Original Research

Blood Pressure and Cholesterol-lowering Efficacy of a Fixed-dose Combination With Irbesartan and Atorvastatin in Patients With Hypertension and Hypercholesterolemia: A Randomized, Double-blind, Factorial, Multicenter Phase III Study

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ABSTRACT

Purpose: A fixed-dose combination of a stain and an antihypertensive drug may be useful for the treatment of patients with hypertension and hyperlipidemia. It may also improve patient drug compliance to help control risk factors of cardiovascular disease. This study was designed to evaluate the blood pressure–lowering and cholesterol-lowering effect of a fixed-dose

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combination of irbesartan-atorvastatin compared with monotherapy by either agent over an 8-week treatment period.

Methods: Patients with comorbid hypertension and hypercholesterolemia were screened for this randomized, double-blind, Phase III study. Eligible study patients were randomly assigned to test groups receiving a combination of irbesartan 300 mg and atorvastatin 40 mg or 80 mg (IRB300 + ATO40 and IRB300 + ATO80). Comparator groups comprised monotherapy groups with irbesartan 300 mg (IRB300) or atorvastatin 40 mg (ATO40) or atorvastatin 80 mg (ATO80), or placebo. Patients who were eligible at screening were subjected to a 4- to 6-week washout period before commencing 8 weeks of therapy per their assigned group. The primary efficacy end points were percent change in LDL-C and sitting diastolic blood pressure (DBP) levels from baseline to end of therapy. Tolerability profiles of combination therapy were compared with other groups.

Findings: A total of 733 patients with comorbid hypertension and hypercholesterolemia were screened for this study; 230 eligible patients were randomized to treatment. The mean age of patients was 58.9 (8.5) years, and their mean body mass index was 25.8 (3.2) kg/m^2. More than two thirds (70.9%) of the study patients were male. Mean LDL-C and sitting DBP levels at baseline were 149.54 (29.19) mg/dL and 92.32 (6.03) mm Hg, respectively. Percent reductions in LDL-C after 8 weeks were 46.74% (2.06%) in the IRB300 + ATO40 group and 48.98% (2.12%) in the IRB300 + ATO80 group; these values were 47.13% (3.21%) and 48.30% (2.98%) in the ATO40 and ATO80 comparator groups. Similarly, a reduction in sitting DBP after 8 weeks was −8.50 (1.06) mm Hg in the IRB300 + ATO40 group and 10.66 (1.08) mm Hg in the IRB300 + ATO80 group compared with 8.40 (1.65) mm Hg in the IRB300 group. The incidence rate for treatment-emergent adverse events was 22.27% and was similar between the monotherapy and combination groups.

Implications: A once-daily combination product of irbesartan and atorvastatin provided an effective, safe, and more compliable treatment for patients with coexisting hypertension and hyperlipidemia. ClinicalTrials.gov identifier: NCT01442987. (*Clin Ther.* 2016;38:2171–2184)

Key words: atorvastatin, combination, hyperlipidemia, hypertension, irbesartan.

INTRODUCTION

Hypertension and hyperlipidemia are 2 of the most important risk factors in the development of cardiovascular disease, and they often coexist.[1–3] These risk factors act synergistically in disease progression, and results from the Framingham Heart Study showed that even a moderate increase in blood pressure (BP) and cholesterol dysregulation has as much of a 10-year congestive heart disease risk as marked elevation of either factor alone.[4] Recent guidelines for the management of hypertension and hyperlipidemia, as recommended by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 2014 (JNC VIII)[5] and the American College of Cardiology/American Heart Association 2013 blood cholesterol guideline,[6] respectively, emphasize the overall assessment of BP and serum lipid levels in evaluating cardiovascular risk rather than assessment of each risk factor individually.[7]

Presently, the drugs with a preferred mechanism of cardiovascular protection for antihypertensive therapy are those that inhibit the renin-angiotensin system (RAS).[8] Two classes of the drugs (the angiotensin-converting enzyme [ACE] inhibitors and the angiotensin II receptor blockers [ARBs]) have been discovered to have RAS inhibitory activity, albeit by different mechanisms. Although ACE inhibitors hinder the production of angiotensin II through the inhibition of ACE, ARBs prevent the interaction of angiotensin II with its receptor (AT_1), which subsequently prevents aldosterone secretion. However, ACE inhibitors may also lead to the production of certain immunomodulatory peptides such as bradykinin and substance P, which can result in dry cough and angioedema. In contrast, ARBs, owing to their specificity for AT_1, provide sufficient BP lowering without these side effects.[9–11]

Many studies have shown a positive correlation between blood cholesterol levels and cardiovascular disease, and thus a reduction in cholesterol levels can significantly reduce the risk.[12,13] Drugs belonging to the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are the most commonly prescribed antihyperlipidemic agents. They act by inhibiting the formation of mevalonate, the rate-limiting step in the biosynthesis of cholesterol. Moreover, statins such as atorvastatin also increase LDL receptors on hepatocytes, thereby enhancing its uptake from blood. The latest, more potent statins such as atorvastatin can also

effectively reduce plasma levels of LDL-C, total cholesterol (TC), apolipoprotein B, VLDL-C, and triglycerides (TG). Atorvastatin therapy has also led to a reduction in the incidence of adverse cardiovascular events in patients with other risk factors in addition to dyslipidemia such as hypertension[14] and type 2 diabetes.[15]

Given the multifactorial nature of cardiovascular disease, physicians have to rely on prescription of multiple drugs to successfully manage the various concomitant pathologies. The resulting polypharmacy, with numerous medications with varying regimens, is one of the major reasons for nonadherence of patients to their prescribed therapies and subsequent failure in managing their disease.[16] Hence, a patient-friendly regimen, preferably with the least number of doses that could be taken simultaneously, may have a huge advantage in ensuring patient compliance. An emerging concept of fixed-dose combination (FDC) therapy in which ≥2 drugs are combined into a single dosage form aims at ensuring adherence to the regimen by reducing the "pill burden" on the patients. The safety and effectiveness, as well as improvement in patient compliance, through the use of FDCs have already been demonstrated.[17,18] In clinical practice, patients with cardiovascular risk factors such as hypertension take antihypertensive agents as well as lipid-lowering agents, and a co-prescription of irbesartan and atorvastatin is already prevalent. Given the pharmacokinetic profile of both drugs, it is possible for them to be administered once-daily. Thus, combining them into 1 formulation could improve patient compliance with their medication.

We hypothesized that a combination of irbesartan and atorvastatin would have excellent therapeutic effect and an equivalent safety profile compared with either drug administered alone in patients with hypertension and hyperlipidemia. To evaluate this theory, these drugs were administered in 2 fixed combinations to eligible patients for an 8-week period; we then compared the change in LDL-C and BP levels in these patients versus those of study patients who received single-agent therapy.

PATIENTS AND METHODS

Study Design and Patient Recruitment

This randomized, double-blind, factorial, multicenter, Phase III study was conducted in 22 study centers throughout the Republic of Korea from June 2011 to February 2013. Eligible patients were aged ≥19 years and ≤75 years, provided informed consent at screening, and presented with hypertension and hyperlipidemia that could be categorized into groups A, B, or C (in increasing order of disease severity) based on BP and fasting serum lipid levels at the randomization visit. The following describes each group:

Group A: 0 to 1 cardiovascular risk factor or ≥2 risk factors and 10-year risk <10%; BP, 140 ≤ systolic BP (SBP) <180 mm Hg and 90 ≤ diastolic BP (DBP) <110 mm Hg; fasting serum lipid, 130 ≤ LDL-C ≤ 250 mg/dL; and TG <400 mg/dL.

Group B: ≥2 cardiovascular risk factors and10-year risk of 10% to 20%; BP, 140 ≤ SBP < 180 mm Hg and 90 ≤ DBP < 110 mm Hg; fasting serum lipid, 130 ≤ LDL-C ≤ 250 mg/dL; and TG <400 mg/dL.

Group C: presence of coronary artery disease, diabetes mellitus (glycosylated hemoglobin level ≥6.5% at visit 1) or other clinical manifestation of atherosclerosis (eg, peripheral artery disease, abdominal aortic aneurysm, symptomatic carotid artery disease); 10-year risk >20%; BP, 130 ≤ SBP < 160 mmHg and 80 ≤ DBP < 100 mm Hg; fasting serum lipid, 100 ≤ LDL-C ≤ 250 mg/dL; and TG, <400 mg/dL.

Exclusion criteria were acute liver disease or hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase levels ≥2 times the upper limit of normal), elevated serum creatinine level (≥2.5 mg/dL), creatinine phosphokinase level >2 times the upper limit of normal, elevated serum TG (≥500 mg/dL), a history of an intervention using a stent in coronary artery disease within the preceding 12 months, hypersensitivity to a hydroxymethylglutaryl coenzyme A reductase inhibitor, uncontrolled hypertension (SBP ≥180 mm Hg or DBP ≥110 mm Hg with antihypertensive medication measured at rest), uncontrolled diabetes mellitus, currently taking any kind of lipid-lowering drugs, diagnosed with myopathy, patients at risk of myopathy (renal impairment or previous renal dysfunction, hypothyroidism, genetic defects or family history of myopathy, experienced previous muscle toxicity with taking statins or fibrates, prior liver disease, or higher intakes of alcohol), participation in other studies within 4 weeks before enrollment, pregnant and breastfeeding women, women not using adequate methods of contraception (women of

childbearing potential had to be using adequate methods of contraception), contraindicated medically or mentally, forbidden legally, unable to participate in clinical trial according to investigator's decision, and concomitant use of drugs that could possibly interact with the study drugs.

The study period lasted 12 to 14 weeks and included 4 patient visits: enrollment (screening), commencement of treatment (baseline), and 2 follow-up visits (4 and 8 weeks [±4 days] after baseline). There was a 4- to 6-week washout period between screening and baseline, during which any antihypertensive or antihyperlipidemic therapy the patient was receiving before enrollment was stopped. In addition, patients were provided nutritional counseling at the start of the washout period to implement lifestyle changes and patient education.

The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study protocol was approved by institutional review boards at each participating center, and all study participants provided written informed consent.

Patient Data Collection

After checking for eligibility and after having obtained informed consent, study patients were questioned about their demographic characteristics, lifestyle habits, personal and familial medical history, and concomitant medications. Patients also underwent a physical examination, and vital signs (bp and heart rate) were measured. Laboratory tests were conducted to evaluate blood count, serum biochemistry (eg, TC, HDL-C, TG, apolipoprotein A1 [apo A1], apolipoprotein B [apo B]), urinalysis, glycosylated hemoglobin, thyroid-stimulating hormone, and β-human chorionic gonadotrophin (for pregnancy, where applicable). These tests were repeated at each subsequent visit (baseline and follow-up visits). Furthermore, data on adverse events were collected from the baseline visit onward. Data were also collected during follow-up visits for medication compliance by evaluating the number of unused tablets in the strips provided to the patients.

Randomization and Study Treatments

Block randomization using the Proc plan procedure of SAS software (SAS Institute, Inc, Cary, NC) was used by an independent randomization officer for assigning the patients to their treatment groups. An arbitrarily selected block size was used for generation of the randomization code in a ratio of 2:1:1 (for co-administration:single agent:placebo). The study cohort was divided into 6 groups: 2 assigned for coadministration of 2 disparate combinations, 3 assigned to single-agent therapy, and 1 group receiving placebo. The packaging officer at the investigational product formulation facility then packaged the study drugs (or matching placebo) for each patient according to the randomization code and delivered these to the study pharmacist at each site before the start of the study.

Study treatments comprised 2 test groups (irbesartan 300 mg + atorvastatin 40 mg [IRB300 + ATO40] and irbesartan 300 mg + atorvastatin 80 mg [IRB300 + ATO80]), 3 comparator single-agent groups (irbesartan 300 mg [IRB300], atorvastatin 40 mg [ATO40], and atorvastatin 80 mg [ATO80]), and 1 comparator placebo group (no active drug). As per the regimen, patients received irbesartan 300 mg* (batch H008 and AVFQ004) or atorvastatin 40 mg† (batch 1108080 and 0979111) or atorvastatin 80 mg† (batch 1021080 or 1161091). Matching placebos were manufactured by Hanmi Pharmaceutical Co Ltd (Seoul, Republic of Korea; batch P1101-1). In effect, each patient, independent of the group he or she was assigned to, consumed 3 tablets once daily: either a combination of 2 drugs and 1 placebo, a single agent and 2 placebos, or all placebos.

Efficacy and Safety Assessment

Primary efficacy end points were percent change from baseline in LDL-C level and change from baseline in mean sitting DBP level after the treatment period of 8 weeks. Secondary efficacy end points assessed were percent change from baseline levels for LDL-C and change from baseline in sitting DBP, sitting SBP, TC, HDL-C, TG, apo A1, and apo B; proportion of patients achieving LDL-C targets as prescribed by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines; and/or bp targets as per JNC VII guidelines between the coadministration and single-agent groups

*Trademark: Aprovel® (Handok Inc, Seoul, Republic of Korea)
†Trademark: Lipitor® (Pfizer Korea Ltd, Seoul, Republic of Korea)

at each follow-up visit (weeks 4 and 8). At screening, bp was measured 3 times on both arms; the arm with the higher mean sitting DBP was used for bp measurements throughout the study (mean of triplicate readings at each visit). A same model of mercury sphygmomanometer (provided by the sponsor, Hammi Pharmaceutical Co Ltd) was used at every site for bp recordings, and if possible, the same investigator measured the bp throughout the study. Patients were advised to avoid caffeine, exercise, and smoking for at least 30 minutes before bp measurements. The blood lipid profile (LDL-C, TC, TG, HDL-C, apo A1, and apo B) was ascertained at local laboratories at screening, and subsequent evaluations were performed at a central facility (Samkwang Medical Laboratories, Seoul, Republic of Korea) to ensure uniformity.

Safety assessment parameters included the incidence of adverse events (AEs), vital signs, laboratory tests, physical examination, and ECG data. AEs were described by using the Medical Dictionary for Regulatory Activities terminology and actual observations, when the former was not possible. AEs were classified as mild, moderate, or severe; their relationship to the study and/or drug was based on the investigator's clinical judgment. Study investigators also recorded any serious AEs and deaths and notified the corresponding authorities.

Statistical Analysis

According to the medical review of amlodipine/atorvastatin fixed combination (US Food and Drug Administration new drug application 021540), atorvastatin lowered sitting DBP by 3.8 to 4 mmHg, whereas irbesartan is known to cause less LDL-C lowering. Sitting DBP was lowered by irbesartan 300 mg by 10.7 mm Hg. Taking a conservative approach and assuming sitting DBP was lowered by irbesartan 300 mg by 10.5 mm Hg and by atorvastatin by 4 mm Hg, the SD of the difference between the combination product and the atorvastatin single agent was 7.03 mm Hg. With a test power of 80% (96% by 5 times of β-adjustment), a 2-sided significance level of 5%, and a dropout rate of 10%, with a ratio of 2:1:1 (for coadministration:single agent:placebo), a target of 230 patients was determined (25 patients each to be included in the monotherapy and the placebo groups, and 50 patients in the FDC group).

End points of this study were tested at a 2-sided significance level of 5%. Categorical data were analyzed by using the Cochran-Mantel-Haenszel test for general association with groups A, B, and C as stratification variables. Continuous variables were analyzed by using a 2×3 factorial ANCOVA model with irbesartan, atorvastatin, irbesartan-by-atorvastatin interaction terms, and baseline values as covariates. Efficacy analysis was performed with last-observation-carried-forward applied only to missing data in the study's efficacy end points or to subjects who had at least 1 postbaseline efficacy assessment. For safety end points, raw data were analyzed because they were without application of last-observation-carried-forward. For continuous variables, means, SDs, and minimum and maximum values were calculated for each treatment group, and 1-way ANOVA was performed. For categorical variables, frequencies and proportions were calculated, and Pearson's χ^2 test or Fisher's exact test was performed.

Primary efficacy end points were the least squares mean (LSM) of the percent change in LDL-C and overall change in sitting DBP after 8 weeks of the assigned regimen. Statistical hypothesis for the primary efficacy end point was tested in a "step-down" process as depicted in Figure 1. Starting with probing for statistical validity of overall drug effect, it moved on to probe for individual drug effect and individual combination effect. If the null hypothesis at each step was rejected stepwise from step 1, the hypothesis at the next step was tested. If the null hypothesis could not be rejected, statistical testing for the next step was not performed, and the result of hypothesis testing at that step was considered to indicate no statistically significant difference. If, by statistical analysis, the upper limit of the 95% two-sided CI was <0 (or the P value was less than the significance level of 5%), superiority of coadministration in mean LDL-C percent change and mean sitting DBP change from baseline to entire treatment period (8 weeks) would be statistically proven.

RESULTS

Patient Disposition, Demographic Characteristics, and Baseline Variables

A total of 733 patients were screened for this study; 230 were randomized to treatment. Of these, 19 (8.3%) patients were withdrawn for various reasons,

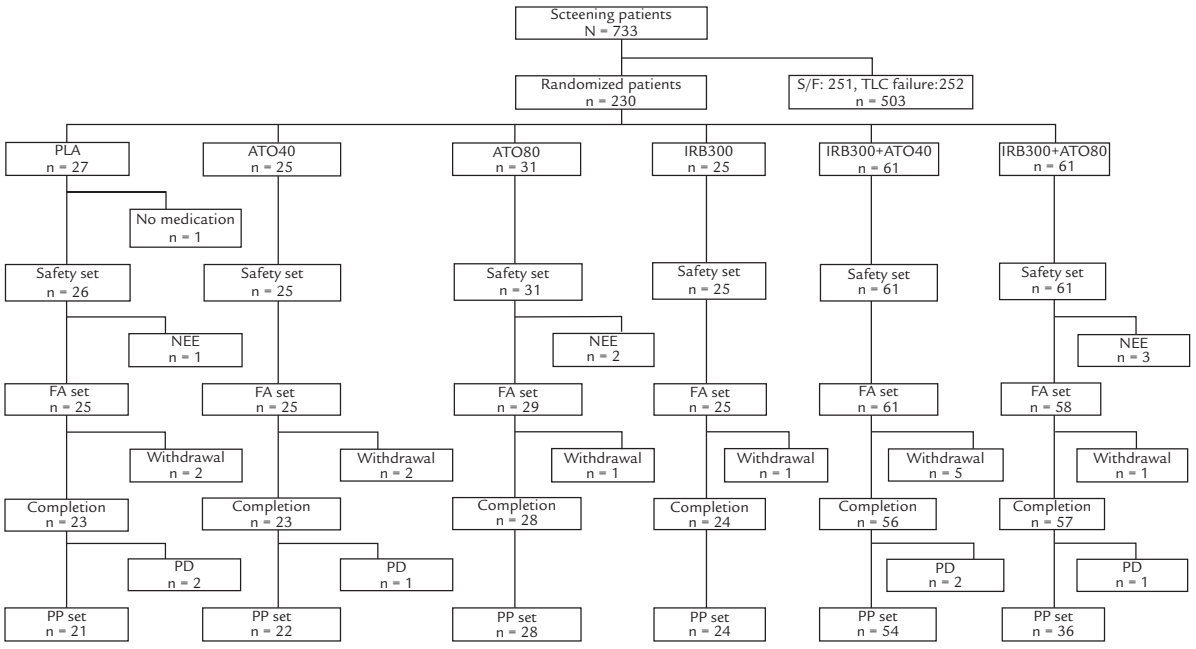

Figure 1. Study flowchart. ATO = atorvastatin; FA = full analysis; IRB = irbesartan; NEE = no efficacy evaluation; PD = protocol deviation; PLA = placebo; PP = per protocol; S/F = screening failure; TLC = therapeutic lifestyle change.

including failure to meet eligibility requirements, unacceptable bp levels, withdrawal of consent, and physician judgment.

The mean age of the study patients was 58.9 (8.5) years, and the cohort included mainly male subjects (n = 158 [70.9%]) (Table I). The patients' mean body mass index was 25.8 (3.2) kg/m^2, and 56.0% (n = 125) of the patients were current smokers or had smoked in the past.

More than one half (n = 131 [58.7%]) of the patients were in group C based on their cardiovascular risk status. At baseline, mean LDL-C and sitting DBP levels were 149.5 (29.2) mg/dL and 92.3 (6.0) mm Hg, respectively. For the parameters of cardiovascular risk factor stratification, serum lipid profile, and sitting DBP, there was no statistically significant difference between the treatment groups with the exception of LDL-C level in group C ($P = 0.0239$).

About two thirds (66.4% [n = 148]) of the patients presented with a medical history in addition to hypertension and hyperlipidemia at the time of screening; the most common disorders were metabolism and nutrition related (48.9% [n = 109]) followed by cardiac disorders (6.3% [n = 14]).

More than three quarters (76.7% [n = 171]) of patients had previously been undergoing medical therapy. The most commonly prescribed class of drugs was lipid-modifying agents, prescribed in 108 (48.4%) subjects, followed by agents acting on the RAS (45.7% [n = 102]). Antidiabetic agents were the most commonly taken concomitant medication during the course of study, reported in 117 (52.5%) subjects.

Primary Efficacy Evaluation

The LSM of percent change in LDL-C from baseline to the end of the study was –46.7% (2.1%) and –49.0 (2.1%) in the IRB300 + ATO40 group and the IRB300 + ATO80 group, respectively (Figure 2**A**). These values were –47.1% (3.2%) in the ATO40 group and –48.3% (3.0%) in the ATO80 group. For the antihyperlipidemic-null group, the LDL-C change was –3.6% (3.2%) and 6.1% (3.2%) in the IRB300 and the placebo groups, respectively. Stepwise end point analysis (Table II) revealed that atorvastatin, alone or in combination with irbesartan, substantially reduced LDL-C levels compared with the placebo or irbesartan-only groups ($P < 0.0001$).

Table I. Patient demographic characteristics, risk stratification variables, and laboratory findings.

Variable	PLA (n = 25)	ATO40 (n = 25)	ATO80 (n = 29)	IRB300 (n = 25)	IRB300 + ATO40 (n = 61)	IRB300 + ATO80 (n = 58)	Total (N = 223)
Age, y*	58.0 (6.9)	58.5 (10.4)	56.9 (7.8)	59.7 (9.3)	59.8 (8.3)	59.2 (8.5)	58.9 (8.5)
Sex, no. (%)							
Female	10 (40.0)	4 (16.0)	10 (34.5)	2 (8.0)	24 (39.3)	15 (25.9)	65 (29.1)
Male	15 (60.0)	21 (84.0)	19 (65.5)	23 (92.0)	37 (60.7)	43 (74.1)	158 (70.9)
BMI, kg/m^2*	26.0 (3.0)	26.0 (3.6)	25.8 (3.1)	27.4 (2.8)	25.2 (3.4)	25.6 (2.9)	25.8 (3.2)
Risk group, no. (%)							
CV risk group A	5 (20.0)	4 (16.0)	4 (13.8)	–	10 (16.4)	11 (19.0)	34 (15.3)
CV risk group B	5 (20.0)	7 (28.0)	7 (24.1)	9 (36.0)	12 (19.7)	18 (31.0)	58 (26.0)
CV risk group C	15 (60.0)	14 (56.0)	18 (62.1)	16 (64.0)	39 (63.9)	29 (50.0)	131 (58.7)
Sitting SBP, mm Hg*	145.7 (7.6)	148.7 (9.6)	143.6 (7.8)	145.4 (11.8)	144.5 (9.1)	146.0 (9.4)	145.5 (9.3)
Sitting DBP, mm Hg*	91.4 (5.2)	94.7 (6.0)	92.8 (6.9)	91.5 (6.1)	91.7 (5.9)	92.5 (6.0)	92.3 (6.0)
LDL-C, mg/dL*	148.4 (33.5)	151.7 (28.9)	152.4 (30.0)	145.5 (28.4)	154.5 (30.5)	144.2 (25.9)	149.5 (29.2)
TC, mg/dL*	224.0 (35.5)	223.6 (32.2)	233.6 (35.0)	216.8 (33.6)	231.2 (34.3)	221.0 (32.3)	225.6 (33.8)
HDL-C, mg/dL*	46.0 (8.6)	48.4 (10.4)	52.6 (11.6)	48.1 (9.2)	49.7 (9.7)	49.5 (10.3)	49.3 (10.1)
TG, mg/dL*	170.4 (55.5)	157.7 (8.4)	169.3 (82.1)	167.5 (70.8)	158.7 (67.0)	164.8 (77.8)	163.9 (69.1)
Apo A1, mg/dL*	139.1 (23.1)	140.0 (31.0)	149.9 (30.7)	139.9 (23.6)	141.9 (24.1)	142.6 (23.2)	142.2 (25.4)
Apo B, mg/dL*	134.0 (23.5)	135.5 (26.4)	138.5 (26.1)	131.9 (28.2)	139.4 (26.8)	130.8 (25.2)	135.2 (26.0)

Apo = apolipoprotein; ATO = atorvastatin; BMI = body mass index; DBP = diastolic blood pressure; IRB = irbesartan; PLA = placebo; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides.
*Mean (SD).

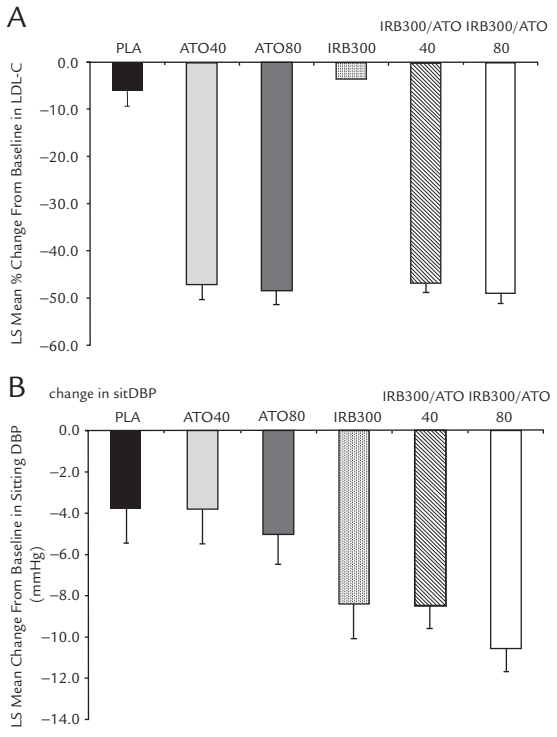

Figure 2. Change in (A) LDL-C (least squares [LS] mean percent change) and (B) sitting diastolic blood pressure (DBP) (least squares mean change) from baseline to week 8. ATO = atorvastatin; IRB = irbesartan; PLA = placebo.

Similarly, the LSM of change in mean sitting DBP by the end of the study was –8.50 (1.06) mm Hg and –10.66 (1.08) mm Hg in the IRB300 + ATO40 and the IRB300 + ATO80 groups, respectively, compared with –8.40 (1.65) mm Hg in the IRB300 group (Figure 2B). The sitting DBP reductions in the other groups were –3.82 (1.66) mm Hg in the ATO40 group, –5.07 (1.53) mm Hg in the ATO80 group, and –3.78 (1.65) mm Hg in the placebo group. The reduction in sitting DBP in groups that received irbesartan in combination was found to be significantly better than in those receiving atorvastatin alone (IRB300 + ATO40 vs ATO40, $P < 0.0186$; IRB300 + ATO80 vs ATO80, $P = 0.0032$), and the reduction in sitting SBP in the irbesartan groups was also significantly better than in the atorvastatin groups (Table III).

Secondary Efficacy Evaluation

By the end of study, the percent reduction in LDL-C was slightly lesser in the groups receiving atorvastatin in combination with irbesartan than in groups receiving atorvastatin alone. However, this difference was not statistically significant (IRB300 + ATO40 vs ATO 40, $P = 0.9193$; IRB300 + ATO80 vs ATO 80, $P = 0.8537$). Similarly, the changes in other serum lipid factors (TC, HDL-C, TG, apo A1, and apo B) were not statistically different between groups receiving atorvastatin in combination or alone. The antihypertensive effect of irbesartan in combination was also not potentiated/attenuated compared with irbesartan alone.

The proportion of patients in the IRB300 + ATO40 group achieving their LDL-C target (according to NCEP ATP III guidelines) after 8 weeks of therapy was 86.9% (n = 53) (Table IV). In

Table II. Stepwise end point analysis summary for levels of LDL-C.

Null Hypothesis	LS Mean Difference	95% CI	*P*
Step 1: No overall effect of atorvastatin	–42.93	–48.11 to –37.75	<0.0001
Step 2: No individual atorvastatin effect			
ATO40 vs ATO not treated	–42.08	–47.94 to –36.23	<0.0001
ATO80 vs ATO not treated	–43.78	–49.52 to –38.05	<0.0001
Step 3: No atorvastatin combination effect			
ATO40 + IRB300 vs IRB300	–43.12	–50.66 to –35.59	<0.0001
ATO80 + IRB300 vs IRB300	–45.36	–52.92 to 37.79	<0.0001

ATO = atorvastatin; IRB = irbesartan; LS = least squares.

Table III. Stepwise end point analysis summary for sitting levels of diastolic blood pressure (DBP) and systolic blood pressure (SBP).

Null Hypothesis	LS Mean Difference	95% CI	*P*
Sitting DBP			
Steps 1 and 2: No overall or individual effect of irbesartan			
IRB treated vs IRB not treated	−4.96	−7.32 to −2.61	<0.0001
Step 3: No irbesartan combination effect			
IRB300 + ATO40 vs ATO40	−4.68	−8.57 to −0.79	0.0186
IRB300 + ATO80 vs ATO80	−5.59	−9.28 to −1.90	0.0032
Sitting SBP			
Steps 1 and 2: No overall or individual effect of irbesartan			
IRB treated vs IRB not treated	−8.18	−13.5 to −2.86	0.0027
Step 3: No irbesartan combination effect			
IRB300 + ATO40 vs ATO40	−7.82	−13.94 to −1.71	0.0124
IRB300 + ATO80 vs ATO80	−8.67	−14.49 to −2.84	0.0037

ATO = atorvastatin; IRB = irbesartan; LS = least squares.

comparison, this finding was 12.0% in the IRB300 group ($P < 0.0001$) and 92.0% in the ATO40 group ($P = 0.5034$). A higher proportion of patients in the IRB300 + ATO80 group (93.1% [n = 54]) achieved their LDL-C target by the end of the study compared with the IRB300 (12.0%; $P < 0.0001$) and ATO80 (79.3%; $P = 0.0658$) groups. Achievement of BP targets (according to the JNC VII guidelines) was not drastically different between the irbesartan + atorvastatin and irbesartan-alone groups either. The proportion of patients achieving their BP targets at week 8 was 48.0% (n = 12) in the IRB300 group, 39.3% (n = 24) in the IRB300 + ATO40 group, and 55.2% (n = 32) in the IRB300 + ATO80 group

Table IV. Proportion of patients achieving LDL-C goal levels as recommended by the National Cholesterol Education Program Adult Treatment Panel III guideline. Values are given as no. (%).

Risk group	ATO40 (n = 25)	ATO80 (n = 29)	IRB300 (n = 25)	IRB300 + ATO40 (n = 61)	IRB300 + ATO80 (n = 58)
Week 4					
Group A	3 (75.0)	4 (100.0)	0	9 (90.0)	11 (100.0)
Group B	7 (100.0)	7 (100.0)	2 (22.2)	11 (91.7)	16 (88.9)
Group C	13 (92.9)	15 (83.3)	1 (6.3)	32 (82.1)	27 (93.1)
Overall	23 (92.0)	26 (89.7)	3 (12.0)	52 (85.3)	54 (93.1)
Week 8					
A	4 (100.0)	4 (100.0)	0	9 (90.0)	11 (100.0)
B	7 (100.0)	6 (85.7)	2 (22.2)	11 (91.7)	15 (83.3)
C	12 (85.7)	13 (72.2)	1 (6.3)	33 (84.6)	28 (96.6)
Overall	23 (92.0)	23 (79.3)	3 (12.0)	53 (86.9)	54 (93.1)

ATO = atorvastatin; IRB = irbesartan.

Table V. Proportion of patients achieving blood pressure targets recommended by the Joint National Committee VII guideline. Values are given as no. (%).

Risk group	ATO40 (n = 25)	ATO80 (n = 29)	IRB300 (n = 25)	IRB300 + ATO40 (n = 61)	IRB300 + ATO80 (n = 58)
Week 4					
Group A	1 (25.0)	1 (25.0)	0	6 (60.0)	10 (90.9)
Group B	0	3 (42.9)	6 (66.7)	7 (58.3)	13 (72.2)
Group C	0	1 (5.6)	4 (25.0)	7 (18.0)	6 (20.7)
Overall	1 (4.0)	5 (17.2)	10 (40.0)	20 (32.8)	29 (50.0)
Week 8					
A	1 (25.0)	2 (50.0)	0	7 (70.0)	9 (81.8)
B	2 (28.6)	3 (42.9)	8 (88.9)	7 (58.3)	14 (77.8)
C	2 (14.3)	4 (22.2)	4 (25.0)	10 (25.6)	9 (31.0)
Overall	5 (20.0)	9 (31.0)	12 (48.0)	24 (39.3)	32 (55.2)

ATO = atorvastatin; IRB = irbesartan.

(Table V). The proportion of patients who achieved their LDL-C goal as well as their BP target by the end of the study was higher in the coadministration groups (34.4% [n = 21] in the IRB300 + ATO40 group and 50.0% [n = 29] in the IRB300 + ATO80 group). In comparison, this finding was lesser in the single-agent groups (data not shown).

Safety Evaluation

Treatment-emergent AEs (TEAEs) were reported in 51 (22.3%) patients (Table VI). These TEAEs were mild (n = 33) or moderate (n = 18), and none was severe. Most of the TEAEs were adjudged as unlikely to be related to the study. Inexplicably, TEAE incidence was the highest in the placebo group and more or less similar in the treatment groups.

The incidence rate of adverse drug reaction was 4.4% (n = 10). There were no serious adverse drug reactions or deaths reported.

Medication Compliance

Overall mean medication compliance was 97.2% (5.4%) and was ≥96.0% in all treatment groups.

DISCUSSION

Our study found that a combination of irbesartan 300 mg and atorvastatin 40 mg or atorvastatin 80 mg, once daily over a period of 8 weeks, was as efficacious as irbesartan alone as an antihypertensive agent and atorvastatin alone as an antihyperlipidemic agent. Moreover, this combination was more effective in lowering sitting DBP and LDL-C than atorvastatin or irbesartan monotherapy, respectively. The safety profile of the irbesartan-atorvastatin combination was comparable to that of monotherapy by either drug, suggesting that the combination is acceptable for clinical management of coexistent hypertension and hyperlipidemia. In terms of achieving the prescribed BP and LDL-C targets (as per JNC VII and NCEP ATP III, respectively), the group receiving IRB300 + ATO80 had the highest incidence (55.2% for BP and 93.1% for LDL-C), although we found no statistical significance for this observation. Understandably, the proportion of patients who achieved both targets was highest in the combination groups (34.4% for IRB300 + ATO40 and 50.0% for IRB300 + ATO80). The most important finding of our study was that a combination of irbesartan and atorvastatin had no effect on the individual therapeutic efficacy of these drugs as an antihypertensive and an antihyperlipidemic, respectively.

To gain the established benefits of the current paradigm (ie, a multifactorial approach to management of cardiovascular risk factors), patient compliance with prescribed therapeutic regimens is a

Table VI. Summary of adverse events. Values are given as no. (%).

Variable	PLA (n = 26)	ATO40 (n = 25)	ATO80 (n = 31)	IRB300 (n = 25)	IRB300 + ATO40 (n = 61)	IRB300 + ATO80 (n = 61)	Total (N = 229)
Subjects with TEAEs	11 (42.3)	6 (24.0)	7 (22.6)	4 (16.0)	14 (23.0)	9 (14.8)	51 (22.3)
By severity							
Mild	6 (23.1)	4 (16.0)	4 (12.9)	3 (12.0)	11 (8.0)	5 (8.2)	33 (14.4)
Moderate	5 (19.2)	2 (8.0)	3 (9.7)	1 (4.0)	3 (4.9)	4 (6.6)	18 (7.9)
Severe	–	–	–	–	–	–	–
Relationship to IP							
Definitely related	–	–	–	–	–	–	–
Probably related	1 (3.9)	-	1 (3.2)	–	1 (1.6)	–	3 (1.3)
Possibly related	1 (3.9)	1 (4.0)	1 (3.2)	–	2 (3.3)	–	5 (2.2)
Unlikely; probably not related	6 (23.1)	2 (8.0)	4 (12.9)	3 (12.0)	9 (14.8)	9 (14.8)	33 (14.4)
Definitely not related; none	3 (11.5)	1 (4.0)	1 (3.2)	1 (4.0)	2 (3.3)	–	8 (3.5)
Unknown; could not be assessed	–	2 (8.0)	–	–	–	–	2 (0.9)

ATO = atorvastatin; IP = investigational product; IRB = irbesartan; PLA = placebo; TEAE = treatment-emergent adverse events.

prerequisite. This theory was illustrated by the observation that patients with higher compliance rates have a significantly lower risk of cardiovascular events compared with those who are less compliant.[19] However, >60% of patients with cardiovascular disease are found to be nonadherent to their prescribed medications, especially when multiple drugs comprise the regimen.[20,21]

The concept of a combination pill containing lipid-lowering drugs and an antihypertensive agent has been studied since 2003, and various trials have revealed promising results.[22–26] However various issues related to patents, drug interactions, regulatory restrictions, and financial aspects have to be addressed before such FDC medications will be freely available for clinical use.[7] Given the usual coexistence of hypertension and hyperlipidemia in cardiovascular disease, designing an FDC that combines drugs that lower BP as well as serum LDL-C offers a rational approach to managing these risk factors. To this end, one of the most tested combinations is that of amlodipine, an antihypertensive that acts by blocking calcium channels in the vascular smooth muscles, and atorvastatin. Earlier studies such as Atorvastatin and Amlodipine in patients with elevated lipids and hypertension (AVALON)[2] and efficacy and safety of fixed-dose combinations of Amlodipine and Atorvastatin in the treatment of patients with concomitant hypertension and dyslipidemia (RESPOND)[3] evaluated co-administered amlodipine and atorvastatin; since then, a single-pill combination with these 2 agents has been shown to have an acceptable efficacy and safety profile and help patients achieve their BP and LDL-C targets and decrease their absolute Framingham risk scores.[18,27–30]

In contrast, an ARB/statin combination has only recently been assessed as an alternative in managing hypertension and hyperlipidemia.[31] Persistent or postprandial hypertriglyceridemia and hyperglycemia are known factors for endothelial damage and dysfunction through oxidative stress, and they can result in atherosclerosis.[32,33] A combination of an ARB and statins has been shown to decrease oxidative stress, possibly due to an associated antioxidant activity,[34] thereby offering a promise of decreasing endothelial damage, an independent cardiovascular risk factor. Irbesartan has also been shown to reduce microalbuminuria and have a renoprotective effect,[35–37] which could offer additional benefit in patients with diabetes (~48.0% of the patients in our study also presented with type 2 diabetes) who are at a risk of diabetic nephropathy. In a previous study assessing the pharmacokinetic properties and drug–drug; unpublished study without reference; a previous study assessing the pharmacodynamic properties and drug–drug interactions.[34]

Despite the promising results of the present research, it does have the inherent limitations of a Phase III study. Study patients were carefully selected based on eligibility criteria, and hence they cannot accurately reflect a real-world scenario. The sample size was small, which could be a significant contributing factor as to why we found no statistically significant differences between the coadministration groups and atorvastatin alone for lowering LDL-C and irbesartan alone as an antihypertensive agent. Moreover, with a compliance rate ≥96.0% in all groups, we could not demonstrate an improvement in patient adherence to the combination therapy of irbesartan and atorvastatin, and we can only speculate that a combined single pill with these 2 drugs would have better patient acceptability. Compared with the chronic nature of cardiovascular risk factors, our study was conducted for only a period of 8 weeks, and it is therefore not feasible to extrapolate the results for a longer duration.

CONCLUSIONS

Development of a once-daily combination product of irbesartan and atorvastatin provided an effective, safe, convenient, and patient-friendly treatment option for coexistent hypertension and hyperlipidemia. More long-term studies in various populations will be required to validate the utility of this combination in the real-world management of cardiovascular disease.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article. The sponsor had no involvement in the design, conduct, or analysis of the study.

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