Fixed-combination, low-dose, triple-pill antihypertensive medication versus usual care in patients with mild-to-moderate hypertension in Sri Lanka: a within-trial and modelled economic evaluation of the TRIUMPH trial

Thomas Lung, Stephen Jan, H Asita de Silva, Rama Guggilla, Pallab K Maulik, Nitish Naik, Anushka Patel, Arjuna P de Silva, Senaka Rajapakse, Gotabhaya Ranasinghe, Dorairaj Prabhakaran, Anthony Rodgers, Abdul Salam, Vanessa Selak, Sandrine Stepien, Simon Thom, Ruth Webster, Tracey Lea-Laba, on behalf of the TRIUMPH Study Group

Summary

Background Elevated blood pressure incurs a major health and economic burden, particularly in low-income and middle-income countries. The Triple Pill versus Usual Care Management for Patients with Mild-to-Moderate Hypertension (TRIUMPH) trial showed a greater reduction in blood pressure in patients using fixed-combination, low-dose, triple-pill antihypertensive therapy (consisting of amlodipine, telmisartan, and chlorthalidone) than in those receiving usual care in Sri Lanka. We aimed to assess the cost-effectiveness of the triple-pill strategy.

Methods We did a within-trial (6-month) and modelled (10-year) economic evaluation of the TRIUMPH trial, using the health system perspective. Health-care costs, reported in 2017 US dollars, were determined from trial records and published literature. A discrete-time simulation model was developed, extrapolating trial findings of reduced systolic blood pressure to 10-year health-care costs, cardiovascular disease events, and mortality. The primary outcomes were the proportion of people reaching blood pressure targets (at 6 months from baseline) and disability-adjusted life-years (DALYs) averted (at 10 years from baseline). Incremental cost-effectiveness ratios were calculated to estimate the cost per additional participant achieving target blood pressure at 6 months and cost per DALY averted over 10 years.

Findings The triple-pill strategy, compared with usual care, cost an additional US$9·63 (95% CI 5·29 to 13·97) per person in the within-trial analysis and $347·75 (285·55 to 412·54) per person in the modelled analysis. Incremental cost-effectiveness ratios were estimated at $7·93 (95% CI 6·59 to 11·84) per participant reaching blood pressure targets at 6 months and $2842·79 (–28·67 to 5714·24) per DALY averted over a 10-year period.

Interpretation Compared with usual care, the triple-pill strategy is cost-effective for patients with mild-to-moderate hypertension. Scaled up investment in the triple pill for hypertension management in Sri Lanka should be supported to address the high population burden of cardiovascular disease.

Funding Australian National Health and Medical Research Council.

Lancet Glob Health 2019; 7: e1359–66

Published Online August 30, 2019 http://dx.doi.org/10.1016/S2214-109X(19)30343-2

See Comment page e1290

The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia (T Lung PhD, Prof S Jan PhD, Prof A Patel PhD, Prof A Rodgers PhD, S Stepien MSc, R Webster PhD, T Lea-Laba PhD); **Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia** (T Lung, Prof S Jan); **Clinical Trials Unit, Department of Pharmacology** (Prof H A de Silva PhD) **and Department of Medicines** (Prof A P de Silva MD), **Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka; Department of Population Medicine and Civilization Diseases Prevention, Faculty of Medicine with the Division of Dentistry and Division of Medical Education in English, Medical University of Bialystok, Bialystok, Poland** (R Guggilla MMeD); **The George Institute for Global Health, University of New South Wales, New Delhi, India** (P K Maulik PhD); **The George Institute for Global Health, University of Oxford, Oxford, UK** (P K Maulik); **All India Institute of Medical Sciences, New Delhi, India** (N Naik MD); **Department of Medicines, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka** (Prof S Rajapakse PhD); **Institute of Cardiology, National Hospital of Sri Lanka, Colombo, Sri Lanka** (G Ranasinghe MD); **Centre for Chronic Disease Control, New Delhi, India** (D Prabhakaran MD); **The George**

Introduction

Elevated blood pressure is the leading risk factor for cardiovascular disease and is a major contributor to mortality worldwide,[1] with the majority of the burden faced by low-income and middle-income countries.[2] Achieving appropriate blood pressure control is challenging for people in low-income and middle-income countries because of therapeutic inertia, which might arise because the treating physician has assumed that the patient's blood pressure has decreased sufficiently or guessed that existing treatment has yet to reach its full effect.[3] Treatment gaps in such settings have contributed to the consequent high costs of hypertension-related hospital care.[4]

Initial or early use of fixed, low-dose, combination therapy for blood pressure reduction is seen as a promising strategy for reducing the burden of cardiovascular disease because of its proven efficacy[5–7] and safety,[8] as well as its potential ability to reduce therapeutic inertia[9] and improve adherence to medication.[10] Several clinical guidelines currently recommend use of dual combination therapy for initiation of treatment; however, currently, triple therapy is only recommended for individuals with severe hypertension not controlled by dual therapy.[11]

Insufficient health economic evidence exists on whether a triple-pill therapy strategy is cost-effective compared with current incremental approaches to blood pressure lowering. A modelling study done in Greece[12] found standard-dose, fixed-combination, triple-pill therapy to be cost-effective compared with its paired components

Institute for Global Health, University of New South Wales, Hyderabad, India (A Salam PhD)**; Department of Epidemiology and Biostatistics, University of Auckland, Auckland, New Zealand** (V Selak PhD)**; and International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, UK** (Prof S Thom MD)

Correspondence to: Dr Thomas Lung, The George Institute for Global Health, University of New South Wales, Sydney, NSW 2042, Australia **tlung@georgeinstitute.org.au**

Research in context

Evidence before this study

We searched PubMed and Embase for economic evaluations of fixed, low-dose, triple-combination antihypertensive therapy published between database inception and Feb 20, 2019, using the search terms ("economic evaluation" OR "cost-effectiveness") AND ("antihypertensive therapy" OR "triple pill" OR "triple combination") AND "hypertension". Only one study was identified in which a standard strength, fixed-combination, triple-pill antihypertensive therapy was cost-effective for the treatment of patients with moderate-to-severe hypertension, compared with its paired components in a high-income country. Currently, no evidence exists on the cost-effectiveness of a fixed, low-dose, triple-pill combination antihypertensive therapy for patients with mild-to-moderate hypertension.

Added value of this study

We did a within-trial and modelled economic evaluation of a fixed-combination, low-dose, triple-pill strategy compared with usual care for individuals with mild-to-moderate hypertension in Sri Lanka, based on findings from the Triple Pill versus Usual Care Management for Patients with Mild-To-Moderate Hypertension (TRIUMPH) trial. Our modelled economic evaluation results suggest that this triple-pill strategy is cost-effective as a first-line treatment option for individuals with mild-to-moderate hypertension, especially older individuals and those with higher blood pressure, through reductions in morbidity and mortality resulting from cardiovascular disease. The modelled results are highly sensitive to variations in the price of the triple pill.

Implications of all the available evidence

Our findings suggest that the use of low-dose, fixed-combination, triple-pill antihypertensive therapy in individuals with mild-to-moderate hypertension is cost-effective in a middle-income country setting. Compared with monotherapy, triple-pill therapy has the potential to lower blood pressure and reduce cardiovascular disease burden in Sri Lanka. This evidence should be used alongside considerations around implementation, feasibility, and budget impact for policy makers when making decisions around health-care resource allocation.

among people with moderate-to-severe hypertension. No evidence currently exists comparing a low-dose, fixed-combination triple pill with usual care as a first-line agent for patients with mild-to-moderate hypertension.

The Triple Pill versus Usual Care Management for Patients with Mild-To-Moderate Hypertension (TRIUMPH) trial[9] found that more patients achieved their blood pressure target (relative risk 1·23 [95% CI 1·09 to 1·39]) and that blood pressure reduction was greater (mean difference in systolic blood pressure [SBP] –9·8 mm Hg [95% CI –7·9 to –11·6]) with initial or early use of a low-dose, fixed-combination, triple-pill antihypertensive therapy than with usual care in Sri Lanka over a 6-month period. We aimed to provide an economic evaluation of the TRIUMPH trial.

Methods

Study design and input population

We did a within-trial (6-month) and modelled (10-year) economic evaluation of the TRIUMPH trial from the health system perspective, comparing the use of a triple-pill strategy with usual care in the treatment of people with mild-to-moderate hypertension. The TRIUMPH trial has been described in detail previously.[9,13,14] In brief, TRIUMPH was a prospective, open-label, randomised controlled trial done in 11 urban hospital outpatient departments in Sri Lanka from Feb 15, 2016, to May 3, 2017. Patients were recruited to the trial if they were aged 18 years and older, had persistent mild-to-moderate hypertension (SBP >140 mm Hg or diastolic blood pressure (DBP) >90 mm Hg; or SBP >130 mm Hg or DBP >80 mm Hg in patients with diabetes or chronic kidney disease), and were currently on no therapy or monotherapy only. Patients were randomly assigned to receive either the triple-pill therapy or usual care, stratified by study centre and use of blood pressure lowering therapy at baseline.

At baseline, the intervention group received the triple pill (with discontinuation of current monotherapy, if applicable) as part of their usual hypertension clinic visits. There were scheduled clinic visits at 6, 12, and 24 weeks (end of study), which included blood pressure measurement, potential changes in medications in line with local guidelines at the discretion of the treating physician, and assessment of adverse events. The triple pill consisted of two versions: lower dose (amlodipine 2·5 mg, telmisartan 20 mg, and chlorthalidone 12·5 mg) and higher dose (amlodipine 5 mg, telmisartan 40 mg, and chlorthalidone 25 mg). The lower-dose version was administered to all participants initially, without any washout period for patients previously taking monotherapy. The higher-dose version and any other blood pressure lowering therapy could be used during follow-up, at the discretion of the treating physician. Further details about the manufacturing, capsulation, and quality of the triple pills used in the study have been described previously.[9]

The control group received usual care. At baseline, participants were administered blood pressure lowering medications as deemed appropriate by the treating physician and had scheduled follow-up clinic visits as per the intervention group. Ethics approval was provided by the Ethics Review Committee, Faculty of Medicine, University of Kelaniya (Kelaniya, Sri Lanka), and Royal Prince Alfred Hospital Ethics Review Committee (Sydney, NSW, Australia). The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612001120864).

Costs

During the trial, health system costs associated with clinic visits, medications, and inpatient hospital admissions were included in the analysis. Prescribed medications were recorded at each clinic visit. Follow-up clinic visits were costed using WHO's Sri Lankan health-centre cost estimates.[15] At each follow-up period, participants from both groups completed questionnaires regarding outpatient clinic visits and inpatient hospital admission costs.

Pharmaceutical prices were obtained from the drug formulary of public hospitals in Sri Lanka, representing the amount paid by the government for each medicine.[16] All drugs were supplied and dispensed through the public health system in this study and thus the cost to the government represents the full cost. For the triple pill, we applied a cost of US$0·16 per day (irrespective of dose version), based on the price of a similar triple pill for hypertension in India. Further details on individual drug and triple-pill pricing are provided in the appendix (p 1).

The modelled economic evaluation focused on health system costs associated with clinic visits, cardiovascular disease-related hospital admissions, and antihypertensive medications. Prescribed antihypertensive medication costs were adopted from trial records (see appendix p 1 for further details), and costs associated with outpatient clinic visits, cardiovascular disease-related hospital admissions, and chronic cardiovascular disease were taken from the literature.[15,17] All costs (when relevant) were inflated and presented in 2017 US dollars.

Cardiovascular disease model

A health economic model was developed to extrapolate trial-based findings of reduced blood pressure to long-term health-care costs and cardiovascular disease-related events and mortality. Similar to previous modelling methodology, we assumed that the medication recommendations at baseline were held constant over a 10-year period.[12]

The aim of this discrete-time simulation model (figure 1) was to predict the occurrence of a first cardiovascular disease event or death. A cardiovascular disease event is defined as either myocardial infarction or stroke, with the model only potentially capturing one cardiovascular disease event per individual over a 10-year period. In the model, all individuals started with no cardiovascular disease and at each annual cycle could experience a cardiovascular disease event and die, experience a cardiovascular event and survive, or die from cardiovascular disease-related or non-cardiovascular disease-related causes.

Fatal and non-fatal cardiovascular disease risk prediction

Data required to inform the model structure and parameters were based on a combination of trial-based data and findings from published academic literature (appendix pp 2–3, 7). 10-year fatal and non-fatal cardiovascular disease risks for the trial population were modelled using cardiovascular disease risk prediction equations known as Globorisk.[18,19] In brief, the Cox proportional hazards regressions developed were based on more than 50 000 individuals in eight large prospective cohort studies, using age as the timescale. Globorisk was recalibrated using Sri Lankan population-specific mean risk factors (age, sex, smoking status, diabetes, total cholesterol, and SBP); however, the recalibrated model is limited to prediction for individuals aged 40–84 years at baseline because of questionable reliability of data in those aged 85 years and older.

Annual fatal and non-fatal cardiovascular disease risks were estimated using the recalibrated Sri Lankan Globorisk equations for each individual trial participant (see appendix pp 3–4 for further details). Baseline values for all individual risk factors were used except for age and SBP. Age was updated at each annual cycle and the end of study SBP measurement was used. Non-cardiovascular disease-specific mortality was calculated using 5-year age-specific and sex-specific Sri Lankan life tables[20] to account for competing risk of mortality. Cardiovascular disease (fatal and non-fatal) risk, cardiovascular disease-specific mortality, and non-cardiovascular disease-specific mortality were converted into annual probabilities and applied to each individual.

See Online for appendix

We assumed a relative risk reduction in cardiovascular disease events (0·80 [95% CI 0·77–0·83]) and all-cause mortality (0·87 [0·84–0·91]) for every 10 mm Hg reduction in SBP, on the basis of a recent systematic review and meta-analysis of randomised controlled trials.[21] We assumed no changes to adherence or non-adherence of antihypertensive medication from the end of study measurements in TRIUMPH in our model. Given the lack of long-term evidence on whether changes in SBP are sustained by the triple pill, we assumed reductions in SBP achieved in the trial to diminish by 30% in the second year for both groups, with no further change in SBP in the following years.

Outcomes

For the within-trial economic evaluation, the primary outcome was the proportion of participants achieving target blood pressure (SBP <130 mm Hg and DBP

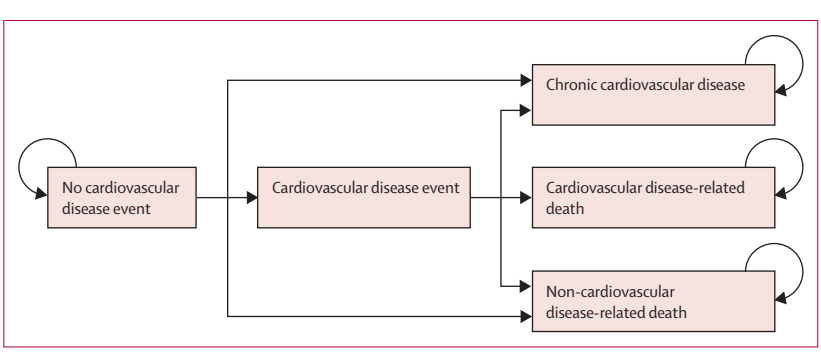

Figure 1: **Structure of the discrete-time simulation model, depicting different health states that individuals could be in at each annual cycle**

	Within-trial analysis		Modelled analysis	
	Triple-pill group (n=318)	Usual care group (n=329)	Triple-pill group (n=261)	Usual care group (n=277)
Age, years	56·2 (11·2)	56·0 (10·7)	57·0 (8·8)	57·2 (9·2)
Sex				
Male	129 (41%)	143 (43%)	96 (37%)	120 (43%)
Female	189 (59%)	186 (57%)	165 (63%)	157 (57%)
Current cigarette or pipe smoker, or tobacco chewer	34 (11%)	32 (10%)	28 (11%)	25 (9%)
Body-mass index, kg/m²	26·0 (4·5)	26·3 (4·4)	25·9 (4·5)	26·2 (4·3)
Systolic blood pressure, mm Hg	154·1 (11·1)	154·2 (11·6)	154·6 (11·5)	154·9 (11·7)
Systolic blood pressure categories				
<130 mm Hg	4 (1%)	2 (1%)	4 (2%)	2 (1%)
130–139 mm Hg	26 (8%)	31 (9%)	19 (7%)	24 (9%)
140–149 mm Hg	94 (30%)	99 (30%)	76 (29%)	81 (29%)
150–159 mm Hg	95 (30%)	89 (27%)	74 (28%)	74 (27%)
≥160 mm Hg	99 (31%)	108 (33%)	88 (34%)	96 (35%)
Total cholesterol, mg/dL	5·2 (1·2)	5·3 (1·2)	5·3 (1·3)	5·3 (1·2)
Using blood pressure lowering medications	126 (40%)	139 (42%)	102 (39%)	114 (41%)
Diabetes	96 (30%)	102 (31%)	75 (29%)	83 (30%)
Coronary artery disease	28 (9%)	21 (6%)	..	..
Cerebrovascular disease	12 (4%)	7 (2%)	..	..

Data are mean (SD) or n (%). Percentages might not sum to 100% as a result of rounding.

Table 1: **Baseline characteristics**

<80 mm Hg for patients with diabetes or chronic kidney disease or SBP <140 mm Hg and DBP <90 mm Hg otherwise) from baseline to 6 months.

In the modelled economic evaluation, the primary outcome was disability-adjusted life-years (DALYs) averted over a 10-year period. DALYs were quantified using WHO and Global Burden of Disease Study methodology.[22] Disability weights for cardiovascular disease were adopted from the literature,[23] using a mean weight attributed to myocardial infarction and moderate-to-severe stroke, resulting in a DALY weight of 0·39 for the year of, and each year subsequent to, the onset of cardiovascular disease (see appendix p 2 for more detail). Following death, a disability weight of 1 was used to value each year of life lost up to 10 years from baseline.

Statistical analysis

Participants from the main trial were excluded from the within-trial analysis if health-care costs were missing or they withdrew consent from the study. Costs and effects were derived from patient-level data in the within-trial analysis; we estimated a log binomial model for participants achieving target blood pressure at 6 months and a longitudinal model for costs, using hospital clinic as a random effect and the stratification factor (whether patients were on monotherapy or naive at baseline) as a fixed effect. Incremental cost-effectiveness ratios (ICERs) were calculated to estimate the cost per additional participant achieving target blood pressure.

Participants were excluded from the modelled economic evaluation if they were not aged between 40 and 84 years at baseline, had a history of cardiovascular disease, did not have their SBP measured at a clinic, or died during the study. The model estimated ICERs per DALY averted over a 10-year period. A discount rate of 3% was used.[24]

To account for uncertainty around the price estimates of the triple pill, we did one-way sensitivity analyses for both within-trial and modelled economic evaluations on two scenarios: triple-pill price of US$0·05 per day and $0·50 per day.

For the modelled economic evaluation, several other scenarios were considered to investigate uncertainty around model inputs and its impact on the ICER. We did separate sensitivity analyses with changes in specific parameters: cardiovascular disease-related hospital admission and clinic visit costs; relative risk estimates associated with SBP reduction and cardiovascular disease incidence and mortality; reductions in SBP achieved in the trial to drop by 60% in the following year; cardiovascular disease-specific DALY weights; and the discount rate. In addition, we did subgroup analyses: younger (40–59 years) and older (60 years and older) age groups, and lower (<155 mm Hg) and higher (≥155 mm Hg) SBP groups. Finally, we included a scenario that incorporated an age-related annual increase in SBP in both triple-pill and usual care groups.[25]

In addition to one-way sensitivity analyses, we did probabilistic sensitivity analyses using 1000 bootstrap replications with replacement for both within-trial and modelled analyses. For the modelled analyses, the bootstrapped cost and DALY pairs were plotted on an incremental cost-effectiveness plane. Using the bootstrapped estimates, a cost-effectiveness acceptability curve was derived to determine the probability that the intervention is below a range of willingness to pay thresholds.[26] We used SAS Enterprise Guide, version 7.15, for the within-trial economic evaluation. We used Stata SE, version 14.2, for the modelled analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

700 participants were enrolled into the trial, with 349 randomly assigned to the triple-pill group and 351 to the usual care group. After application of our exclusion criteria, there were 318 individuals in the triple-pill group and 329 individuals in the usual care group for the within-trial analysis. The modelled economic evaluation consisted of 261 individuals in the triple-pill group and 277 individuals in the usual care

	Mean total costs (95% CI)			Mean outcomes (95% CI)			ICER per outcome (95% CI)
	Triple-pill group	Usual care group	Mean difference	Triple-pill group	Usual care group	Relative risk or mean difference (95% CI)	
Blood pressure target achieved at 6 months (within-trial analysis)	$29·56 (26·31 to 32·81)	$19·93 (16·78 to 23·07)	$9·63 (5·29 to 13·97)	66·04% (60·59 to 71·98)	54·36% (49·16 to 60·11)	1·21 (1·08 to 1·37)	$7·93 (6·59 to 11·84)
DALYs averted over 10 years (modelled analysis)*	$863·90 (821·08 to 905·88)	$516·15 (469·70 to 563·81)	$347·75 (285·55 to 412·54)	0·39 (0·26 to 0·51)	0·51 (0·38 to 0·65)	0·13 (–0·07 to 0·31)	$2842·79 (–28·67 to 5714·24)

DALYs=disability-adjusted life-years. ICER=incremental cost-effectiveness ratio. *Costs were discounted (3%) to 2017 US dollars.

Table 2: **Mean outcomes, mean costs (US$), and difference and incremental cost-effectiveness ratios per person by triple-pill and usual care groups, for 1000 bootstrapped replications**

	Prevalence of cardiovascular disease (95% CI)		Mean total costs (US$)			Mean DALYs			ICER per DALY averted
	Triple-pill group (n=261)	Usual care group (n=277)	Triple-pill group (n=261)	Usual care group (n=277)	Difference	Triple-pill group (n=261)	Usual care group (n=277)	Difference	
Base case	15·15%	19·73%	$864	$516	$348	0·39	0·51	0·13	$2843
Triple-pill cost $0·05 per day	15·15%	19·73%	$539	$516	$23	0·39	0·51	0·13	$172
Triple-pill cost $0·50 per day	15·15%	19·73%	$1869	$516	$1353	0·39	0·51	0·13	$11 098
Hospital admission and clinic visit costs reduced by 25%	15·15%	19·73%	$766	$406	$360	0·39	0·51	0·13	$2741
Hospital admission and clinic visit costs increased by 25%	15·15%	19·73%	$962	$626	$335	0·39	0·51	0·13	$2976
Change in SBP effect on cardiovascular disease-specific and all-cause mortality reduced by 25%	17·01%	21·52%	$80	$536	$344	0·43	0·55	0·12	$3839
0% discount rate	15·15%	19·73%	$982	$588	$394	0·46	0·61	0·15	$3642
5% discount rate	15·15%	19·73%	$798	$476	$322	0·34	0·46	0·11	$2427
DALY weight reduced by 25%	15·15%	19·73%	$864	$516	$348	0·35	0·46	0·11	$2238
DALY weight increased by 25%	15·15%	19·73%	$864	$516	$348	0·42	0·56	0·14	$2705
Age group 40–59 years	10·09%	13·75%	$832	$473	$359	0·24	0·36	0·12	$4081
Age group 60 years and older	23·05%	28·22%	$915	$575	$340	0·61	0·72	0·11	$2691
Baseline SBP <155 mm Hg	16·41%	17·41%	$858	$557	$301	0·40	0·48	0·08	$3858
Baseline SBP ≥155 mm Hg	13·84%	22·17%	$871	$482	$389	0·37	0·54	0·17	$1778
Reductions in SBP achieved within-trial to reduce by 60% after first year	16·90%	21·10%	$881	$532	$349	0·43	0·55	0·12	$5618
0·48 mm Hg increase in SBP per year	15·80%	20·54%	$870	$525	$345	0·40	0·53	0·13	$2649

DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. SBP=systolic blood pressure.

Table 3: **One-way sensitivity analysis of modelled costs, disability-adjusted life-years averted, cardiovascular disease prevalence, and incremental cost-effectiveness ratios over a 10-year period**

group. Table 1 presents the characteristics of the study participants.

The triple-pill strategy, compared with usual care, cost an additional US$9·63 (95% CI 5·29 to 13·97) per person in the within-trial analysis and $347·75 (285·55 to 412·54) per person in the modelled analysis. Over a 6-month period, the bootstrapped analysis indicated an ICER of $7·93 (95% CI 6·59 to 11·84; table 2) per participant reaching blood pressure targets. The modelled economic evaluation showed the triple pill to be cost-effective compared with usual care over a 10-year period. The base case analysis showed that the triple-pill group had a 10-year cardiovascular disease prevalence of 15·15% (95% CI 8·43 to 21·46), compared with 19·73% (12·27 to 27·44) in the usual care group, which translates to 0·13 DALYs averted. The ICER was estimated at $2842·79 (95% CI –28·67 to 5714·24) per DALY averted.

In the sensitivity analysis, ICERs were robust to uncertainties around specific parameters, with some key exceptions (table 3; appendix p 8). Using a triple-pill price of US$0·05 per day and $0·50 per day resulted in the largest changes, with ICERs estimated at $0·82 and $29·90 per individual reaching blood pressure targets for the within-trial economic evaluation (appendix p 8) and $172 and $11 098 per DALY averted for the modelled economic evaluation (table 3), respectively. Changes in cardiovascular disease-related health-care costs and DALY weights, the effect size of SBP reduction on cardiovascular disease and all-cause mortality, increase in SBP in the year following the trial, an annual increase in SBP, and the

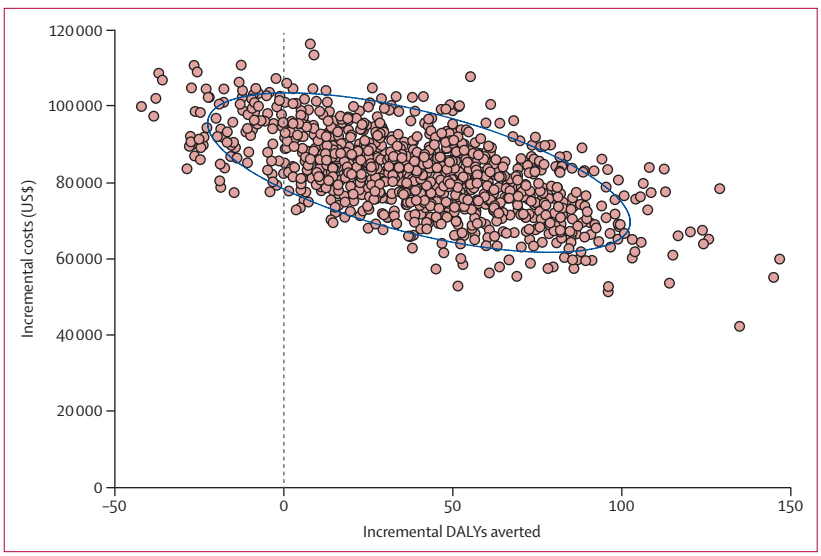

Figure 2: **Incremental cost-effectiveness plane of 1000 bootstrap replications assessing the additional cost per disability-adjusted life-year (DALY) averted, comparing the use of the triple pill versus usual care**

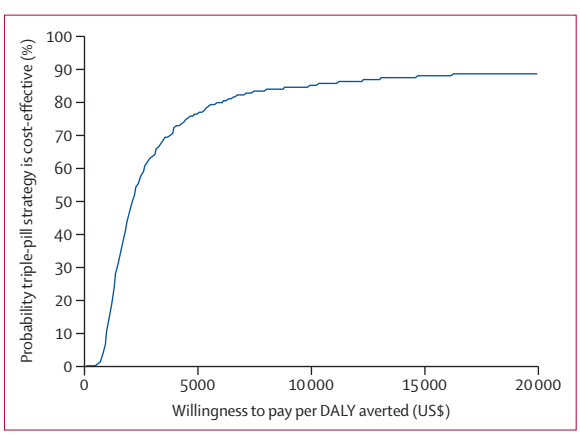

Figure 3: **Cost-effectiveness acceptability curve**
The probability that the triple-pill strategy is cost-effective compared with usual care for individuals with mild-to-moderate hypertension at different willingness to pay thresholds for each disability-adjusted life-year (DALY) averted.

discount rate resulted in small changes to the ICER, ranging from $2238 to $5618 per DALY averted (table 3).

The incremental cost-effectiveness plane (figure 2) and cost-effectiveness acceptability curve (figure 3) of the 1000 bootstrapped estimates of the modelled base case analysis showed that 80% of bootstrapped ICERs were cost-effective at a hypothetical threshold of $6100 per DALY averted.

Discussion

To our knowledge, this is the first economic evaluation of a low-dose, fixed-combination, triple-pill strategy compared with usual care for treatment of people with mild-to-moderate hypertension. Our within-trial analysis showed ICERs of US$7·93 per participant reaching blood pressure targets and $2842·79 per DALY averted. The modelled ICER suggests that the triple-pill strategy is cost-effective, with a high proportion of bootstrapped replications being cost-effective at increasing willingness to pay thresholds.

The deterministic sensitivity analysis indicated that the findings were robust to variations in all key parameters except the price of the triple pill. Sri Lanka does not currently have any triple-pill antihypertensive combinations on the market, and the price used for the base case analysis (US$0·16 per day) was based on an Indian triple pill. At this price, the triple pill is cost-effective. Given that the cost of the individual components of the triple pill are around $0·09 per day, this represents a 75% mark-up in price and is not an unreasonable assumption. The sensitivity analysis indicates that the triple pill remains cost-effective up to a cost of around US$0·50 per day.

The major strength of the study is that data used to inform the economic evaluations were from a randomised controlled trial and supplemented with additional Sri Lankan population-specific information when required. Findings from this study support the results of a study[12] that showed that a standard-dose, fixed-combination, triple pill was cost-effective compared with its paired components, albeit in a high-income country, for individuals with moderate-to-severe hypertension. Our subgroup analyses for individuals with higher SBP (table 3) corroborate these findings, reaffirming that triple-pill therapy is cost-effective for individuals with a high cardiovascular disease risk.

Our findings are important because they demonstrate the cost-effectiveness of an antihypertensive triple-pill strategy relative to usual care for primary prevention in a population with mild-to-moderate hypertension. In limited-resource settings such as Sri Lanka, where there are large and increasing gaps in treatment for cardiovascular disease, the study provides a strong economic case for scaling up this intervention as a means of addressing the population burden of cardiovascular disease. Sri Lankan policy makers can use this evidence alongside context-specific considerations around feasibility, implementation, and budget impact when making funding decisions.

We believe our results are conservative because of several assumptions made in the analyses. A key argument for the triple-pill strategy versus usual care is that one would expect an improvement of adherence and persistence to treatment, which translates to improved SBP control and ultimately reductions in cardiovascular disease. Evidence exists for improved adherence to combination therapy containing multiple different drug classes compared with usual care in patients with cardiovascular disease.[27] Additionally, large-scale administrative databases have shown improvements in adherence as well as clinical events specifically related to initiation of hypertension therapy with dual combinations.[28] However, there is insufficient literature as yet suggesting a similar effect for the triple pill to treat hypertension. Thus,

we have conservatively assumed no changes in long-term medication adherence, based on findings from TRIUMPH's 6-month trial period.[9] The model assumed individuals would incur up to one cardiovascular disease event over a 10-year period, an assumption that is not unreasonable given the relatively low risk in these individuals. Our results showed that the triple pill reduced the occurrence of a primary cardiovascular disease event, which would presumably lower the likelihood of recurrent cardiovascular disease events and subsequently reduce health-care costs. We have assumed costs associated with the triple pill to be substantially more than the sum of the three individual components, reflecting the expensive entry price as a branded formulation. As generic formulations enter the market, the costs of the triple pill will decrease over time[29] and subsequently become increasingly cost-effective, as can be seen in our sensitivity analyses.

There are some potential limitations to our study, which are due mainly to limitations of available data. We assumed the treatment effect of the trial to persist for 10 years, with a 30% reduction in treatment effect after the first year and then no subsequent change in following years. Other medication costs that are associated with cardiovascular disease risk management, such as lipid lowering therapy or escalation of antihypertensive treatment, were not included in the analysis, although one would not expect these costs to differ between treatment groups. We were unable to distinguish between different cardiovascular disease event types because of paucity of Sri Lankan data. The complexities surrounding changes in risk factors associated with cardiovascular disease risk over time meant that we restricted our analysis to a 10-year horizon. Although the main trial found no significant differences in the occurrence of serious adverse events between the triple-pill and usual care groups over a 6-month period, further research is required to observe serious adverse events over a long-term period. Finally, although we cannot rule out a potential Hawthorne effect within the TRIUMPH trial, we believe that it is unlikely to bias the reduction in SBP between groups. However, long-term effectiveness data from longitudinal large-scale administrative databases can be used to inform this future research question.

The TRIUMPH trial showed a strategy of initial or early use of a triple-pill combination to be effective compared with usual care in Sri Lanka and, in the long term, a highly cost-effective first-line strategy to lower cardiovascular disease risk in people with mild-to-moderate hypertension. The solid economic case for scaling up this intervention to a population level can be further strengthened with economies of scale and future reductions in the price of such medicines.

Contributors

TL did the modelled analysis and drafted the manuscript. SS prepared the data and did the within-trial analysis. TL, TL-L, and SJ conceived the study. AP, AR, SJ, RW, and TL-L provided guidance on the analyses. AS and HAdS provided guidance on sources for cost data. All authors critically revised the manuscript for important intellectual content.

Declaration of interests

RG is a minority shareholder in three Indian multinational pharmaceutical companies (Ajanta Pharma, Divis Laboratories, and NATCO Pharma). RW and AP reported receiving a salary from George Health Enterprises, which is the social enterprise arm of the George Institute for Global Health. George Health Enterprises has received investment funds to develop fixed-dose combination products containing aspirin, statin, and blood pressure lowering drugs and has submitted a patent for the treatment of hypertension. AR is listed as an inventor on this patent; however, he does not have a financial interest in it.

Acknowledgments

This study was funded by grants (APP1041052 and APP1052555) from the Australian National Health and Medical Research Council (NHMRC) Global Alliance for Chronic Disease. TL is currently supported by a NHMRC Early Career Fellowship (APP1141392) and National Heart Foundation Postdoctoral Fellowship (award ID 101956). SJ is supported by an NHMRC Principal Research Fellowship (APP1119443). RW is supported by a NHMRC Early Career Fellowship (APP1125044). PKM is a UK Wellcome Trust/DBT India Alliance intermediate career fellow. RG is currently supported by a Marie Sklodowska-Curie Actions Research Fellowship (EU H2020 grant agreement ID 754432). AR is supported by a NHMRC principal research fellowship (APP1066280). AP is supported by a NHMRC Principal Research Fellowship (APP1136898). ST is supported by the UK National Institute for Health Research Biomedical Research Centre at Imperial College Healthcare NHS Trust and Imperial College London (London UK). TL-L is supported by an NHMRC Early Career (Sidney Sax) Fellowship (APP1110230). We thank Peter Ueda for providing the Stata code and data for the Globorisk equations. We acknowledge the TRIUMPH study group members: Keshinie Samarasekara, Chiranthi Kongala Liyanage, Verni Sopan,Wasantha Kumara, Hansika Pathirana, Lumbini Perera, Manisha Somasiri, Aruna Wijesinghe, Jayamini Jayantha, Sonali Liyanagamage, Muditha de Silva, Chandika Jayawardena, Dilini Karunarathna, Mitrakrishnan Rayno Navinan, Zumra Shukri, Charitha Herath, Nadeeja Seneviratne, Amila Isurangana, Zulaiha Liyakath, Thamal Dasitha, Gerald Rajakulenthiran, Aaisha Azam, Chandika Jayawardena, Manori Jayawardena, Vinodhan Sunderalingam, Milinda Withana, Anushiya Annaraja, Keshini Soza, Dulani Dasanayake, Keshini Soza, Dhanushka de Silva, and Shakoor Niyasdeen (National Hospital, Colombo, Sri Lanka); Uthpala Chandradeva, Safiya Fathima, and Aruna Jayawardana (Colombo South Teaching Hospital, Colombo, Sri Lanka); Ranasinghe Chathurika, Manik de Mel, Tharini Mendis, Saumya Withanage, Kandula Pieris, Manik de Mel, Gayathri Fernando, Chamila Mettanda, Saumya Withanage, and Kandula Pieris (Colombo North Teaching Hospital, Colombo, Sri Lanka); Eshani de Silva and Imali Wijerathna (Sri Jayawardenapura General Hospital); Jeevaraj Thanushanthan, Devaki Dharmawardena, Shehan Gnanapragasam, Shalomi Weerawardena, Matheesha Suduwelikandage, Ingrid de Silva, SachiniWathsala, Ruchiranga Ekanayaka, Anuradha Dahanayaka, Vindhya Fernando, Lakmal Jayaweera, and Namal Wijesinghe (RemediumOne, Colombo, Sri Lanka); and Murali Dhakshinamurthy, Ullas Arabhavi, Harish Sankarankutty, Mohammed Muddaseer, Sarath Gudivada, Aditi Moitra, Ayesha Tazeen, Karuna Acharya, Prakash Velappan, Ambika Yoganathan, Vipin Jose, MPharm (George Clinical, Bangalore, India).

References

1 Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365:** 217–23.

2 Sarki AM, Nduka CU, Stranges S, Kandala NB, Uthman OA. Prevalence of hypertension in low- and middle-income countries: a systematic review and meta-analysis. *Medicine* 2015; **94:** e1959.

3 Ferrari P. Reasons for therapeutic inertia when managing hypertension in clinical practice in non-Western countries. *J Hum Hypertens* 2009; **23:** 151–59.

4 Wagner AK, Valera M, Graves AJ, Laviña S, Ross-Degnan D. Costs of hospital care for hypertension in an insured population without an outpatient medicines benefit: an observational study in the Philippines. *BMC Health Serv Res* 2008; **8:** 161.

5 Chow CK, Thakkar J, Bennett A, et al. Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review. *Lancet* 2017; **389:** 1035–42.

6 Wald DS, Morris JK, Wald NJ. Randomized polypill crossover trial in people aged 50 and over. *PLoS One* 2012; **7:** e41297.

7 Mahmud A, Feely J. Low-dose quadruple antihypertensive combination: more efficacious than individual agents—a preliminary report. *Hypertension* 2007; **49:** 272–75.

8 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:** 1427.

9 Webster R, Salam A, de Silva HA, 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:** 566–79.

10 Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010; **55:** 399–407.

11 Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018; **39:** 3021–104.

12 Stafylas P, Kourlaba G, Hatzikou M, Georgiopoulos D, Sarafidis P, Maniadakis N. Economic evaluation of a single-pill triple antihypertensive therapy with valsartan, amlodipine, and hydrochlorothiazide against its dual components. *Cost Eff Resour Alloc* 2015; **13:** 10.

13 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:** 127–32.

14 Webster R. Protocol changes to the TRIUMPH study. *Am Heart J* 2017; **191:** e1.

15 WHO. Choosing interventions that are cost effective (WHO-CHOICE). Sri Lanka: estimates of unit costs for patient services for Sri Lanka. http://www.who.int/choice/country/lka/cost/en/ (accessed June 1, 2018).

16 State Pharmaceuticals Corporation of Sri Lanka. State Pharmaceuticals Corporation price list. http://www.spc.lk/pub/pricelistretail.pdf (accessed Oct 15, 2018).

17 Walker IF, Garbe F, Wright J, et al. The economic costs of cardiovascular disease, diabetes mellitus, and associated complications in South Asia: a systematic review. *Value Health Reg Issues* 2018; **15:** 12–26.

18 Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol* 2015; **3:** 339–55.

19 Ueda P, Woodward M, Lu Y, et al. Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys. *Lancet Diabetes Endocrinol* 2017; **5:** 196–213.

20 WHO. Life tables by country: Sri Lanka. http://apps.who.int/gho/data/view.main.LT62220?lang=en (accessed June 1, 2018).

21 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:** 957–67.

22 WHO. Metrics: disability-adjusted life year (DALY). http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/ (accessed June 7, 2018).

23 Salomon JA, Haagsma JA, Davis A, et al. Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob Health* 2015; **3:** e712–23.

24 WHO. Cost effectiveness and strategic planning (WHO-CHOICE). https://www.who.int/choice/cost-effectiveness/en/ (accessed June 1, 2018).

25 Singh GM, Danaei G, Pelizzari PM, et al. The age associations of blood pressure, cholesterol, and glucose: analysis of health examination surveys from international populations. *Circulation* 2012; **125:** 2204–11.

26 Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001; **10:** 779–87.

27 Webster R, Patel A, Selak V, et al. Effectiveness of fixed dose combination medication ('polypills') compared with usual care in patients with cardiovascular disease or at high risk: a prospective, individual patient data meta-analysis of 3140 patients in six countries. *Int J Cardiol* 2016; **205:** 147–56.

28 Verma AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: a population-based retrospective cohort study. *PLoS Med* 2018; **15:** e1002584.

29 DiPette DJ, Skeete J, Ridley E, et al. Fixed-dose combination pharmacologic therapy to improve hypertension control worldwide: clinical perspective and policy implications. *J Clin Hypertens* 2019; **21:** 4–15.