Efficacy and Safety of Triple versus Dual Combination Blood Pressure Lowering Drug Therapy - A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background and objectives: Most patients with hypertension need ≥2 drugs to achieve goal blood pressure. This systematic review assessed efficacy and safety of triple vs. dual combination therapy for the management of hypertension.

Methods: Publication databases, clinical trials registries and regulatory agency websites were searched until April 2018 for double-blind randomised controlled trials (RCTs) comparing triple with dual therapy of BP lowering drugs, for ≥3 weeks, among patients with hypertension. Meta-analyses for efficacy and safety outcomes were performed using random-effects model. Regimen efficacy was predicted using the Therapeutic Intensity Score (TIS) and the Law et al. method (which predict dose doubling increases efficacy by 100% and around 20%, respectively), and compared with observed efficacy.

Results: Fourteen RCTs (11,457 participants) were included. Overall, triple compared to dual therapy reduced BP by 5.4/3.2 mmHg (P<0.001), and improved BP control by 58% vs. 45%, (relative risk (RR) 1.33 [95% CI 1.25-1.41]), while incidence of withdrawals due to adverse events (AEs) were 3.3% vs. 3.4% (RR 1.24 [95% CI 1.00-1.54], p=0.05). Law et al. method was superior to TIS in predicting differences in efficacy between triple and dual therapies. For patients uncontrolled on sub-maximal dose dual therapy, adding a third drug achieved on average approximately four times more BP reduction than doubling the dose of dual therapy component drugs (6.0/3.7 vs. 1.5/0.8 mmHg, respectively).

Conclusion: Addition of a third drug is likely to be more efficacious without increasing AEs, compared to increasing dose of existing dual therapy. Early use of triple therapy can significantly improve hypertension control.

Introduction

Most people with hypertension require two or more blood pressure (BP) lowering drugs to achieve BP control under 140 mmHg systolic BP (SBP) [1, 2]. However, only about 30% of people treated for hypertension receive such therapy [3]. Recent evidence from randomised controlled trials (RCTs) has confirmed that further BP lowering within the 120-140 mmHg SBP range for individuals at high cardiovascular risk would prevent more cardiovascular events [4, 5]. This suggests there will be even greater clinical interest in therapies containing two or three BP lowering drugs. Currently there is inconsistency across guidelines, with some recommending triple combination only after titration to maximal dose of dual combination [6], other recommending "add third drug/optimise doses of drugs" [7], while some other providing no specific recommendations [1, 2, 8]. Evidence on dose-response relationship of individual drugs suggest triple combination even at submaximal doses would be more efficacious and tolerable than dual combination at maximal dose [9]. This systematic review of RCTs was therefore undertaken to assess the efficacy and safety of triple versus dual combination therapy in adults with hypertension.

Methods

The protocol for this systematic review was registered at PROSPERO (CRD42014006977) before screening for eligible studies to be included in the review.

Literature search and selection of studies

Cochrane Central Registry of Controlled Trials, MEDLINE, and Embase were systematically searched until April 2018 to identify relevant literature. The search strategy was developed using appropriate Medical Subject Headings and free-text terms including key words. Search

was restricted to RCTs in humans without any language restriction (Supplement Table S1). Other electronic sources searched were: Google Scholar, clinicaltrial.gov, World Health Organisation - International Clinical Trials Registry Platform, and the websites of Food and Drug Administration, European Medicines Agency, and Therapeutic Goods Administration of Australia. References of relevant reviews and included trials were also reviewed to identify any additional eligible trials.

Two reviewers (AS & BH) independently reviewed titles and abstracts to exclude clearly irrelevant studies. Two reviewers independently screened the full text of potentially eligible studies against predefined inclusion criteria. The inclusion criteria were: RCTs of triple vs. dual combinations of angiotensin converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], calcium channel blockers [CCBs], beta-adrenergic blockers [BBs], or thiazide/like diuretics [TDs]), in hypertensive (baseline mean SBP≥ 140 or DBP≥ 90 mmHg) adults; with a treatment duration of ≥3 weeks, with at least one treatment group randomized to triple combination; and at least one treatment group randomized to dual combination; and reported data on efficacy (mean change in SBP/DBP from baseline to endpoint). Patients enrolled in the included studies could be either receiving antihypertensive drugs or untreated at baseline. Studies were excluded if they focused on secondary hypertension or if the use of triple or dual combinations was optional (e.g. to reach BP targets). Studies were not excluded based on the presence or absence of any disease at baseline. A third reviewer helped to resolve any disagreement between the primary reviewers.

Data extraction and assessment of risk of bias in included studies

Two reviewers (AS, BH) extracted data independently using a standard, piloted, data extraction form including, study and participant characteristics, interventions and outcomes.

Information relevant for this review but missing from published reports was requested from publication authors or study sponsors. Two reviewers (AS & EA) independently assessed risk of bias in each included study using Cochrane's risk of bias assessment tool [10].

Data management and analysis

Different drugs and their doses in the triple and dual combinations are a potential source of heterogeneity in treatment effects. To explore this, we predicted difference in efficacy between triple and dual combination by two published methods and compared them with observed difference in efficacy: the method of Law et al. [9], and Therapeutic Intensity Score (TIS) [11] (both summarised in Supplementary Table S2).

Changes in SBP and diastolic blood pressure (DBP) (change in mean from baseline to end of treatment) were summarised as a between treatment group difference in mean along with 95% confidence intervals (CI). Proportion of participants achieving the study's target BP at the end of treatment were summarised as relative risks (RR) with 95% confidence intervals (CI). Safety outcomes, defined as withdrawals due to adverse events (WDAEs) and any adverse events (AAEs) were summarised as RR (95% CI). Meta-analyses were performed using random-effects model with inverse variance weighting. Heterogeneity was detected by Q test and quantified by I^2 statistics [12]. For trials that involved more than one triple and/or dual combination group, to avoid the issue of double counting when multiple comparisons from a trial are included in the meta-analysis, the number of patients (and number events for binary outcomes) were divided appropriately [12]. To investigate publication bias, a funnel plot [13] was produced for the primary outcome of change in BP by combining effects of all triple combinations and dual combinations within each trial such that each trial contributed only

one comparison. Data were prepared in Microsoft Excel and analysed using Comprehensive meta-analysis software (V3) [14].

Results

Search results

The PRISMA flow diagram (Supplement Figure S1) shows the number of studies identified, included and excluded. Overall, fourteen trials (40 treatment groups, 11,457 participants) were included in this review.

Characteristics of included trials

Characteristics of included trials are summarised in Supplement Table S4. All included trials were double-blind, parallel group, and multicenter. The proportion of male participants ranged from 46% to 83%, and mean age ranged from 53 to 63 years. Overall, baseline mean BP was 163/101 mmHg. In all trials BP was measured in-clinic in seated position; at trough in ten trials, and four trials did not report the measurement time. All included trials assessed triple vs. dual therapy of ACEI/ARB, CCB and TDs. In all but one trial, the dual therapy included component drugs of the triple therapy: in one trial [15] the ARB used in triple was valsartan, whereas the dual therapy group used losartan. Treatment duration averaged 8 weeks (range 4 to 10 weeks).

Five trials [15–19] with a total of 8150 participants had a variable 1 to 4 weeks pre-randomisation washout of previous BP lowering drugs, and then randomisation to triple or dual therapy. Those randomised to triple therapy initially received sub-maximal dose dual therapy, in all but one trial [17], before forced-up-titration to triple therapy.

The other nine trials [20–28] including a total of 3307 participants, had a variable 4 to 8 weeks pre-randomisation run-in on sub-maximal dual therapy, in all but one trial [20], before randomisation to either triple therapy (with the addition of an extra drug) or continued dual therapy.

Goal BP levels to define BP control were similar across trials: <140 & <90 in seven trials [16–18, 21–24], <140 & <90 or (<130 & <80 in those with diabetes and/or kidney disease) in five trials [15, 19, 20, 27, 28], DBP <90 or ≥10 mmHg reduction in DBP from baseline in two trials [25, 26].

Risk of bias in included studies

Overall, none of the 14 studies had high risk of bias for any of the six domains that were assessed. Most trials inadequately reported random sequence generation and allocation concealment. These were judged as unclear risk of bias but were considered a reporting deficiency given the trial organisation and settings (Supplement Figure S2). The funnel plot based on difference in mean SBP reduction did not show asymmetry in dispersion of studies (Supplement Figure S3).

Efficacy

Figure 1 shows change in SBP from baseline to endpoint by treatment groups across all included trials. Overall, in trials with drug-free baseline (mean BP 169/103 mmHg), BP fell on average by 36/23 mmHg with triple, compared to 32/19 mmHg with dual combination. In trials with active run-in on dual therapy at baseline (mean BP 150/95 mmHg), BP fell on average by 14/9 mmHg with triple compared to 9/6 mmHg with continued dual combination. Mean BP at endpoint for triple vs. dual therapy was lower for trials with drug free baseline

(132/81 vs. 138/85 mmHg), compared to trials with dual therapy run-in (137/86 vs. 141/89 mmHg).

Overall, triple compared to dual therapy reduced SBP by 5.4 mmHg (95% CI 4.6 to 6.3; I^2=60%) and DBP by 3.2 mmHg (95% CI 2.6 to 3.8; I^2=69%), with similar effects seen in trials with drug-free baseline compared to those with dual therapy run in (5.2/3.0 vs. 6.0/3.7 mmHg). In sensitivity analysis, overall results were similar if each trial provided only one estimate of triple vs. dual combination, by pooling all the triple and/or dual groups in the 4 trials [15–17, 20] with more than two treatment groups: a reduction in SBP by 6.2 mmHg (95% CI 4.9-7.5, I^2=80%) and DBP by 3.8 mmHg (95% CI 2.9-4.7, I^2=85%). Again, similar effects were seen in trials with a drug-free baseline compared to those with dual therapy run-in (6.0/3.7 mmHg vs. 6.3/3.9 mmHg, respectively). Overall, triple combination achieved goal BP in significantly more participants compared to dual combination (58% vs. 45%, RR 1.33 [95% CI 1.25-1.41]).

For predicting difference in efficacy between triple and dual combination, and hence to explain the heterogeneity in effects observed, the Law et al. method was better than TIS (Figure 2). The TIS method overestimated the efficacy of high dose dual therapies (incorrectly predicting it would be superior to some triple combinations) and also overestimated the efficacy of high dose triple therapies. In contrast the Law et al. prediction method matched reasonably well with the observed efficacy, correctly predicting that all triple therapies would be superior to all dual regimens. However, the observed BP differences tended to be moderately smaller than the Law et al.'s predicted BP differences, as seen in Figure 2 and 3.

The type of drug added to dual combinations did not make a substantial difference to the amount of SBP reduction, with the exception that somewhat lower reductions were seen with adding hydrochlorothiazide (HCTZ), compared to adding chlorthalidone or amlodipine at

equivalent standard dose (Supplement Figure S4). One comparison indicated that sub-maximal dose triple (olmesartan 20 + amlodipine 5 + hydrochlorothiazide 12.5 mg) was non-significantly superior to maximum dose dual therapy (olmesartan 40 + amlodipine 10) (0.4/0.4 mmHg lower BP in triple therapy group). Two comparisons assessed the efficacy of double the dose of one component drug within dual combination vs. dual combination (i.e. 2*A+B vs. A+B), and additional BP reduction was 1.5/0.8 mmHg (p>0.5). Twenty-three comparisons assessed adding a third drug to dual combinations (i.e. A+B+C vs. A+B, with A and B at same doses) and the additional BP reduction was 6.0/3.8 mmHg (p=0.0001). Thus on average adding a third drug to dual combination is about four times more efficacious than doubling the dose of one of the components of dual combinations. One comparison assessed the efficacy of double the dose of both components of dual combination (2*A+2*B vs. A+B) and found an additional BP reduction of 2.9/1.6 mmHg (p<0.02) i.e. about half as efficacious as adding a third drug.

Safety

Overall, from 13 trials (33 comparisons), for triple vs dual therapy, there was no significant difference in incidence of WDAEs (3.3% vs. 3.4%, RR 1.24 [95% CI 1.00-1.54], p=0.05, I^2=0%), and AAEs (33.5% vs. 40%, RR 1.02 [95% CI 0.96-1.07], p=0.55, I^2=0%).

In the meta-analyses by subgroups defined by difference of third drug between triple and vs therapy, HCTZ 25 mg had higher incidence of WDAEs (3.4% vs. 2.6%, RR 1.68 [1.08-2.60]), and HCTZ 12.5 mg had higher incidence of AAEs (29.6% vs. 26.0%, RR 1.20 [1.03-1.41]) (Supplement Figure S5 and S6). Finally, there was no significant difference for WDAEs (3.5% vs. 4.5%, RR 0.79 [0.18-3.43]) and AAEs (27.3% vs. 29.2%, RR 0.93 [0.57-1.52]) for sub-maximal dose triple compared to maximal dose dual therapy.

Discussion

This review demonstrated that triple combination achieves greater BP reduction and control compared to dual combination. The absolute benefits were large in terms of improved hypertension control. For patients not controlled on sub-maximal dose dual combination, adding an extra drug to dual combination could be approximately four times more efficacious than doubling the dose of one of the component drugs of dual combination. Efficacy of triple combination was similar in patients with drug free baseline and those who were on dual therapy. Overall, there was no significant difference in safety outcomes of WDAEs and AAEs, however, in subgroup analyses, excess of WDAEs or AAEs seen with triple therapy were potentially related to HCTZ when it was one of the component drug along with an ARB and a CCB.

All included trials in this systematic review were double-blind RCTs, and included data from more than 11,000 participants. We searched extensively to identify relevant studies, data for unpublished studies were sought from the study sponsors, and the review was conducted as per the Cochrane Handbook for Systematic Reviews of Interventions [12]. The review also was the first to demonstrate that the difference in efficacy of triple and dual combination was well predicted by Law et al. [9] but not well predicted by the Therapeutic Intensity Score [11]. There are some limitations to consider however. The lack of individual patient data prevented more detailed exploration of heterogeneity, and the study of association between predicted and observed BP reduction was limited due to small number of available studies. Although steps were taken to deal with the issue of double counting when multiple comparisons from some trials were included in the meta-analysis, it will not fully account for correlation between comparisons. Also, by including multiple comparisons from trials, a random-effects

model will inflate the heterogeneity between comparisons as it considers these comparisons as separate studies. Finally, while heterogeneity in treatment effects was mostly explained by regimen potency as explained by Law et al method, further refinements are required.

A systematic review of 11 studies, including 7563 participants, of triple vs. dual combinations was previously published [29]. However, it only assessed efficacy of triple combination of ARBs, CCBs and diuretics, and some of the included studies were uncontrolled. This review reported 5.8/3.5mmHg reduction in BP with triple combination which is consistent with the finding in our study. The results of our review are also consistent with the predicted effects of triple vs. dual combinations from the analysis of Law et al. [9].

Two other trials compared triple combination to placebo or no treatment, but were not included in this analysis because not all included patients had hypertension and there was no dual combination group included. Wald et al. [30] conducted a crossover trial of a polypill (amlodipine 2.5 mg, losartan 25 mg, HCTZ 12.5 mg and simvastatin 40 mg), essentially a triple combination of BP lowering drugs each at half standard dose, and reported placebo subtracted BP reduction of 17.9/9.8 mmHg, which was closely consistent with the predictions from Law et al's previous review [9]. The TIPS trial [31] tested Polycap (HCTZ 12·5 mg+ atenolol 50 mg + ramipril 5 + simvastatin 20 + aspirin 100) versus regimens with no BP lowering (simvastatin and/or aspirin) and reported less than expected BP reduction (6.3/4.5 mmHg). The reasons remain unclear, although the low starting baseline BP of 134/85 mmHg and non-adherence to treatment are possible reasons [32]. Finally, a recent trial [33] compared low-dose triple therapy with usual care among 700 patients with hypertension, either untreated or on monotherapy. This trial demonstrated a large improvement in

hypertension control rates, with no increase in adverse effects, among those receiving low-dose triple therapy [34].

Currently, there is discrepancy between clinical guidelines on the use of triple combination therapy, with some recommending use only in patients not controlled on maximal dose dual therapy, others recommending earlier use of triple therapy, and others recommending clinicians can choose between the options. This review suggests that guidelines should recommend early use of triple therapy, i.e. before using maximal dose dual therapy. However, it is important to note that although triple therapy was more efficacious than dual therapy, it achieved BP under 140/90 mmHg in only about 60% of the participants, and most patients failed to achieve SBP<130 mmHg as recommended for several patient groups in recent hypertension guidelines [1, 2]. These data therefore suggest that achieving lower BP goals in the range 120-130 mmHg will require early use of three drugs in most patients with hypertension.

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References

[1] Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36(10): 1953–2041.

[2] Whelton PK, Carey RM, Aronow WS*, et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017: 24430.

[3] Chow CK, Teo KK, Rangarajan S*, et al.* Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013; 310(9): 959–68.

[4] Ettehad D, Emdin CA, Kiran A*, et al.* Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387(10022): 957–67

[5] A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015; 373(22): 2103–16.

[6] Gabb GM, Mangoni AA, Anderson CS, Cowley D, Dowden JS, Golledge J, Hankey GJ, Howes FS, Leckie L, Perkovic V, Schlaich M. Guideline for the diagnosis and management of hypertension in adults—2016. *Med J Aust* 2016;205(2):85-9.

[7] Seedat YK, Rayner BL, Veriava Y. South African hypertension practice guideline 2014. *Cardiovasc J Afr* 2014; 25(6): 288–94.

[8] Leung AA, Nerenberg K, Daskalopoulou SS*, et al.* Hypertension Canada's 2016 Canadian hypertension education program guidelines for blood pressure measurement, diagnosis,

assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2016; 32(5): 569–88.

[9] Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; 326(7404): 1427

[10] Higgins JPT, Altman DG, Gotzsche PC*, et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343(oct18 2): d5928-d5928.

[11] Levy P, Willock RJ, Burla M*, et al.* Total Antihypertensive Therapeutic intensity score and its relationship to Blood Pressure Reduction. *J Am Soc Hypertens* 2016;10(12):906-16.

[12] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. *John Wiley & Sons* 2011.

[13] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315(7109): 629–34.

[14] Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. Comprehensive meta-analysis version 3. Biostat, Englewood, NJ 2013; 2016.

[15] Volpe M, Christian Rump L, Ammentorp B, Laeis P. Efficacy and safety of triple antihypertensive therapy with the olmesartan/amlodipine/hydrochlorothiazide combination. *Clin Drug Investig* 2012; 32(10): 649–64.

[16] Calhoun DA, Lacourciere Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension* 2009; 54(1): 32–9.

[17] Oparil S, Melino M, Lee J, Fernandez V, Heyrman R. Triple therapy with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide in adult patients with hypertension: The TRINITY multicenter, randomized, double-blind, 12-week, parallel-group study. *Clin Ther* 2010; 32(7): 1252–69.

[18] Rakugi H, Shimizu K, Sano Y, Nishiyama Y, Kinugawa Y, Terashio S. Effects of triple combination therapy with azilsartan/amlodipine/hydrochlorothiazide on office/home blood pressure: A

randomized-controlled trial in Japanese essential hypertensive patients. *Blood Press Monit* 2018; 23(2): 91–102.

[19] Wright RF, Duprez D, Purkayastha D, Samuel R, Ferdinand KC. Combination angiotensin-receptor blocker (ARB)/calcium channel blocker with HCTZ vs the maximal recommended dose of an ARB with HCTZ in patients with stage 2 hypertension: the exforge as compared to losartan treatment in stage 2 systolic hypertension (EXALT) study. *J Clin Hypertens* 2011; 13(8): 588–97.

[20] Merck Sharp & Dohme Australia. Extract from the Clinical Evaluation Report for Olmesartan medoxomil, Amlodipine (as besilate) and Hydrochlorothiazide. CS8635-A-E303. Australia: *Therapeutic Goods Administration*, Australia; 2013.

[21] Higaki J, Komuro I, Shiki K*, et al.* Effect of hydrochlorothiazide in addition to telmisartan/amlodipine combination for treating hypertensive patients uncontrolled with telmisartan/amlodipine: a randomized, double-blind study. *Hypertens Res* 2017; 40(3):251.

[22] Higaki J, Komuro I, Shiki K*, et al.* The efficacy and long-term safety of a triple combination of 80 mg telmisartan, 5 mg amlodipine and 12.5 mg hydrochlorothiazide in Japanese patients with essential hypertension: a randomized, double-blind study with open-label extension. *Hypertens Res* 2017; 40(1): 51–60.

[23] Hong SJ, Jeong HS, Han SH*, et al.* Comparison of Fixed-dose Combinations of Amlodipine/Losartan Potassium/Chlorthalidone and Amlodipine/Losartan Potassium in Patients With Stage 2 Hypertension Inadequately Controlled With Amlodipine/Losartan Potassium: A Randomized, Double-blind, Multicenter, Phase III Study. *Clin Ther* 2017; 39(10): 2049–60.

[24] Mourad J-J, Amodeo C, Champvallins M de, Brzozowska-Villatte R, Asmar R. Blood pressure-lowering efficacy and safety of perindopril/indapamide/amlodipine single-pill combination in patients with uncontrolled essential hypertension: A multicenter, randomized, double-blind, controlled trial. *J Hypertens* 2017; 35(7):1481-95.

[25] Rakugi H, Tsuchihashi T, Shimada K*, et al.* Efficacy and safety of fixed-dose losartan/hydrochlorothiazide/amlodipine combination versus losartan/hydrochlorothiazide

combination in Japanese patients with essential hypertension. *Clin Exp Hypertens* 2015; 37(3): 260–6.

[26] Rakugi H, Tsuchihashi T, Shimada K*, et al.* Add-on effect of hydrochlorothiazide 12.5 mg in Japanese subjects with essential hypertension uncontrolled with losartan 50 mg and amlodipine 5 mg. *Hypertens Res* 2015; 38(5): 329–35.

[27] Sohn IS, Kim C-J, Oh B-H*, et al.* Efficacy and Safety Study of Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide Combination Therapy in Patients with Hypertension Not Controlled with Olmesartan Medoxomil and Hydrochlorothiazide Combination Therapy: Results of a Randomized, Double-Blind, Multicenter Trial. *Am J Cardiovasc Drugs* 2016; 16(2): 129–38.

[28] Sung K-C, Oh Y-S, Cha D-H*, et al.* Efficacy and Tolerability of Telmisartan/Amlodipine+ Hydrochlorothiazide Versus Telmisartan/Amlodipine Combination Therapy for Essential Hypertension Uncontrolled With Telmisartan/Amlodipine: The Phase III, Multicenter, Randomized, Double-Blind TAHYTI Study. *Clin Ther* 2018; 40(1): 50-63. e3.

[29] Kizilirmak P, Uresin Y, Yildiz OB. The Efficacy and Safety of Triple vs Dual Combination of Angiotensin II Receptor Blocker and Calcium Channel Blocker and Diuretic: A Systematic Review and Meta-Analysis. *J Clin Hypertension* 2013; 15(3): 193–200.

[30] Wald DS, Morris JK, Wald NJ. Randomized Polypill crossover trial in people aged 50 and over. *PLoS One* 2012; 7(7): e41297.

[31] Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. The Lancet 2009; 373(9672): 1341–51.

[32] Wald N, Law M. The Indian Polycap Study (TIPS). *Lancet* 2009; 374(9692): 781.

[33] Salam A, Webster R, Singh K*, et al.* TRIple pill vs Usual care Management for Patients with mild-to-moderate Hypertension (TRIUMPH): Study protocol. *Am Heart J* 2014; 167(2): 127–32.

[34] Webster R, Salam A, Silva HA de*, et al.* Fixed Low-Dose Triple Combination Antihypertensive Medication vs Usual Care for Blood Pressure Control in Patients With Mild to Moderate Hypertension in Sri Lanka: A Randomized Clinical Trial. *JAMA* 2018; 320(6): 566–79.