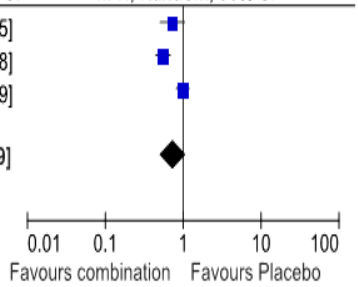
Study or Subgroup	Perindopril & Indapamide Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
HYVET	51	1933	69	1912	29.2%	0.72 [0.50, 1.05]
PROGRESS	150	1770	255	1774	35.0%	0.55 [0.45, 0.68]
ADVANCE	215	5569	218	5571	35.7%	0.99 [0.81, 1.19]
Total (95% CI)		**9272**		**9257**	**100.0%**	**0.73 [0.49, 1.09]**
Total events	416		542			

Heterogeneity: Tau² = 0.11; Chi² = 15.78, df = 2 (P = 0.0004); I² = 87%

Test for overall effect: Z = 1.52 (P = 0.13)



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Meta-analysis

Combination of perindopril/indapamide in secondary prevention of stroke and other vascular events: A combined analysis of ADVANCE, PROGRESS and HYVET trials

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Abstract

Perindopril/indapamide combination has been shown to reduce cardiovascular risk in different groups of patients. A total of 18,529 patients (9,272 receiving perindopril/indapamide and 9,257 receiving placebo) were included in this meta-analysis involving three large randomized clinical trials-ADVANCE, PROGRESS and HYVET. A non-significant reduction in fatal and non-fatal stroke was seen (odds ratio 0.73; 95% confidence interval 0.5 to 1.1; z=1.5 and p=0.13). The fixed combination perindopril and indapamide was associated with a significant reduction of vascular death (odds ratio 0.79; 95% Confidence Interval 0.7 to 0.9; z=3.5 and p=0.0005) and major cardio-vascular events (odds ratio 0.72; 95% Confidence Interval 0.5 to 1.0; z=2.2 and p=0.03). However, effect on stroke needs further evaluation.

Introduction

Hypertension is one of major contributor to global mortality and is responsible for approximately 7.1 million deaths each year (Kearney et al., 2005). It increases the risk of heart attack, heart failure, stroke, and kidney disease (Chobanian et al., 2003; Stamler et al., 1993).

The primary aim of an effective antihypertensive treatment strategy is to lower elevated blood pressure to target levels and to achieve a maximum reduction in risk. Many clinical trials have shown that blood pressure reduction by a variety of strategies reduces the risk of stroke by approximately 35%, congestive heart failure by 42% and coronary heart disease by 28% (ALLHAT, 2002; Gueyffier et al., 1996; Psaty et al., 1997 and SHEP, 1991).

Monotherapy has been the standard initial treatment approach in most patients with hypertension and combination therapy is initiated when stepwise increases in the dose of the single agent fail to achieve the required blood pressure reduction.

The rationale behind combination therapy, using two or more drugs with different and complementary mechanisms of action, is the potential to improve blood pressure control by the combined effects and, by allowing lower doses of the drugs, to reduce unwanted side-effects. Significant discrepancies exist on the question of which combinations of antihypertensive drugs should be employed. While JNC-7 recommends a diuretic to be included in a 2-drug combination strategy, the European guideline recommends various combinations both with and without a diuretic (Chobanain et al., 2003 and Mancia et al., 2007). More specifically, the recently revised European (ESC/ESH) guidelines recommend the following options for 2-drug combinations: Diuretic plus either calcium channel blocker or renin–angiotensin system blocker (ACE inhibitor or angiotensin receptor blocker) or calcium channel blocker plus renin–angiotensin system blocker (Mancia et al., 2009). Also, the use of ACE-inhibitors is recommended in guidelines on the management of stable coronary artery disease, myocardial infarction, and heart failure (Fox et al., 2006; Wood et al., 1998;

Lopez-Sendon et al., 2004).

Among all the ACE-inhibitors, perindopril has been extensively investigated in this regard and has been shown to improve endothelial function and neuro-humoral balance, and inhibit remodelling of the coronary arteries (Bots et al., 2007; Rodriguez-Granillo et al., 2007 and Ceconi et al., 2007). The beneficial effects of combination of perindopril and Indapamide, a diuretic in reducing blood pressure have been demonstrated in many trials and meta-analysis. Perindopril/indapamide provided additional antihypertensive efficacy when compared with each component used alone and major efficacy on systolic blood pressure, an important predictor of cardiovascular risk compared with current monotherapy. It also reduced pulse pressure, large-vessel arterial stiffness and microcirculatory alterations (Rodriguez-Granillo et al., 2007). Perindopril/indapamide also reduced target organ damage in patients at high cardiovascular risk (Gosse, 2006). Most of these studies were conducted in patient populations with vascular disease in a single vascular territory or with a metabolic disorder such as diabetes. Thus, a study that included patients of various age groups with a wider spectrum of vascular disease is needed. As there is paucity of literature which analyzes perindopril/indapamide combination for risk reduction, the present analysis is conducted.

Materials and Methods

Identification, inclusion and exclusion

Literature searches were performed using MEDLINE/PubMed and CENTRAL (Cochrane Central Register of Controlled Trials) up to May 2011 with the following search terms: "Perindopril" and "Indapamide" or "Perindopril Indapamide" or "Perindopril Indapamide secondary prevention". These search terms resulted in 302 primary articles from the PubMed database which included 50 reviews. The resulting articles were then manually screened and duplicates removed. Articles were included if the trial is a) double blind randomized clinical trial, b) include any of the Secondary Prevention parameter- stroke, cardiovascular mortality, etc, c) had a follow-up for at least 1 year, and d) article in English language.

J-PADOC trial was excluded as it was an observational study. P.I.X.C.E.L, PREMIER and REASON study were also excluded as secondary prevention criteria was not met. Thus, three large clinical trials-ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation), HYVET (Hypertension in the Very Elderly Trial) and PROGRESS (Perindopril Protection Against Recurrent Stroke Study) were included for analysis (Figure 1).

End points

The endpoints of interest for the present analysis were prevention of fatal or non-fatal strokes, major cardiovascular event, vascular death, myocardial infarction and all cause mortality.

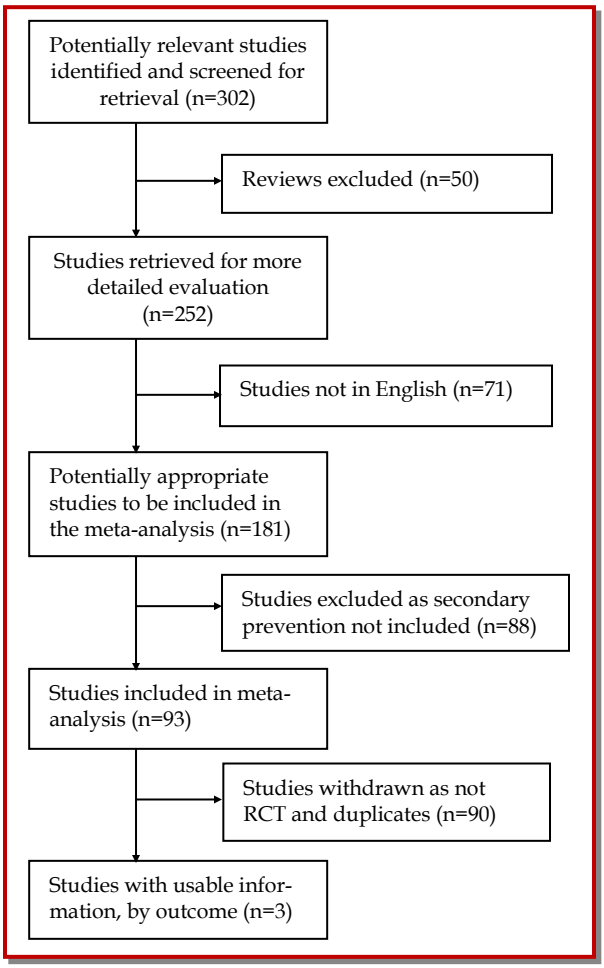

Figure 1: Flow-diagram of included studies

Statistical analysis

Trial data experiencing a clinical outcome and the total number of study participants for each arm were used to determine odds ratios for each study and were analyzed using Review Manager (RevMan) version 5.0. As all data were dichotomous, the Mantel-Haenszel method was used for all odds ratio. Statistical heterogeneity was determined by using χ^2 test. A *p*-value of less than 0.10 indicates heterogeneity. A random effects model was used for all analyses. Ninety-five percent confidence interval was used throughout and P values less than 0.05 was considered statistically significant.

Results

The present study aims to analyze the effect of combination of perindopril and indapamide and hence included patients of various ages. Three large multi-centric double-blind randomized placebo controlled trials-(ADVANCE, 2007); (Beckett, 2008) and (PROGRESS, 2001) were included for the present analysis.

A total of 18,529 patients (9,272 receiving combination of perindopril and indapamide and 9,257 receiving placebo) were included in this meta-analysis. 43.7% of the total patients were females (Table I). Patients receiving either combination of perindopril and indapamide or receiving double placebo in PROGRESS study were included in the present analysis. Data involving single drug or involving both single and combination drugs were not included for analysis. So in PROGRESS trial, data involving 3,544 out of a total of 6,105 patients were analyzed.

All the three studies reported stroke as a primary or secondary endpoint (Table II). The number of patients experiencing fatal or non-fatal stroke included in this analysis were 958 (5.2% of total) of which 416 (4.5% of combination) received combination of perindopril and indapamide and 542 (5.9% of placebo) received placebo (Figure 2 and 3). A non-significant reduction in fatal and non-fatal stroke was seen (Odds ratio 0.7; 95%

Table I

Main features of the ADVANCE, PROGRESS and HYVET trials

Characteristics	AD-VANCE	PRO-GRESS*	HYVET
Number of subjects	11,140	3,544	3,845
Mean age (± SD)	66 (6)	63 (9)	83.5 (3.2)
Number of females (%)	4,735 (42.5)	1,043 (29)	2,326 (60.5)
History of stroke (%)	13	71	7
History of myocardial infarction (%)	12	7	3
History of heart disease (%)	39	18	12
History of diabetes (%)	100	12	7
Current smoker (%)	15	20	7
Mean systolic blood pressure in mm of Hg (± SD)	145 (21)	149 (19)	173 (8.5)
Mean diastolic blood pressure in mm of Hg (± SD)	81 (11)	87 (11)	91 (8.5)

*Combination=perindopril plus indapamide, or double placebo only

Table II

Baseline characteristics patients in the ADVANCE, PROGRESS and HYVET trials

Features	ADVANCE	PROGRESS	HYVET
Main inclusion criteria			
Age at entry (year)	> 55	Not specified	> 80
Type of patients (entry)	Diabetes mellitus	Stroke or TIA	
Main exclusion criteria			
Known congestive heart failure	No	No	Yes requiring treatment with antihypertensive medication
Stroke	-	Within 5 years	Within 6 months
ACE-inhibitor and target daily dose	Perindopril 4 mg/ indapamide 1.3 mg	Perindopril 4 mg/ indapamide 2.5 mg (except Japan 2 mg)	Perindopril 4 mg/ indapamide SR 1.5 mg
Main outcomes			
Primary (composite)	Major macro- or microvascular events	Fatal or non-fatal stroke	Fatal or nonfatal stroke
Secondary and others	All-cause mortality, cardiovascular mortality, non-fatal MI, fatal- and non-fatal stroke, revascularization, heart failure admissions, new or worsening nephropathy	All-cause mortality, cardiovascular mortality, non-fatal MI, fatal- and non-fatal stroke, revascularization, heart failure admissions	death from any cause, death from cardiovascular causes, death from cardiac causes, and death from stroke
Recruitment period	June 2001 to March 2003	May 1995 to November 1997	2001 to 2007
Mean follow-up duration	4.3 years	3.9 years	2.1 years

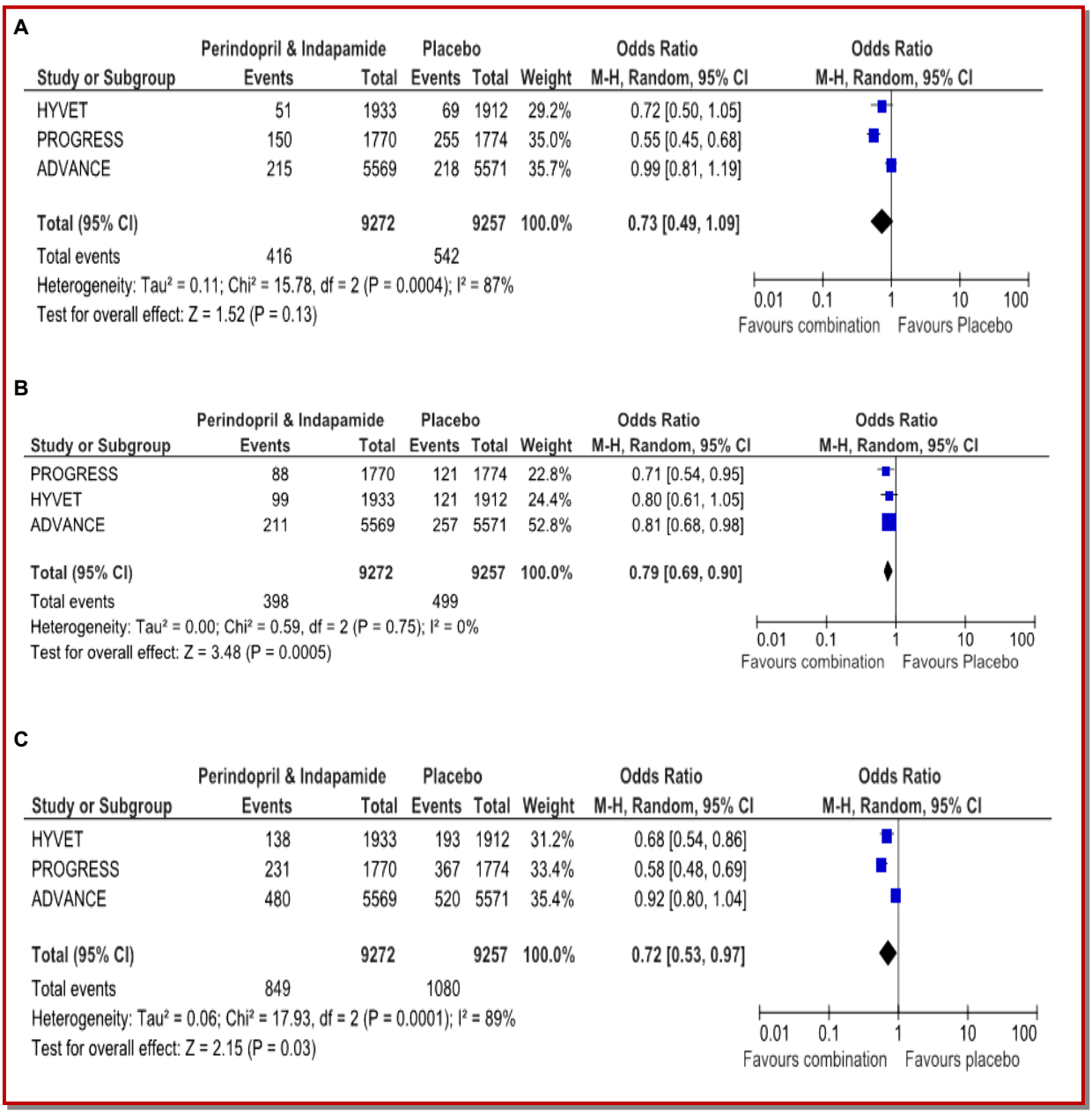

Figure 2: Forest plots of the effect of perindopril/Indapamide in patients with/without prior stroke or TIA on odds on (A) subsequent stroke (fatal and nonfatal); (B) vascular death; (C) major cardio-vascular events (combined stroke, MI, or vascular death). The weights represents relative weight given to study. The final column gives point estimates of Odds ratio and 95% confidence interval

Confidence Interval 0.5 to 1.1). This combination reduces the odds of fatal and non-fatal stroke by 27% of what they were in placebo group. However, a significant reduction in fatal and non-fatal stroke (Odds ratio 0.6; 95% Confidence Interval 0.5 to 0.8) is observed if HYVET and PROGRESS trials are only analyzed (Figure 4).

There were 4.3% vascular deaths in patients using combination as compared to 5.4% using placebo (Figure 2 and 3). This combination significantly decreased the vascular death (Odds ratio 0.8; 95% Confidence Interval 0.7 to 0.9). Thus, this combination reduces the odds of vascular deaths by 21% of what they were in placebo group. However, more weight was given to ADVANCE.

Major cardio-vascular events comprised of combined stroke, myocardial infarction, or vascular death. Significant reduction was also seen in major cardiovascular

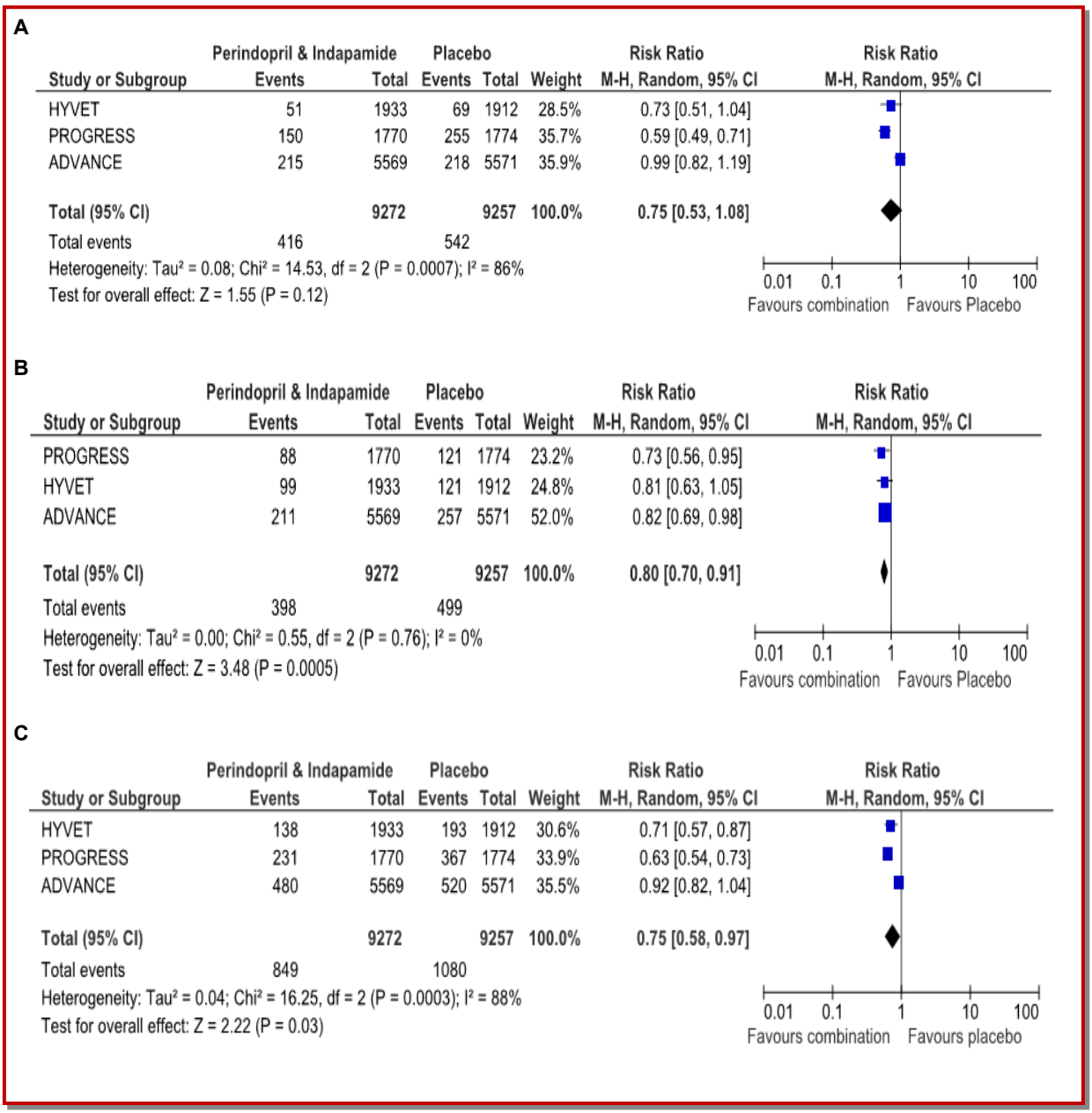

Figure 3: Forest plots of the effect of perindopril/Indapamide in patients with/without prior stroke or TIA on risk of (A) subsequent stroke (fatal and nonfatal); (B) vascular death; (C) major cardiovascular events (combined stroke, MI, or vascular death). The weights represents relative weight given to study. The final column gives point estimates of risk ratio and 95% confidence interval

events (odds ratio 0.7; 95% confidence interval 0.5 to 1.0). This combination reduces the odds of major cardiovascular event by 28% of what they were in placebo group (Figure 2 and 3).

A considerable degree of heterogeneity was found in analysis of fatal or non-fatal stroke (I^2 = 87%; p= 0.0004) and major cardio-vascular events (I^2 = 89%; p= 0.0001). However, no heterogeneity was found in analysis of vascular deaths (I^2 = 0%; p=0.75) and fatal or non-fatal stroke excluding ADVANCE (I^2 = 36%; p= 0.21).

Non-availability of data for myocardial infarction and all cause mortality for the combination in PROGRESS study lead to only analyze fatal or non-fatal strokes, major cardiovascular event and cardiovascular mortality.

Discussion

JNC 7 states that most patients with hypertension will require 2 or more antihypertensive medications to

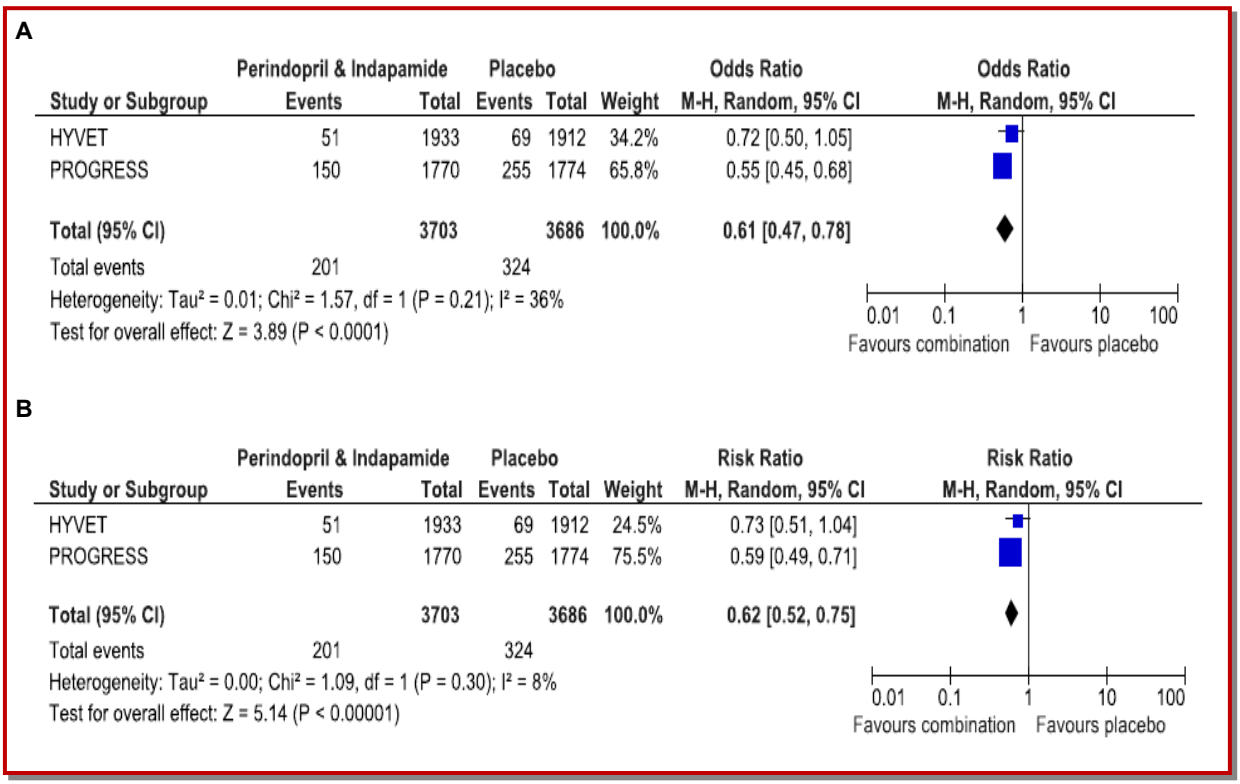

Figure 4: Forest plots of the effect of perindopril/Indapamide on (A) odds and (B) risk on subsequent stroke (fatal and nonfatal) excluding Advance. The weights represents relative weight given to study. The final column gives point estimates of Odds ratio and 95% confidence interval

achieve goal blood pressure (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease); If blood pressure is more than 20/10 mm Hg above goal blood pressure, consideration should be given to initiating therapy with 2 agents, 1 of which usually should be a thiazide-type diuretic (Chobanian et al., 2003). Indapamide is called a thiazide-like diuretic but structure lacks the thiazo-ring and its fixed dose combination with perindopril offers as an alternative to treat patients requiring these two class of drugs.

Two meta-analysis (Kang et al., 2004; Laurent, 2003) demonstrated fixed, low-dose perindopril/indapamide combination's favorable safety profile and effectiveness as first-line treatment for patients with mild to moderate essential hypertension. This combination also reduced the incidence of hypokalemia seen with indapamide alone (McClellan and Markham, 1999). Cardiovascular prevention with perindopril, in combination with indapamide, has been also shown in the elderly and patients with diabetes, cardio- and cerebrovascular diseases in large randomized clinical trials. A broad use of perindopril/indapamide for the long-term improvement of prognosis in hypertensive patients as well as in patients with diabetes was also supported (Mancia and Grassi, 2009). The low-dose perindopril/indapamide can be applied as first-line treatment by physicians who care for patients with elevated blood pressure or, more broadly, those with cardiovascular disease was also stated (De Leeuw, 2011).

So, the present analysis tested perindopril-indapamide combination in secondary prevention. Data from PROGRESS which involved single drug have been not taken into account in this analysis so as to analyze only the combination effect. Base on the result from this analysis, this combination did not significantly reduce fatal or non-fatal stroke but reduced vascular deaths and decreased major cardio-vascular events. However, perindopril/indapamide reduced the risk of fatal or non fatal stroke by 25% of what it was with placebo. Three trials (6,216 patients) studied a diuretic (Carter, 1970; Hypertension study, 1974; PATS, 1995); the largest of these, PATS (5,665 patients), reported that indapamide reduced stroke recurrence by 29%. Similar results of indapamide in reducing stroke were also seen in meta-analysis (Liu et al., 2009; Brodszky et al., 2007). A meta-analysis of perindopril (Snyman and Wessels, 2009) demonstrated a highly significant reduction in event rate of stroke (OR 0.8/; 95% CI: 0.7–0.9; p< 0.0001). Individual large trial such as PROGRESS showed dual antihypertensive therapy (perindopril and indapamide) was superior to mono therapy (perindopril) in reducing stroke recurrence (relative risk reduc-

tion 43 vs 5%) and HYVET observed 30% reduction in stroke. ADVANCE showed low stroke reduction and no treatment benefit with this combination. So, analysis excluding ADVANCE was done and combined analysis of HYVET and PROGRESS not only showed significant reduction in stoke event but also 38% risk reduction with no heterogeneity. The author was unable to find published meta-analysis of stroke reduction with perindopril/indapamide combination for comparing the result of analysis.

Perindopril/indapamide significantly reduced the risk of vascular death by 20% and of major cardiovascular events by 25% of what it was with placebo in this analysis. Vascular death was also reduced significantly in individual trials such as HYVET 19%, ADVANCE 18% and PROGRESS 27% relative risk reduction. A significant 11% reduction in mortality with perindopril alone in six outcome trials was found (Snyman and Wessels, 2009). Thus, by result of this meta-analysis, it can be said that perindopril/indapamide reduces more vascular death than perindopril alone. The same trend is also seen in reduction of major cardio-vascular event. Although no meta-analysis showing effect of perindopril/indapamide combination on major cardiovascular events were published till date, the result of this meta-analysis is as par with the result of Rashid et al. (2003) who found combination of ACE inhibitor and diuretic reduces major vascular events. The present analysis confirms the opinion (Ghiadoni, 2011) that combination therapy with indapamide or amlodipine with perindopril reduces cardiovascular events and mortality in hypertensive patients. A study (Brugts et al., 2009) also provided strong evidence for a consistent cardiovascular protection with an ACE-inhibitor treatment regimen (perindopril-indapamide) by improving survival and reducing the risk of major cardiovascular events across a broad spectrum of patients with vascular disease. Major cardiovascular events were reduced by 29% in HYVET, 36% in PROGRESS and low of 8% in ADVANCE of what it was with placebo. The pooled analysis of these trials in this analysis shows that the combination reduces the risk of major cardio-vascular events by 4 percentage points.

There is ample evidence that perindopril/indapamide has actions on the heart and blood vessels that may reduce cardiovascular disease. Apart from animal studies, clinical trials exploded action of both these drugs as well as combination. Comparing with atenolol, Ghiadoni et al. (2009) found improvement of endothelium-dependent vasodilation with treatment with perindopril/indapamide in comparison with atenolol. Also, improvement in endothelium-independent and sympathetic-associated vasodilation was also observed in the study. The study results suggested long-term therapy with a fixed-dose combination of perindopril/indapamide affords vascular protection in hypertensive patients. Recent HYVET study (Bulpitt et al., 2011) also discussed greater benefits of the combination due to unknown properties of indapamide or perindopril. Debbabi et al. (2010) found that blood pressure controlled hypertensive patients had normalized capillary density and endothelial function with perindopril/indapamide whereas other anti-hypertensive treatments, excluding ACE inhibitors or diuretics, had less effect despite similar blood pressure control. Thus, the result of this analysis may reflect the class effect of ACE inhibitors in combination with diuretics. As the present analysis compared combination of active drug with placebo, randomized clinical trials and analysis of this drug combination with active competitor needs to be carried out.

This work has several limitations

Limitation 1: Trial-level data rather than individual patient data were assessed since the latter were not available. Analyses based on individual patient data are generally superior and also allow subgroup analyses to be performed.

Limitation 2: Assessment of the effect of lowering blood pressure in patients with different secondary outcomes could not be assessed as since all the trials included did not report these data separately.

Limitation 3: The baseline blood pressure varied among the trials included- in HYVET was approximate 173/91 mm Hg whereas other two trials was approximate 147/84 mm Hg. This might have also affected the outcomes.

Limitation 4: Fatal or disabling stroke would have been more relevant in Patient's view. It was not possible to analyze fatal stroke due to non-availability of data.

Limitation 5: There was significant heterogeneity in this analysis. Such heterogeneity can be related to differences across trials in patient selection, concomitant medication, length of follow-up, etc. The result from indirect comparisons, are only exploratory, with a weak level of evidence and will not be possibly assessed even in a meta-analysis on individual patient data.

Limitation 6: The dose of Indapamide was different in each included trials- 1.3 mg in ADVANCE, 2.5 mg in PROGRESS (2 mg in Japan) and 1.5 mg in HYVET. This might have affected the outcome as PROGRESS used double dose of indapamide as compared to ADVANCE

Limitation 7: As data involving reduction of heart failure, myocardial infarction (fatal or non-fatal), hospital admission, etc were not available from the included trial, the analysis of these secondary parameters could not be performed.

Conclusion

Evaluation of three large randomized clinical trials, fixed-combination of perindopril and indapamide substantially reduced major cardiovascular event and vascular death. However, effect on stroke needs further evaluation.

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