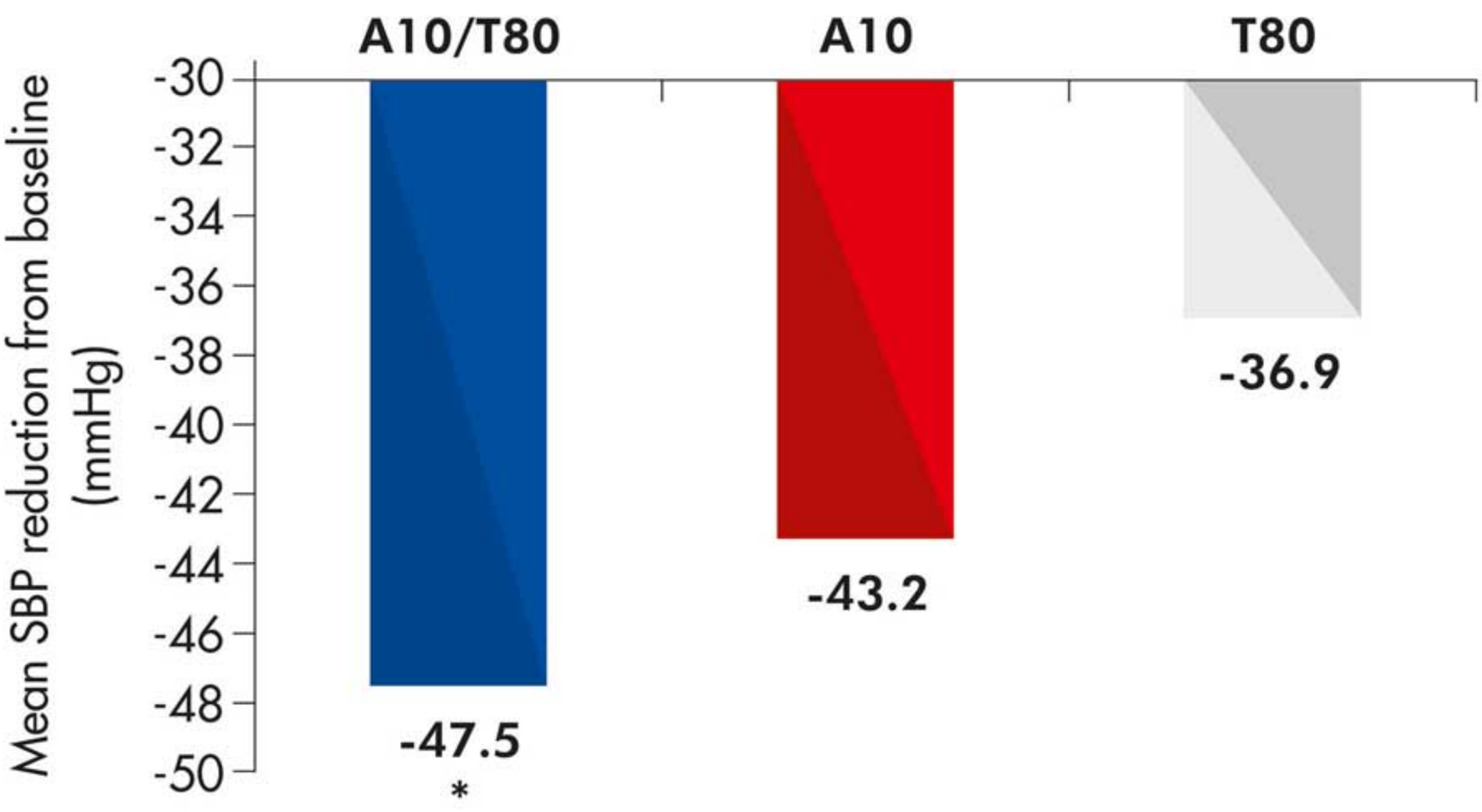
In severe hypertension

Combination of

Amlodipine + Telmisartan

vs. monotherapy

Significantly greater
BP reduction[2]



A10 - *Amlodipine 10 mg,* **T80** - *Telmisartan 80 mg,*
** P<0.0001 vs. T80 monotherapy; P=0.0002 vs. A10 monotherapy*

Combination of Amlodipine and Telmisartan more efficacious than individual monotherapy in achieving BP control in patients with severe hypertension

India at the brink of a hypertension epidemic!

Globally >1 billion adults suffer from hypertension and this figure is expected to rise to 1.5 billion in the next decade.[1] Evidence from the Indian National Family Health Survey showed that nearly 40.6% of Indians in the age group of 15 to 49 years are affected by hypertension.[2]

The presence of comorbidities along with hypertension complicates the disease process. Coexistence of diabetes and hypertension was found in 4.5% of the populace with simultaneous presence of diabetes, hypertension and dyslipidaemia in 1.8% of the residents.[3] Comorbidities are correlated with worse health outcomes in patients with their management being more complex.[4] It is suggested that nearly 3 out of every 4 patients suffer from uncontrolled hypertension[5] and it is thus imperative that severe hypertension with or without comorbidities should be managed swiftly and effectively to reduce the cardiovascular (CV) burden associated with this condition.

Combination therapy more effective than monotherapy in those with elevated or severe hypertension

Latest guidelines approve the use of any of the first-line antihypertensive agents for treatment of hypertension[6-8] and acknowledge that combination therapy is often needed, more so as a single-pill combination (SPC), to achieve better control/adherence in patients with uncontrolled hypertension. Combination of agents from two distinct classes was also found to be five times more effective in lowering blood pressure (BP) than up-titrating dose of one agent.[9] In this regard, the combination of a renin angiotensin system (RAS) blocker with a calcium channel blocker (CCB) has been suggested as one of the preferred combinations. Treatment with ARBs has resulted in lower discontinuation and adverse event rates amongst all other antihypertensive therapies.[8] Thus a SPC of an ARB and CCB, which have complementary mechanisms of action, constitutes a rational combination[5] and can be highly effective in the treatment of hypertension uncontrolled on monotherapy. The efficacy of one such SPC is discussed here.

The TEAMSTA Severe study - Greater efficacy & comparable tolerability with SPC vs individual agents[5]

Amlodipine is a first-line antihypertensive agent with proven effects on outcomes in several studies.[10] The antihypertensive efficacy of ARBs is well-known with Telmisartan having the longest half-life amongst them.[8,11] The complementary pharmacokinetic and side-effect profiles of both Telmisartan and Amlodipine make their combination suitable for a SPC which provides 24-hr BP control.[9,10,11] The TEAMSTA severe study evaluated the efficacy and safety of the SPC of Telmisartan 80 mg and Amlodipine 10 mg (A10/T80) vs monotherapy with its individual components i.e. Amlodipine 10 mg (A10) and Telmisartan 80 mg (T80) in patients with severe hypertension [systolic/diastolic blood pressure (SBP/DBP) ≥180/95 mmHg)].[5]

Design of the study: The TEAMSTA severe study was a multinational, multicenter, randomized, double-blind, parallel-group, forced-titration study conducted over 8 weeks. Patients (n=858) were recruited from 114 centers across 11 countries. After screening, suitable patients underwent a 1 day to 2 week single-blind, placebo run-in period and were randomized to one of the 3 treatment groups - A10/T80 SPC, A10 monotherapy or T80 monotherapy. Those on Amlodipine were assigned to lower doses for 2 weeks (i.e. A5/T80 or A5) and then

up-titrated to A10/T80 or A10 for the remaining 6 weeks of the study. Those on T80 monotherapy remained on the same treatment throughout the 8-week period.

The treatment groups were SPC of A10/T80 (n=421), T80 monotherapy (n=217) and A10 monotherapy (n=220). The trial medication was taken in the morning once daily at around the same time. Other antihypertensive/ related medications which may impact BP were not allowed during the study.

Inclusion criteria: Adult patients (≥18 yrs) with mean seated cuff SBP ≥180 mmHg and DBP ≥95 mmHg able to stop their current antihypertensive therapy without substantial risks.

Exclusion criteria: (a) patients with suspected or known secondary hypertension, (b) those with mean seated cuff SBP ≥200 mmHg and/or mean seated cuff DBP ≥120 mmHg, (c) those with symptomatic congestive heart failure, clinically relevant cardiac arrhythmias or hepatic impairment, severe renal impairment, unstable/ uncontrolled diabetes or any other condition that would not allow for the safe completion of the protocol, (d) women who were pregnant, nursing or premenopausal or those of childbearing potential not using adequate birth control, (e) patients with previous symptoms characteristic of angioedema when on RAS blocker therapy, (f) those with history of drug or alcohol dependency <6 months prior to the study and (g) those who were not compliant with the study medication during the run-in treatment period.

HIGHLIGHTS

- In patients with severe hypertension, effective and safe control of BP levels is very important
- The SPC of Amlodipine and Telmisartan achieved swift reduction in BP levels along with higher BP goal achievement and response rates in nearly all patients with severe hypertension compared to monotherapy with the individual components

Primary endpoint after 8 weeks of therapy: Change from baseline in mean seated in-clinic trough cuff SBP.

Secondary endpoints after 1, 2, 4 and 6 weeks: (a) change from baseline in mean seated in-clinic trough cuff SBP of treatment, (b) SBP control (SBP <140 or <130 mmHg) or DBP control (DBP <90 or <80 mmHg) and (c) overall BP goal achievement (SBP <140 and DBP <90 mmHg).

Pre-specified subgroup analyses: SBP categories in 10 mmHg increments (≥180 to <190 mmHg and ≥190 to <200 mmHg) and presence or absence of metabolic syndrome (i.e. patients with type 2 diabetes and body mass index ≥30 kg /m^2).

Adverse events: All adverse events, including reported or diagnosed oedema, that occurred throughout the entire study period were recorded.

Results:

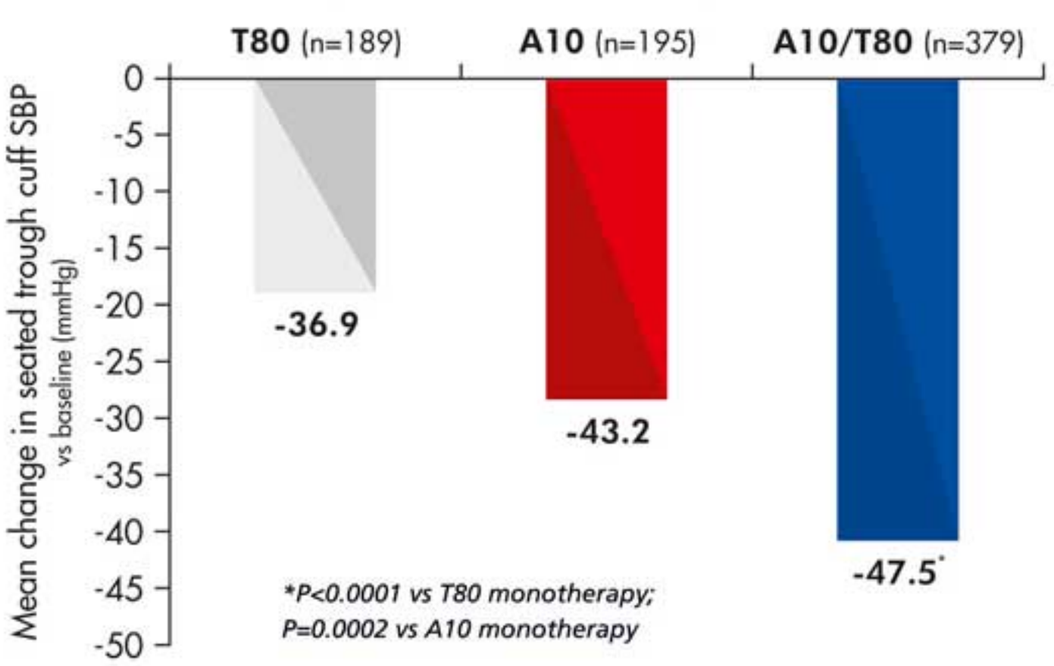
Treatment with the SPC of A10/T80 resulted in:

- **Nearly 48 mmHg reduction in SBP with A10/T80 SPC**

At the end of 8 weeks, treatment with A10/T80 resulted in greater reductions from baseline in seated trough cuff SBP vs T80 or A10 monotherapy (Figure 1). The adjusted mean reduction in seated trough cuff SBP was significantly greater with A10/T80 compared to T80 (10.6 mmHg; p<0.0001) and A10 (4.4 mmHg; p=0.0002) monotherapy (Figure 1). The reductions in seated trough cuff SBP were maintained irrespective of the baseline SBP category.

Fig 1: Mean change in seated trough cuff SBP vs baseline

[Adapted from Neutel JM et al.[5]]



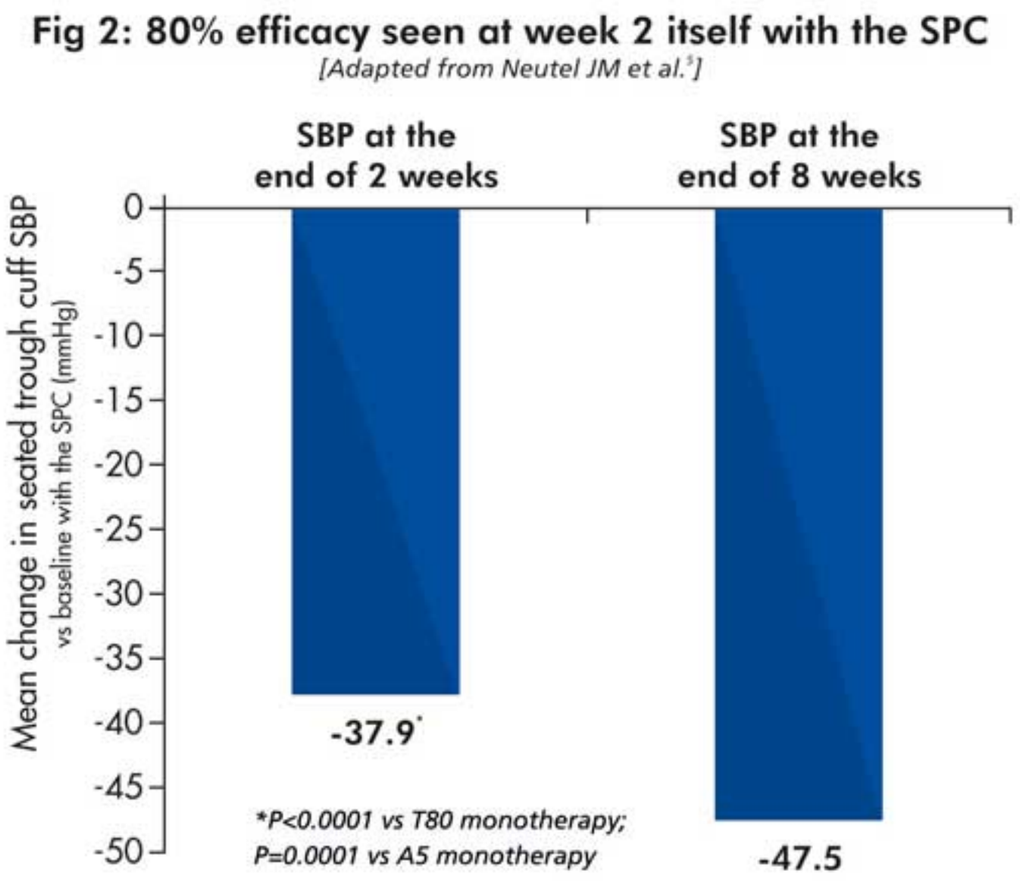
80% of maximum SBP reduction with A10/T80 SPC achieved within the first 2 weeks of therapy

The reduction in the adjusted mean SBP in the A10/T80 SPC group was significantly greater than that seen with either monotherapy group at all time points of BP measurement (overall, P<0.0001 vs T80 and P≤0.0077 vs A10).

In fact, **80% of maximum effect on SBP was achieved with the SPC in the first 2 weeks itself (Figure 2).** The reduction at week 2 with A10/T80 was also significantly greater than that for individual monotherapies at that time point [7.8 mmHg and 4.6 mmHg more reduction in SBP when compared to T80 (P<0.0001) and A5 (P=0.0001), respectively].

Fig 2: 80% efficacy seen at week 2 itself with the SPC

[Adapted from Neutel JM et al.[5]]



Changes in seated trough cuff DBP vs baseline were similarly significantly greater with A10/T80 SPC (-18.7 mmHg) compared to individual T80 (-13.8 mmHg; p<0.0001) or A10 (-16.3 mmHg; p=0.0006) monotherapy at the end of 8 weeks.

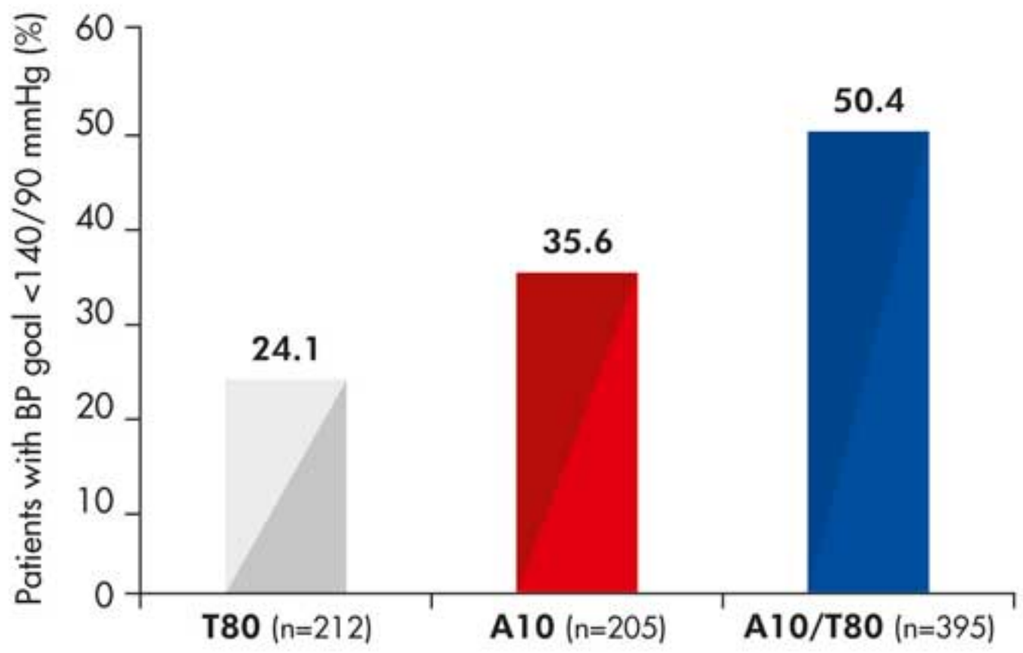
Subgroup analyses showed that the mean reduction in SBP vs baseline remained greater with the SPC as compared to the monotherapy groups for all patient groups irrespective of age, race, body mass index, type 2 diabetes and presence of metabolic syndrome.

2 times greater patients achieved BP goal (<140/90 mmHg) with A10/T80 SPC

Greater proportion of patients reached the BP goals of <140/90 mmHg BP in the A10/T80 SPC groups than either of the monotherapy groups. In fact, **BP goal was achieved by 2 times more number of patients with A10/T80 SPC than with T80 monotherapy (Figure 3).**

Fig 3: BP goal achievement with monotherapy and SPC

[Adapted from Neutel JM et al.[5]]



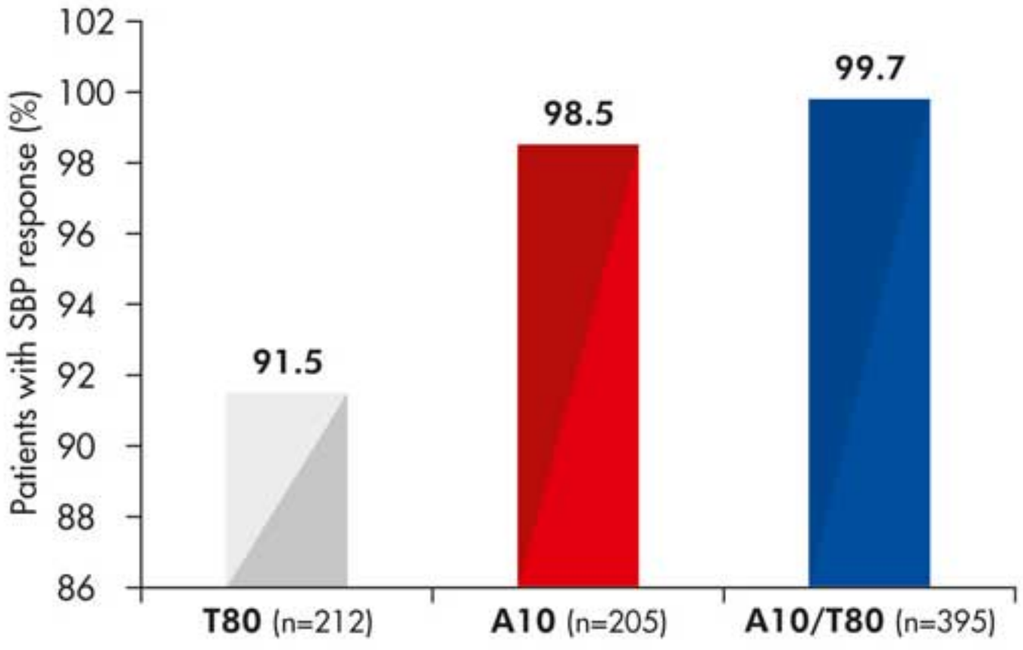
The 24-hour ambulatory BP goal of <130/80 mmHg was also achieved by >2 times the number of patients on A10/T80 SPC than those on A10 monotherapy (82.7% vs 37.9%; P<0.0001).

99.7% of patients achieved SBP response with A10/T80 SPC

The SBP/DBP response rates (i.e. SBP <140 or ≥10 mmHg reduction and DBP <90 or ≥10 mmHg reduction) were higher with the A10/T80 SPC compared with either monotherapy.

Overall, 99.7% patients in the A10/T80 group had an SBP response compared to the T80 and A10 monotherapy groups (Figure 4). Even in the case of the more stringent SBP response (<140 or ≥15 mmHg reduction) the response rates were 99%, 88.7% and 98.5% for the A10/T80 SPC, T80 and A10 groups, respectively.

Fig 4: SBP response rates with SPC vs monotherapy
[Adapted from Neutel JM et al.[5]]



DBP response rates were also higher with A10/T80 (91.4%) than for the T80 (69.3%) and A10 (83.9%) groups.

The SPC of A10/T80 was safe and well tolerated with adverse event rates similar to the monotherapy groups. Most of them (98.5%) were of mild-to-moderate intensity.

Conclusion

The high prevalence of uncontrolled hypertension with or without the presence of comorbidities has necessitated the use of combination therapy to achieve BP targets. The TEAMSTA severe study showed that the A/T SPC was more efficacious than the individual components in decreasing BP levels and improving BP goal achievement/response rates in adults with severe hypertension. Moreover this efficacy was swift (within 2 weeks), sustained over the study period and across patient groups irrespective of the presence of comorbidities. Thus, the A/T SPC is an effective treatment modality in this increasingly difficult-to-treat population and can help reduce the long-term burden of CV morbidity and mortality associated with hypertension.

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In severe hypertension

Combination of

Amlodipine + Telmisartan

vs. monotherapy

80 % of maximum effect on SBP was achieved as early as 2 weeks[2]

99.7 % patients achieved SBP response (<140 or ≥10 mmHg reduction)[2]

2x more patients achieved the BP goal ^[2]

BP - Blood Pressure, **HTN -** Hypertension, **SPC -** Single-Pill Combination, **SBP -** Systolic Blood Pressure, ^ BP goal <140/90 mmHg, **1.** Neldam S, Lang M, Jones R; TEAMSTA-5 Investigators. Telmisartan and amlodipine single-pill combinations vs amlodipine monotherapy for superior blood pressure lowering and improved tolerability in patients with uncontrolled hypertension: results of the TEAMSTA-5 study. J Clin Hypertens (Greenwich). 2011 Jul;13(7):459-66, **2.** Neutel JM, Mancia G, Black HR, Dahlöf B, Defeo H, Ley L et al. TEAMSTA Severe HTN Study Investigators. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. J Clin Hypertens (Greenwich). 2012 Apr;14(4):206-15.

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In severe hypertension

Combination of

Amlodipine + Telmisartan

vs. monotherapy

Quick BP Reduction
as early as week 1[3]

Consistent BP Control
over 24 hours[3]

GGI-CO-Chronic 1-ZE-30665-300030665-LL-D21-360

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Dr. Reddy's Laboratories Ltd., Global Generics - India, 7-1-27, Ameerpet, Hyderabad-500 016, India www.drreddys.com