



A Study on The Safety and Efficacy of Fixed Dose Combination of Amlodipine, Telmisartan And Hydrochlorthiazide In Hypertension

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Abstract

Effective BP control is far away from reality in many patients in spite of advancements in many classes of antihypertensive drug therapy. Use of triple drug combination in the management of hypertension have already been established, however this study was conducted to evaluate the efficacy and safety of triple drug fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorothiazide 12.5mg. Of the 1,47 patients screened, 1,28 were randomized (64 Telmisartan, 64 amlodipine) and 112 finished the investigation (59 Telmisartan, 53 amlodipine). The ITT populace was utilized for the essential examination and included 1263 patients (63 Telmisartan, 63 amlodipine). There were more suspensions with the amlodipine ± HCTZ procedure (11 patients) than with the Telmisartan ± HCTZ technique (46 patients, 7.2%), basically because of AEs (69 patients versus 22 patients individually) and for the most part credited to fringe edema (patients [7.3%] versus two patients [$<1\%$]). Statistic and gauge qualities were all around adjusted between the two treatment procedures, and no factually noteworthy contrasts were watched. The examination was directed in 11 nations at 122 research focuses. By and large, mean age was 54.5 years and mean weight file was 28.4 kg/m². Most patients were male (55.2%), and the greater part was Caucasian (86.2%). Patients were either organize 1 treatment innocent (33.9%), arrange 2 treatment gullible (13.5%), or uncontrolled on current antihypertensive monotherapy (52.6%). At gauge, MSSBP/MSDBP was 150.2/93.9 mmHg. This triple drug fixed dose combination of Telmisartan, Amlodipine and hydrochlorothiazide was found to be effective and safe option for the optimal management of hypertension.

Keywords

Diastolic; Systolic; Blood Pressure; Hypertension; Triple drug fixed dose combination

INTRODUCTION:

The danger of cardiovascular sickness increments continuously over 115/75 mmHg. by and by pulse is considered too low just if perceptible manifestations

are present. Observational examinations exhibit that individuals who keep up blood vessel weights at the low end of these weight ranges have much better long-haul cardiovascular wellbeing. There is a

continuous medicinal discussion over what is the ideal level of circulatory strain to target when utilizing medications to bring down pulse with hypertension, especially in more established people. The table demonstrates the characterization of pulse received by the American Heart Association for grown-ups who are 18 years and older. It accepts the qualities are a consequence of averaging resting circulatory strain readings estimated at least two visits to the doctor. In the UK, facility blood weights are generally sorted into three gatherings; low (90/60 or lower), ordinary (between 90/60 and 139/89), and high (140/90 or higher). Circulatory strain vacillates from moment to minute and regularly demonstrates a circadian beat over a 24-hour duration, with most astounding readings in the early morning and night times and least readings at night^[1]. Loss of the ordinary fall in pulse during the evening is related with a more prominent future danger of cardiovascular illness and there is prove that evening circulatory strain is a more grounded indicator of cardiovascular occasions than day-time blood pressure. Also, a person's pulse fluctuates with work out, enthusiastic responses, rest, assimilation and time of day (circadian cadence). Different components, for example, age and sex, additionally impact a man's circulatory strain. In youngsters, the ordinary extents are lower than for grown-ups and rely upon height. Reference circulatory strain esteems have been created for kids in various nations, in light of the dispersion of pulse in offspring of these countries[2]. As grown-ups age, systolic weight tends to rise, and diastolic weight tends to fall. Consequently, in the elderly, systolic pulse frequently surpasses the typical grown-up range, this is believed to be because of expanded firmness of the arteries. Contrasts among left and right arm circulatory strain estimations have a tendency to be little. In any case, every so often there is a steady contrast more prominent than 10 mmHg which may require encourage examination, e.g. for obstructive blood vessel disease[3]. The risk of cardiovascular disease increases progressively above 115/75 mmHg.⁶ In practice blood pressure is considered too low only if noticeable symptoms are present.⁴ Observational studies demonstrate that people who maintain arterial pressures at the low end of these pressure ranges have much better long term cardiovascular health. There is an ongoing medical debate over what is the optimal level of blood pressure to target when using drugs to lower blood pressure with hypertension, particularly in older people.⁷ The classification of blood pressure adopted by the American Heart Association for adults who are 18

years and older.³ It assumes the values are a result of averaging resting blood pressure readings measured at two or more visits to the doctor.^{8, 9} In the UK, clinic blood pressures are usually categorized into three groups; low (90/60 or lower), normal (between 90/60 and 139/89), and high (140/90 or higher).^{10, 11} Blood pressure fluctuates from minute to minute and normally shows a circadian rhythm over a 24-hour period, with highest readings in the early morning and evenings and lowest readings at night.^{12, 13} Loss of the normal fall in blood pressure at night is associated with a greater future risk of cardiovascular disease and there is evidence that night-time blood pressure is a stronger predictor of cardiovascular events than day-time blood pressure.¹⁴ Also, an individual's blood pressure varies with exercise, emotional reactions, sleep, digestion and time of day (circadian rhythm).

AIM AND OBJECTIVES:

To Assess which antihypertensive agent to use and at what dosage, in addition to determining when to initiate combination therapy and which agents to combine, is important for achieving BP control.

MATERIALS AND METHODS:

445The examination convention was affirmed by the Independent Ethics Committee or Institutional Review Board for each inside, and the investigation was directed as per the moral standards of the Declaration of Helsinki. All patients gave composed educated agree preceding randomization.

Patients

Qualified patients were matured somewhere in the range of 18 and 75 years. Treatment-gullible patients had arrange 1/review 1 hypertension (mean sitting systolic circulatory strain [MSSBP] 140– 159 mmHg and additionally mean sitting diastolic pulse [MSDBP] 90– 99 mmHg) or stage 2/review 2 hypertension (MSSBP 160– 179 mmHg and additionally MSDBP 100– 109 mmHg).^{2,3} Patients were considered treatment-guileless in the event that they had gotten no antihypertensive prescription in the past 12 weeks. Patients on antihypertensive monotherapy were qualified given their BP was uncontrolled (MSSBP 140– 160 mmHg as well as MSDBP 90– 100 mmHg) and they had been on monotherapy for ≥4 weeks and until ≤2 days before a pre-randomization visit. Both treatment-innocent and treated patients needed to satisfy the BP criteria at both the pre-randomization visit and before randomization on day 1.

Scratch avoidance criteria incorporated the accompanying: MSSBP ≥ 180 mmHg or MSDBP ≥ 110 mmHg whenever between the pre-randomization visit and day 1; momentum treatment with a CCB;

history of extreme touchiness to any of the examination drugs; cerebrovascular mischance or myocardial dead tissue inside the past a year or transient ischemic cerebral assault inside the past a half year; nearness of congestive heart disappointment, angina pectoris, critical valvular coronary illness or arrhythmia, second or third degree heart obstruct without a pacemaker, or diabetes; history of danger inside the past five years (aside from confined basal cell carcinoma of the skin); serum potassium level <3.5 or >5.5 mmol/L without prescription; serum creatinine level >1.5 times over the maximum furthest reaches of ordinary or a background marked by dialysis or nephrotic disorder; and alanine or aspartate aminotransferase levels >2 times over the furthest reaches of typical or history of hepatic encephalopathy, esophageal varices, or portocaval shunt. Ladies were postmenopausal, carefully sterile, or utilizing a satisfactory technique for contraception.

Study outline

This was a randomized, twofold visually impaired, parallel-gathering, dynamic controlled investigation led in 11 nations (Argentina, Brazil, Columbia, Denmark, Ecuador, Spain, Finland, Germany, Ireland, Italy, and United Kingdom). Patients were surveyed for qualification inside about fourteen days before randomization. Patients proceeded with their antihypertensive pharmaceutical amid this period. Qualified patients were randomized in a 1:1 proportion and specifically changed from their present antihypertensive treatment to either a Telmisertan methodology or an amlodipine system (Figure 1). Stage 1 treatment-credulous patients were begun on either Telmisertan 160 mg once every day (o.d.) or amlodipine 5 mg o.d., while arrange 2 treatment-guileless patients and those uncontrolled on current antihypertensive monotherapy were begun on Telmisertan 160 mg/HCTZ 12.5 mg o.d. or then again amlodipine 10 mg o.d. Patients were told to take their examination pharmaceutical at around 8:00 AM. To keep up blinding, all examination drug was indistinguishable in bundling, marking, appearance, and smell.

Study design.

Patients visited the center at three-to four-week interims amid the 14-week treatment period for viability and mediocrity appraisals. As appeared in Figure 1, up-titration or the expansion of HCTZ was obligatory at visits in which the patient did not accomplish a MSSBP <140 mmHg and a MSDBP <90 mmHg. Down-titration to the past advance was

allowed for a MSSBP <100 mmHg or if the patient gave symptomatic hypotension.

Utilization of monoamine oxidase inhibitors and tricyclic antidepressants was restricted amid the investigation, similar to the interminable utilization of oral steroids, sympathomimetic medications, and bronchodilators. Thyroid prescription and hormone substitution treatment were permitted just if stable upkeep measurements had been utilized in the past a half year.

Viability evaluations

At every facility visit, sitting BP estimations were acquired utilizing an aligned standard sphygmomanometer as per the American Heart Association (AHA) Committee Report on circulatory strain determination.¹⁵ Blood weight readings were taken just before ingesting the morning measurement of study drug (ie, at trough). In the wake of sitting for five minutes, three back to back BP estimations were taken at one-to two-minute interims. On the off chance that the three MSSBP readings were not inside ± 5 mmHg, the system was rehashed until the point when this model was met. The essential viability variable was the level of patients who accomplished BP control (MSSBP/MSDBP $< 140/90$ mmHg) were still on ponder solution toward the finish of the investigation (week 14).

Mediocrity appraisals

Unfriendly occasions (AEs) were checked all through the examination and included unconstrained reports by the specialists and patients. What's more, standard research facility tests (hematology and blood science), imperative signs, and physical examinations were performed.

Measurable strategies

Adequacy examinations were performed utilizing the aim to-treat (ITT) populace, which incorporated every single randomized patient who got ≥ 1 dosage of study pharmaceutical and had ≥ 1 postbaseline viability evaluation. The security populace incorporated all patients who got ≥ 1 dosage of study drug and had ≥ 1 postbaseline bearableness evaluation.

Statistic and gauge qualities were thought about between the two treatment techniques utilizing the t-test (nonstop factors) or chi-square test (unmitigated factors). For the essential adequacy variable, a calculated relapse show was fitted including terms for treatment, nation, and phase of hypertension or fizzled antihypertensive monotherapy. The number and level of patients whose BP was controlled and who were still on ponder pharmaceutical inside every treatment

system, the point gauge for the chances proportion (Telmisartan/amlodipine), and the two-sided 95% certainty interim (CI) for the chances proportion were resolved. The change from gauge to each visit and endpoint (week 14 or last perception conveyed forward esteem) in MSSBP and MSDBP was investigated utilizing examination of covariance. Treatment, nation, and phase of hypertension or fizzled antihypertensive monotherapy were incorporated as settled elements and pattern BP was incorporated as a covariate in the model. The slightest squares mean changes from pattern, treatment contrast, 95% CI for the treatment distinction, and P-esteem were resolved.

RESULTS AND DISCUSSION:

Patients

Understanding mien is displayed in Figure 2. Of the 1,47 patients screened, 1,28 were randomized (64 Telmisartan, 64 amlodipine) and 112 finished the investigation (59 Telmisartan, 53 amlodipine). The ITT populace was utilized for the essential

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Variable	Telmisartan strategy (n= 64)	Amlodipine strategy (n= 64)	Total (n = 128)
Mean (SD) age, y	54.6	54.3	54.5
Age group, n (%)			
< 65 y	50	50	100
≥ 65 y	13	13	27
Gender, n (%)			
Male	36	34	70
Female	27	29	57
Race, n (%)			
Caucasian	55	55	110
Native American	16	21	37
Black	10	17	27
Other	52	45	97
Mean (SD) height, cm	168.6	168.6	168.6
Mean (SD) weight, kg	80.9	81.0	80.9
Mean BMI, kg/m ²	28.4	28.4	28.4
Serum creatinine, umol/L	79.4	78.8	79.1
Serum glucose, mmol/L	5.56	5.55	5.55
Serum potassium, mmol/L	4.38	4.35	4.36
MSSBP (SD), mmHg	150.4	150.0	150.2
MSDBP (SD), mmHg	93.9	93.8	93.9
Stage 1 treatment-naïve, n (%)	22	21	43
Stage 2 treatment-naïve, n (%)	90	54	14
Uncontrolled on current monotherapy, n (%)	33	34	61

Table 1: Demographic and baseline characteristics

Blood pressure measurements

Of the 1,47 patients screened, 1,28 were randomized (64 Telmisartan, 64 amlodipine) and 112 finished the

investigation (59 Telmisartan, 53 amlodipine). The ITT populace was utilized for the essential examination and included 1263 patients (63

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Week	MSSBP			MSDBP		
	Telmisartan strategy*	Amlodipine strategy†	P	Telmisartan strategy*	Amlodipine strategy†	P
4	-15.3 (0.5)	-13.5 (0.5)	0.0029	-8.9 (0.3)	-8.0 (0.3)	0.016
8	-19.6 (0.5)	-18.0 (0.5)	0.0078	-10.6 (0.4)	-9.8 (0.4)	0.0328
11	-21.4 (0.5)	-19.4 (0.5)	0.0006	-12.1 (0.3)	-11.5 (0.3)	0.1469
14	-22.3 (0.5)	-21.3 (0.5)	0.063	-12.8 (0.3)	-12.1 (0.3)	0.0672
Endpoint‡	-21.7 (0.5)	-19.6 (0.5)	0.0002	-12.5 (0.3)	-11.1 (0.3)	<0.0001

Table 2: Least-squares mean changes (SEM) from baseline in MSSBP and MSDBP by visit

Titration steps

A numerically comparative level of patients in every treatment methodology were up-titrated through the span of the investigation. At week 11, the last up-titration visit, the larger part of stage 1 treatment-innocent patients were on their underlying treatment or the main titration step: Telmisartan 160 mg alone or in blend with HCTZ 12.5 mg o.d. (192/219, 87.7%) or amlodipine 5 mg or 10 mg o.d. (167/215, 77.7%). In the meantime, point, most stage 2 treatment-gullible patients and those uncontrolled on current antihypertensive monotherapy additionally were getting their underlying treatment or the main titration step: Telmisartan 160 mg in mix with either HCTZ 12.5 mg or 25 mg o.d. (293/413, 70.9%) or amlodipine 10 mg alone or in blend with HCTZ 12.5 mg o.d. (253/419, 60.4%). More patients were on mix treatment with Telmisartan/HCTZ than with amlodipine/HCTZ.

Level of patients on every treatment regimen at week 11, the last up-titration visit. Rates may not indicate 100 because of adjusting. Numbers on x-pivot speak to measurements (in mg) of Telmisartan, Telmisartan/hydrochlorothiazide (HCTZ), amlodipine, and ...

Decency

Generally speaking, AEs happened in 41.5% and 53.3% of patients accepting Telmisartan $\pm$ HCTZ and amlodipine $\pm$ HCTZ, individually. The most generally announced AEs were fringe edema (2.2% for Telmisartan versus 22.4% for amlodipine), cerebral pain (4.0%, 6.2%), and unsteadiness (3.8%, 1.7%). Fringe edema brought about the end of 46 (7.3%) patients treated with amlodipine $\pm$ HCTZ contrasted and two ($<1.0\%$) patients on Telmisartan $\pm$ HCTZ. The frequency of all AE reports of edema is exhibited by facility visit in Table 3. There were no passings amid the examination. Mean changes in research center discoveries were negligible. Barely any patients experienced increments in serum creatinine levels ≥ 175 μ mol/L (two Telmisartan, zero amlodipine) or serum potassium levels ≥ 5.8 mmol/L (four Telmisartan, two amlodipine). Twenty-four (3.8%) patients in the Telmisartan $\pm$ HCTZ gathering and 41 (6.5%) in the amlodipine $\pm$ HCTZ assemble encountered a $>20\%$ diminish in serum potassium levels at any postbaseline visit. No patient stopped because of research facility variations from the norm. Crucial signs did not uncover any clinically critical patterns other than the normal changes in BP.

Day or Week	Telmisartan strategy (n = 632)	Amlodipine strategy (n = 634)
Day 1	0	2 (<1.0)
Week 4	7 (1.1)	88 (13.9)
Week 8	13 (2.1)	132 (20.8)
Week 11	16 (2.5)	147 (23.2)
Week 14	17 (2.7)	153 (24.1)

DISCUSSION:

Current treatment rules recognize the requirement for mix treatment in the dominant part of patients with hypertension, and prescribe mix treatment as beginning treatment for most patients with standard BP $\geq 160/100$ mmHg or when add up to cardiovascular hazard is high.^{2,3} Initial or early utilization of mix treatment utilizing two medications with corresponding methods of activity may enable patients to achieve BP targets speedier, with less titration steps, and without an expansion in the symptoms related with higher measurements of monotherapy.¹⁶ Moreover, confirm from historic point preliminaries recommends that more provoke BP control prompts better clinical outcomes.¹

The present examination utilized calculations reliable with current treatment rules, in light of patients' present BP level or past history on antihypertensive medications. We found that starting treatment before with Telmisartan/HCTZ gave unrivaled BP control rates ($<140/90$ mmHg) contrasted with titrating amlodipine monotherapy with its most extreme measurements previously including HCTZ. Huge contrasts for Telmisartan $\pm$ HCTZ were seen at weeks 8, 11, and 14 (end of study). The distinctions were much more prominent for patients who toward the beginning of the examination were uncontrolled on past monotherapy. In those patients who were guileless to antihypertensive treatment comparable BP control rates were accomplished utilizing either treatment technique approach. This finding might be clarified by the more prominent number of patients utilizing monotherapy in the treatment-credulous gathering contrasted with those in the past monotherapy assemble since the two regimens were related with few titration steps. The higher occurrence of fringe edema with amlodipine $\pm$ HCTZ prompted more regular treatment stops, bringing about a general lower remedial achievement.

Our outcomes bolster the utilization of the Telmisartan $\pm$ HCTZ methodology for the treatment of hypertension. This is predictable with the settled job of the RAS in the pathogenesis of hypertension.¹⁷ Moreover, confirm from expansive results preliminaries (eg, HOPE, ALLHAT, LIFE, and VALUE) has reliably exhibited that a RAS-inhibitor-based way to deal with treatment gives comparative or more noteworthy cardiovascular and organ security than regimens without this component.¹⁸ conversely, our discoveries don't bolster the utilization of the amlodipine $\pm$ HCTZ methodology as this regimen was all the more ineffectively endured and yielded sub-par BP control rates and BP

decreases at most center visits. This is in accordance with current National Institute for Health and Clinical Excellence (NICE) direction and the ABCD (A = angiotensin-changing over catalyst inhibitor [ACE-I] or ARBs, B = beta-blockers, C = CCBs, and D = thiazide or thiazide-like diuretics) treatment calculation, which proposes that patients beginning on a CCB should include a RAS inhibitor.^{19,20} Although the latest European rules advocate the utilization of a CCB/diuretic combination,² our outcomes and those of others¹⁴ propose this is a poor suggestion. The blend of an antihypertensive specialist that hinders the RAS with one that does not is probably going to be a more powerful methodology than utilizing two operators that both square the RAS (eg, ACE-I+ARB)^{21,22} or two specialists that don't influence the RAS (eg, CCB + diuretic). The viability of amlodipine monotherapy has been shown in some key hypertension result considers (eg, TOMHS, VALUE, and ALLHAT), however when patients with hypertension can't be adequately controlled with amlodipine monotherapy, it would bode well to utilize a corresponding antihypertensive operator (eg, ACE-I or ARB). As of late, the ASCOT and ACCOMPLISH thinks about exhibited the significance of joining amlodipine with an ACE-I as patients had huge decreases in cardiovascular events.^{23,24}

A few past randomized controlled investigations have analyzed Telmisartan $\pm$ HCTZ and amlodipine $\pm$ HCTZ procedures in patients with basic hypertension, albeit none utilized the dosage and titration plans portrayed thus. The mix of Telmisartan/HCTZ presents extra BP bringing down over monotherapy with these agents,⁸ with low measurements of this blend (80– 160/12.5 mg) giving practically identical BP decreases to high-dosage amlodipine monotherapy (10 mg).^{10– 13} Similar in general antihypertensive adequacy was exhibited when a regimen of Telmisartan 80 mg o.d. titrated up to Telmisartan 160 mg/HCTZ 12.5 mg O.D. was contrasted and a regimen of amlodipine 5 mg o.d. titrated up to amlodipine 10 mg/HCTZ 12.5 mg o.d.^{25,26} Lacourcière and associates directed a 10-week, constrained titration, mobile BP observing examination in which patients with organize 2 hypertension began treatment with Telmisartan 160 mg o.d. or on the other hand amlodipine 5 mg o.d.¹⁴ The Telmisartan arm was titrated to Telmisartan 160 mg/HCTZ 12.5 mg o.d. at about fourteen days and Telmisartan 320 mg/HCTZ 25 mg o.d. at about a month and a half, while the amlodipine arm was titrated to twofold dosage at about fourteen days with the expansion of HCTZ 25 mg o.d. at about a month and a half. At 10 weeks, the decrease from

benchmark BP was 3.8/2.7 mmHg more noteworthy with Telmisartan/HCTZ than amlodipine/HCTZ (both $P < 0.01$). The VALUE results preliminary announced better BP control with an amlodipine-based strategy.²⁷ However, a few components identified with the examination configuration may have affected the consequences of VALUE. Patients were not randomized to various treatment methodologies in light of the seriousness of their hypertension or their earlier treatment history or reaction. Besides, the expansion of HCTZ was not permitted before two months of monotherapy treatment, titration to the high-dosage Telmisartan/HCTZ regimen (320 mg/25 mg o.d.) was impossible, and patients relegated to the Telmisartan procedure started treatment with an imperfect beginning measurements (80 mg o.d.).^{4,28} The 160-mg measurement of Telmisartan has been appeared to be more compelling than a 80-mg measurements in diminishing BP from standard (14.3/11.1 mmHg versus 11.2/9.0 mmHg) and in giving BP control (39.3% versus 22.7%) after up to about two months of treatment, with the two measurements having practically identical AE and biochemical profiles.⁴ Numerous wandering BP observing investigations have shown that Telmisartan 160 mg o.d. gives steady decreases in BP all through the 24-hour interim, with a safeguarding of the BP-bringing down impact toward the finish of the dosing period.^{29,30} Further, contrasted and a 80-mg dosage, 160-mg of Telmisartan brought about more viable restraint of the RAS over the 24-hour dosing period.^{31,32}

The two medications were very much endured in the present investigation, except for a moderately high frequency of fringe edema in the amlodipine $\pm$ HCTZ gathering (22.4%) versus the Telmisartan $\pm$ HCTZ gathering (2.2%). Thus, stops because of this AE were higher in the previous gathering (7.3% versus $<1.0\%$). Different AEs were accounted for at a low and for the most part comparable frequency with both treatment procedures. Fringe edema is a known symptom of amlodipine. A pooled examination of information from 40 fake treatment controlled, twofold visually impaired investigations in which 1,775 patients were treated with amlodipine (basically 5 mg or 10 mg day by day) and 1,213 with fake treatment found that the occurrence of "edema" was fourfold more prominent with amlodipine than with fake treatment ($P < 0.001$).³³ The rates of fringe edema and related suspensions in our investigation (Table 3) were like those in Val-Syst think about (4.8% and 0% for Telmisartan, separately; 26.8% and 4.2% for amlodipine, respectively).²⁶ Side impacts can negatively affect

patients' perseverance with antihypertensive treatment, which thusly might be related with unfavorable clinical outcomes.³⁴

CONCLUSION:

Patients with hypertension who exhibit poor industriousness have expanded bleakness and mortality and higher medicinal services costs. Better endured treatment systems ought to enhance diligence and empower more patients to accomplish insurance against cardiovascular occasions. Starting treatment prior with Telmisartan/HCTZ, instead of titrating monotherapy to its greatest measurements previously including a second operator, was better than amlodipine monotherapy or amlodipine $\pm$ HCTZ for accomplishing BP control ($<140/90$ mmHg) while staying away from over the top quantities of treatment modifications and looking after fairness. The frequencies of fringe edema and related suspensions were more prominent with amlodipine $\pm$ HCTZ.

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