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Treatment of microalbuminuria in hypertensive subjects with elevated cardiovascular risk: Results of the IMPROVE trial

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Microalbuminuria independently predicts increased cardiovascular risk in hypertensive patients, especially in those with concomitant diabetes or established cardiovascular disease. Drugs that target the renin–angiotensin–aldosterone system reduce microalbuminuria regardless of diabetic status. The Irbesartan in the Management of PROteinuric patients at high risk for Vascular Events was a multicenter, randomized, double-blind, placebo-controlled paralleled group study in which hypertensive patients with microalbuminuria and increased cardiovascular risk were randomized to 20 weeks treatment with ramipril plus irbesartan or to ramipril plus placebo. Patients discontinued or tapered previous antihypertensive therapy during a 14-day placebo lead-in period. Change in albumin excretion rate from baseline to week 20 was the primary end point. Adjusted week 20 baseline geometric ratios for ramipril plus irbesartan and ramipril plus placebo were not significantly different. Although differences in blood pressure reductions were observed between the two treatments, these changes did not affect microalbuminuria. More patients on dual therapy achieved target blood pressure goals at week 20 than with monotherapy. The incidence of adverse effects and treatment-related adverse effects was similar in both groups. Our results suggest that patients with cardiovascular risk and relatively low albumin excretion rates in early-stage disease may only require monotherapy with renin–angiotensin–aldosterone blocking agents.

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Albuminuria is common in hypertensive and diabetic patients and, independent of diabetes or renal function impairment, is also an indicator of decreased kidney function, increased cardiovascular (CV) risk, and a predictor of both morbidity and mortality.[1–5] In individuals with high CV risk, the presence of even small quantities of albumin in urine, or microalbuminuria (MAU), is an independent predictor of poor CV prognosis.[6,7] Since the association between MAU, albuminuria, and CV risk is continuous, early and effective intervention to halt the loss of kidney function—thereby improving long-term CV prognosis—is imperative. *Post hoc* analyses of data from the HOPE, LIFE, RENAAL, IDNT, and AASK studies have demonstrated quite clearly that a reduction in albuminuria correlated, in a wide range of different hypertensive patients, with a decrease in the risk of end-stage renal disease, CV events, and death.[8–12] Baseline proteinuria is also an indicator of long-term prognosis.

Although blood pressure reduction remains the gold standard for CV and renal protection,[13] blood pressure control even within strict targets does not completely eliminate albuminuria and MAU in hypertensive patients. This has led to an increased focus on therapeutic strategies designed toward optimal reduction of MAU in addition to tight blood pressure control.

Agents such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, that block the renin–angiotensin–aldosterone system (RAAS), have been shown to reduce MAU more effectively in high-risk patients than non-RAAS-targeted therapies[14,15] and are currently recommended as part of an antihypertensive regimen in diabetic and non-diabetic patients with renal impairment.[13,16] Their renoprotective and cardioprotective effects are believed to act at least in part independently of systemic blood pressure control.[17–19]

Furthermore, evidence from the converting enzyme inhibitor in non-diabetic renal disease (COOPERATE) trial has suggested that, in combination, an ACE inhibitor and

angiotensin receptor blocker can achieve significant additional reductions in advanced macroalbuminuric kidney disease to that achieved with either agent alone, at least in patients with high levels of proteinuria.[20,21] A total of 11% of patients on combination therapy ($n=85$) reached the combined primary end point (time to doubling of serum creatinine concentration or end-stage renal disease) compared with 23% on trandolapril alone (hazard ratio (HR) 0.38, 95% confidence interval (CI) 0.18–0.63, $P=0.018$; $n=85$) and 23% on losartan alone (HR 0.40, 95% CI 0.17–0.69, $P=0.016$; $n=85$).

The Irbesartan in the Management of PROteinuric patients at high risk for Vascular Events (IMPROVE) study was a large, randomized controlled trial designed to determine whether combination therapy with the ACE inhibitor ramipril and angiotensin receptor blocker irbesartan was more effective than ramipril alone in reducing albumin excretion rate (AER) in hypertensive patients at high CV risk and with evidence of MAU despite prior treatment with ACE inhibitors.

RESULTS

Patient disposition

A total of 838 patients were enrolled in the study, 405 of whom were randomized; 204 to ramipril plus irbesartan and 201 to ramipril plus placebo (see Figure 1 for CONSORT diagram). Most patients who were enrolled but not randomized did not meet AER criteria after placebo lead-in. Of the 405 patients randomized to double-blind therapy, 369 (91.1%) completed the study. In total, 20 (9.8%) and 16 (8.0%) patients in the ramipril plus irbesartan and ramipril plus placebo groups, respectively, discontinued study medication. Adverse events were the main reason for discontinuation, accounting for 7 (3.4%) and 10 (5.0%) premature withdrawals in the ramipril plus irbesartan and ramipril plus placebo groups, respectively. Equivalent numbers of patients in both treatment arms received the highest titrated dose of study medication.

Baseline characteristics

Treatment groups were similar at baseline with respect to demographics and medical history (Table 1). Patients (mean age of 65.7 years) were predominantly male (62.0%), white (93.1%), and diabetic (89.1%). All patients reported a CV history and risk factors, and all but one patient had a history of hypertension. Baseline mean seated blood pressures were 163/90 mm Hg and 164/89 mm Hg in the ramipril plus irbesartan and ramipril plus placebo groups, respectively. With one exception, all randomized patients reported prior ACE inhibitor use (99.8%); treatment with enalapril (126/405, 31.1%) and ramipril (104/405, 25.7%) was most common. In the majority of patients (71.1%), diabetes was the primary cause of MAU. Table 2 shows baseline geometric means for AER for patients in the two treatment groups.

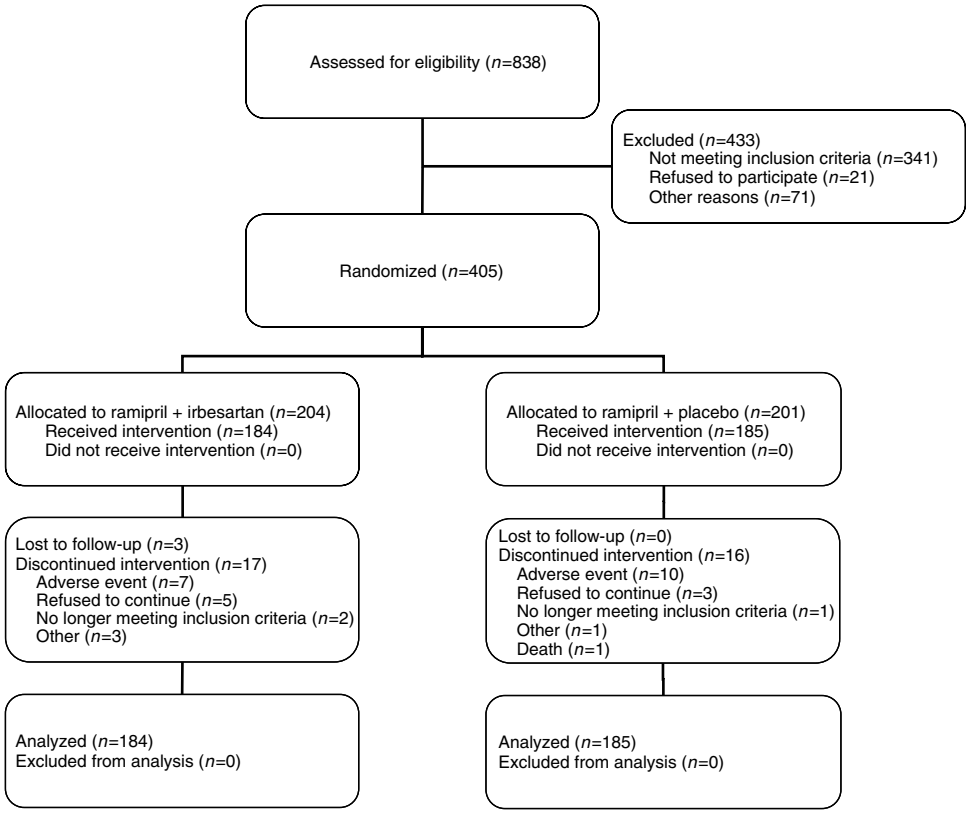

Figure 1 | CONSORT diagram for the IMPROVE study.

Table 1 | Patient demographics and medical history at baseline (randomized patients)

	Treatment group	
	Ramipril plus irbesartan (*n*=204)	Ramipril plus placebo (*n*=210)
Male/female (%)	123/81 (60.3/39.7)	128/73 (63.7/36.3)
Mean age (range) years	65.6 (54–91)	65.8 (54–82)
Race no. (%)		
White	186 (91.2)	191 (95.0)
Black/African American	3 (1.5)	3 (1.5)
Asian	6 (2.9)	1 (0.5)
Other	9 (4.4)	6 (3.0)
Mean weight (range) kg	86.9 (54–145)	87.6 (55–148)
Medical history		
Hypertension (%)	204 (100)	200 (99.5)
Type II diabetes (%)	176 (86.3)	176 (87.6)
Mean duration ± s.e. (years)	11.3 ± 7.8	10.1 ± 8.0
Type I diabetes (%)	7 (3.4)	2 (1)
Mean duration ± s.e. (years)	23.1 ± 14.7	7.1 ± 4.4
Hypercholesterolemia (%)	132 (64.7)	132 (65.7)
Stable angina pectoris (%)	68 (33.3)	70 (34.8)
Myocardial infarction (%)	41 (20.1)	41 (20.4)
Peripheral vascular disease (%)	23 (11.3)	28 (13.9)
Current smoker (%)	27 (13.2)	20 (10.0)
Unstable angina pectoris (%)	17 (8.3)	21 (10.4)
Stroke (%)	17 (8.3)	19 (9.5)
TIA (%)	8 (3.9)	11 (5.5)
Primary cause of albuminuria		
Diabetes (%)	156 (76.5)	132 (65.7)
Hypertension (%)	44 (21.6)	68 (33.8)
Non-diabetic/non-hypertensive renal disease (%)	2 (1.0)	0 (0)
Unknown (%)	2 (1.0)	1 (0.5)
Mean duration albuminuria (range) months[a]	33.91 (−0.16 to 177.8)	27.32 (−3.61 to 327.9)

TIA, transient ischemic attack.
[a]Duration of albuminuria was calculated as: (date of informed consent–date of diagnosis +1)/30.4375. Two subjects had negative values because they were diagnosed with albuminuria after screening.

Table 2 | AER at baseline in the ramipril plus irbesartan and ramipril plus placebo groups (geometric mean ± s.e. μg/min)

	Treatment group	
	Ramipril plus irbesartan (n=204)	Ramipril plus placebo (*n*=201)
All patients (*n*=204/201)	101.9 ± 7.40	106.12 ± 7.45
Microalbuminuric (<200 μg/min) patients only (*n*=145/137)	58.91 ± 3.12	61.28 ± 3.39
Overt nephropathy (⩾200 μg/min) patients only (*n*=59/64)	391.77 ± 20.43	343.80 ± 18.42

AER, albumin excretion rate.

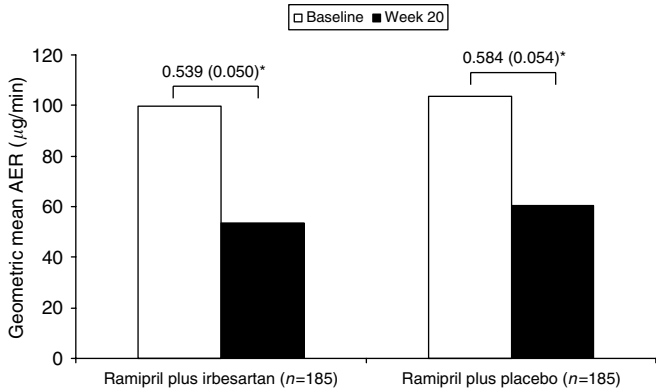

Figure 2 | Adjusted geometric mean AER from baseline to week 20 (excluding patients with AER below 20 μg/min (randomized patients)). *Indicates adjusted geometric mean ratio (± s.e.). Treatment difference (ratio of adjusted geometric mean ratios) = 0.922 (95% CI 0.711–1.195; $P = 0.54$).

Efficacy

AER baseline geometric means for subjects included in the primary efficacy analysis were 99.6 and 103.4 μg/min in the ramipril plus irbesartan and ramipril plus placebo groups, respectively (Figure 2). Adjusted baseline to week 20 geometric mean ratios were 0.539 for the ramipril plus irbesartan group, a 46% decrease, and 0.584 for the ramipril plus placebo group, a 42% decrease (Figure 2). The treatment difference (ratio of the adjusted mean ratios) was 0.922 ($P = 0.540$) with a 95% CI of 0.711–1.195. Thus, the combination of ramipril plus irbesartan was no more effective in reducing AER than ramipril plus placebo. Results showed that the ramipril plus irbesartan adjusted geometric mean ratio was 7.8% less than the adjusted mean ratio for ramipril plus placebo. However, the 95% CI for the point estimate was wide indicating that the actual ramipril plus irbesartan adjusted geometric mean ratio was anywhere from 28.9% less to 19.5% greater than that for ramipril plus placebo. Furthermore, the actual s.d. for the primary AER analysis was 1.27 and much higher than the s.d. of 0.73 used in the planning of the study.[22]

Results for the two secondary, supportive analyses were consistent with the primary efficacy analysis. No earlier post-randomization data were collected for the first of these analyses and in the second, the inclusion of subjects with an AER of <20 μg/min had no significant effect on the results. The study population contained only three patients with an AER of <20 μg/min.

Subgroup analyses based on baseline AER classification showed that for patients with MAU there was no clinically significant difference between treatments (Figure 3). In contrast, for subjects with overt nephropathy (baseline AER ⩾200 μg/min), the geometric mean AER ratio, comparing week 20 to baseline between treatment groups, was larger, suggesting the possibility that dual RAAS blockade provides greater reduction of albuminuria in patients with overt nephropathy. However, as this group included only 108 patients and the 95% CIs were large in both treatment groups, these results must be interpreted with caution. Change in AER from baseline to week 20 in patients with type II diabetes showed that AER was also reduced in this subgroup (Figure 3).

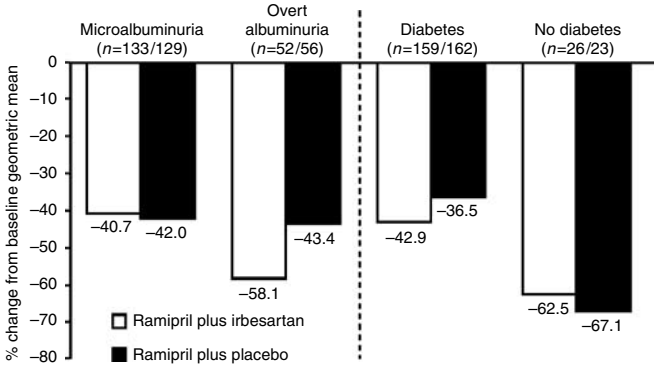

Figure 3 | Percentage change in AER from baseline to end point (week 20) in the ramipril plus irbesartan and ramipril plus placebo groups by patient subgroup.

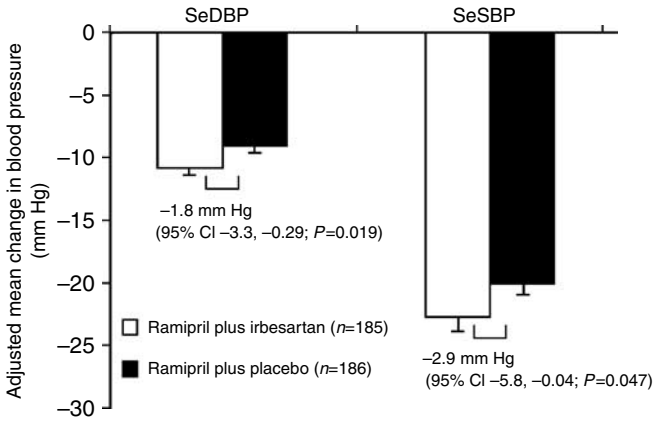

Figure 4 | Mean change in blood pressure from baseline at 20 weeks. Adjusted mean change from baseline to week 20 in trough (**a**) SeDBP and (**b**) SeSBP. Mean baseline blood pressures measurements were 162.9/89.9 and 163.3/89.3 for the ramipril plus irbesartan and ramipril plus placebo groups, respectively.

Both treatment groups experienced reductions in blood pressure over the 20-week double-blind treatment period (Figure 4). Although relatively small, the reduction in both diastolic (DBP) ($P = 0.019$) and systolic blood pressure (SBP) (0.047) was significantly greater in patients receiving ramipril plus irbesartan compared with those receiving ramipril plus placebo. At week 20, more patients in the ramipril plus irbesartan group achieved study target blood pressure of $<130/80$ and $<140/90$ mm Hg compared with those on ramipril and placebo (17.3 vs 10.8% and 51.9 vs 35.5%, respectively). No significant difference was observed in trough seated diastolic blood pressure (SeDBP) or seated systolic blood pressure (SeSBP) between the treatment groups in relation to baseline AER or with respect to type II diabetes (data not shown).

Use of concomitant antihypertensive therapy increased similarly in both groups from the end of the placebo lead-in to the end of the study. At the end of the placebo lead-in, 98 (48%) patients in the ramipril plus irbesartan group were using antihypertensive medication compared with 113 (56.2%) patients in the ramipril plus placebo group. This increased to 121 (59.3%) and 136 (67.7%) patients, respectively, by the end of the study. β-Blockers and calcium channel blockers were the most commonly used antihypertensives other than study medication.

Table 3 | Frequency of treatment-emergent adverse events and marked laboratory abnormalities (⩾2%)

	Treatment group	
	Ramipril plus irbesartan (*n*=204)	Ramipril plus placebo (*n*=210)
Treatment-emergent adverse events, n (%)		
Total	87 (42.6)	85 (42.3)
Dizziness	8 (3.9)	2 (1.0)
Headache	6 (2.9)	12 (6.0)
Hyperkalemia	6 (2.9)	6 (3.0)
Influenza	6 (2.9)	5 (2.5)
Back pain	5 (2.5)	2 (1.0)
Upper RTI	5 (2.5)	4 (2.0)
Nasopharyngitis	5 (2.5)	2 (1.0)
Cough	4 (2.0)	3 (1.5)
Diarrhea	4 (2.0)	6 (3.0)
Dyspnea	4 (2.0)	0 (0.0)
Nausea	4 (2.0)	1 (0.5)
Hypertension	3 (1.5)	7 (3.5)
Peripheral edema	3 (1.5)	4 (2.0)
Acute MI	0 (0)	4 (2.0)
Clinical chemistry, n (%)		
High serum glucose	8/187 (4.3)	1/180 (0.6)
High potassium	3/195 (1.5)	5/194 (2.6)
High creatinine	5/194 (2.6)	6/194 (3.1)

MI, myocardial infarction.

Safety and tolerability

The addition of irbesartan to ramipril therapy was well tolerated by patients in this study. Only seven (3.4%) patients in the ramipril plus irbesartan group discontinued therapy because of adverse events compared with ten (5.0%) in the ramipril plus placebo group. The overall incidence of adverse events and of treatment-related adverse events was similar in the two treatment arms (Table 3). Hyperkalemia was among the most frequently reported treatment-related adverse events, affecting 2.5% of patients in both treatment groups. Serious adverse events were infrequent and in the majority of cases judged unrelated to study medication. Two patients in the ramipril plus irbesartan group experienced serious adverse events that may have been related to study drugs; one patient experienced moderate acute renal failure, and the second moderate urticaria. One patient in the ramipril plus placebo group died from circulatory collapse during the study, but this was not attributed to study medication.

High serum glucose, potassium, and creatinine were the most frequently reported clinical laboratory abnormalities (Table 3). However, mean changes from baseline to week 20 in creatinine and potassium were similar and minimal in the two treatment groups; 0.04 mg/dl and 0.03 mEq/l in the ramipril plus irbesartan group and 0.02 mg/dl and 0.0 mEq/l in the ramipril plus placebo group, respectively.

DISCUSSION

IMPROVE was a multicenter, randomized, double-blind, parallel arm study designed to compare the antiproteinuric effects of once-daily treatment of dual RAAS blockade with irbesartan and ramipril in patients at elevated CV risk relative to those who were receiving treatment with ramipril alone. Secondary objectives were to compare the change from baseline in SeDBP and SeDBP within and between treatment groups, and to characterize the safety profile of the two treatment strategies.

As the results of the study showed, dual RAAS blockade with ramipril and irbesartan did not reduce MAU to a greater extent than treatment with ramipril alone. There was marked variability in AER values between patients, with the 95% CI for the primary efficacy analysis much wider than anticipated. As such, the result obtained does not 'prove' a lack of benefit. Numerically, the largest absolute difference between study arms with respect to albuminuria reduction occurred in the subgroup of patients with overt nephropathy (macroalbuminuria). However, they represented fewer than one-third of the total study population. With the caveat that there were only 108 patients in this subgroup and the 95% CIs were large, this observation is nonetheless consistent with previous studies that have suggested that the effect of RAAS blockade may depend on the prevailing level of albuminuria.[20,21,23] In any case, researchers designing trials to assess strategies to treat MAU should be aware of the substantial variability in this condition in the target population.

Results of IMPROVE suggest that patients with early-stage disease and a relatively low AER may only require monotherapy with RAAS-blocking agents and that dual blockade may provide improved reductions in AER in people with macroalbuminuria, most of whom were likely to have diabetic nephropathy in this study.

Significant DBP and SBP reductions were observed in patients receiving ramipril plus irbesartan compared with the ramipril plus placebo group. Responder rates were also higher in patients receiving combination therapy compared with ramipril alone. Both the JNC-7 and ESH guidelines recommend first-line combination therapy for patients with blood pressures of 20/10 mm Hg above goal—patients with moderate or severe hypertension.[13,16] A majority of patients in IMPROVE required concomitant blood pressure-lowering therapies to try and attain goal and usage increased during the study and to a similar extent in both treatment groups.

Dual RAAS blockade with irbesartan and ramipril was safe and well tolerated by patients in this study, with the incidence of adverse events and treatment-related adverse events similar in the two treatment groups. The frequency of adverse events typically associated with RAAS blockade, such as hyperkalemia and increased serum creatinine, was also similar in the two groups. In fact, the observed increases in serum potassium and creatinine were consistent with what is expected from treatment with ACE inhibitors.

IMPROVE was designed specifically to determine whether the combined use of irbesartan and ramipril was more effective than ramipril alone in reducing AER in hypertensive patients with albuminuria and high global CV disease risk. Providing similar blood pressure, control was achieved in both treatment groups; it was assumed that any difference that emerged with respect to reductions in albuminuria would likely reflect differences in the therapeutic model of RAAS blockade working independently of blood pressure control.[22] As our results show, the study failed to meet its primary end point. It is important to stress that the study had a number of limitations, not least the fact that the study ended up being underpowered—despite careful planning—and that it failed to recruit patients with high levels of albuminuria. Indeed, while the majority of patients had MAU, the study population had overall lower MAU levels than those reported for most of the trials looking at the effects of RAAS blockade. Conducted over a 20-week period, the study may still have been too short to demonstrate a positive treatment effect on MAU in the combination treatment arm. In AASK, changes in MAU and overt albuminuria were not evident until patients had received treatment for at least 6–12 months.[24,25] Finally, the lead-in washout phase was short at only 14 days, which may not have been long enough for albuminuria to return to maximum levels before the active-treatment phase of the study. It would have been unethical to withhold active treatment for any longer, but this decision means that the study results may have been affected.

It is known that AER rates can vary according to sex and race; for example, men and Blacks found to have higher rates in general than women or Whites.[26] With over 90% of patients being classified as White, any effect of race on the study results is highly unlikely, although the conclusions of the trial can therefore only be applied with confidence to this particular ethnic group. IMPROVE enrolled men and women in a 3:2 ratio, respectively; as men generally have higher AER values, the unadjusted overall rates observed in this study may have been artificially increased. However, since the proportion of men to women was comparable between treatment groups, this factor should not have affected the major findings.

In conclusion, the IMPROVE study failed to demonstrate that dual RAAS blockade with irbesartan and ramipril over 20 weeks provides better albuminuria reduction than ramipril alone. These findings suggest that patients with CV risk and relatively low AER in early-stage disease may only require monotherapy with RAAS blocking agents. However, for the treatment of hypertension, combination achieves greater blood pressure reduction.

MATERIALS AND METHODS

The design and methodology of the IMPROVE trial has been described in detail previously.[22] In summary, eligible patients included men and women aged $\geqslant$55 years with an elevated CV risk and documented history of hypertension ($>$140/90 mm Hg)

and albuminuria, as well as receiving treatment with an ACE inhibitor (dosage equivalent to $\geqslant$5 mg ramipril) for a minimum of 2 months before study entry. Increased CV risk was defined as the presence of diabetes, advanced coronary artery disease (previous myocardial infarction, unstable angina, or angina pectoris), peripheral vascular disease, or cerebrovascular accident. Before randomization into the active treatment phase, a confirmed AER of 20–700 μg/min in two consecutive overnight urine collections and a SBP $\geqslant$150 mm Hg and/or a DBP $\geqslant$95 mm Hg was required.

The major exclusion criteria were SBP $<$115 or $\geqslant$200 mm Hg and/or DBP $\geqslant$115 mm Hg; febrile disease, urinary tract infection, documented uncontrolled diabetes (HbA1c $\geqslant$10%), acute glomerulonephritis, or other conditions affecting proteinuria; renovascular disease or renal insufficiency; concurrent congestive heart failure; chronic autoimmune disease; or malignancy. While pregnant or lactating women were not eligible to participate, those of childbearing potential could take part providing they had a negative pregnancy test at enrollment and were using an approved method of contraception.

Institutional and Ethical Review Board approval for the study protocol was granted at all participating centers, and all patients gave written informed consent before entry into the study. The study was conducted in accordance with the ethical principles of the current Declaration of Helsinki Principle and consistent with the International Conference on Harmonization Good Clinical Practice.

Study design and treatment

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group 20-week study, in which eligible patients were randomized to ramipril (10 mg) plus irbesartan (150–300 mg) or ramipril (10 mg) plus placebo, following a 14-day placebo lead-in period.[22] During this time, patients discontinued or tapered previous ACE inhibitor and other antihypertensive therapy. In this elevated CV risk population, patients receiving β-blockers or calcium channel antagonists for reasons other than hypertension, for example coronary artery disease, continued stable dosing during the placebo lead-in period. At the end of this period (week 0), all eligible patients received open-label ramipril (5 mg once daily), titrated to 10 mg at week 1.

At week 0, patients were also randomized in a 1:1 ratio to irbesartan or placebo. In the irbesartan arm, following 2 weeks of placebo to enable safe titration to target ramipril dose, irbesartan was initiated at week 2 (150 mg once daily) for 2 weeks and then titrated to 300 mg for the remaining 16 weeks of the study. Patients unable to tolerate titration to maximal dose irbesartan or matching placebo had their dosage tapered to the lower dose of irbesartan. The control arm received ramipril plus placebo for the entire 20-week treatment period.

During the active treatment phase, patients were set a blood pressure goal of $<$130/80 mm Hg. To achieve and sustain this goal, adjunctive antihypertensive therapy, excluding ACE inhibitors and angiotensin receptor blockers, was permitted once patients had been randomized to double-blind treatment and titrated to the highest dose of study medication.

Efficacy assessments

All patients randomized to study medication were included in the analyses of efficacy; patients with an AER below 20 μg/min, when averaged over the two baseline qualifying measurements, were excluded from the primary analysis (see statistical analyses). The primary efficacy outcome measure was the change in AER from baseline to week 20. AER was measured in two timed overnight urine collections performed at baseline (days 12 and 13) and before study completion at week 20. As described previously,[22] all urine samples were analyzed at a central laboratory to ensure assay consistency. AER was calculated using the following formula: AER (μg/min) = urine microalbumin (mg/l) $\times$ 1/1000 (l/ml) $\times$ 1000 (μg/mg) $\times$ (urine volume/collection period (ml/h)) $\times$ 0.0166 (h/min).

Secondary efficacy outcome measures were the change from baseline to week 20 in SeSBP and SeDBP. Blood pressure measurements were performed at all study visits from screening to days 7 and 14 of the placebo lead-in phase and weeks 0, 1, 2, 4, 6,12, and 20 of the active treatment phase. Mean SeSBP and mean SeDBP values were calculated from three consecutive readings.

Safety and tolerability assessments

All patients who received at least one dose of double-blind study medication were included in the safety analysis. Safety was assessed throughout the study with respect to the nature, frequency, and severity of adverse events, and their relationship to study medication as well as frequency of discontinuations due to adverse events. Other safety measures included clinically relevant changes from baseline to final physical examination in vital signs and changes from baseline to end point in clinical laboratory tests.

Statistical analyses

Details of the statistical procedures used in the IMPROVE trial have been described previously.[22] In summary, change from baseline in AER at week 20 was analyzed (with baseline and on-therapy values transformed to their natural logarithms), using an analysis of covariance—consisting of treatment as the main effect and the baseline (log) value as covariate—to compare the ramipril plus irbesartan and ramipril plus placebo groups. Change in either group was expressed as a geometric mean ratio of week 20 to baseline. With approximately 200 subjects randomized to each treatment arm, the study had more than 80% power to detect a 20% reduction in the geometric mean ratio for irbesartan relative to placebo, if such a difference truly existed. This sample size included allowance for a 10% dropout rate and assumed an s.d. of 0.73 natural logarithm units for the logarithmically transformed ratio of post- to baseline AER and two-sided testing at an α-level of 0.05 for the primary analysis.

Baseline differences in characteristics were not examined statistically. If any clinically relevant differences were observed between groups at baseline, a secondary supportive analysis of the primary efficacy variable would have been carried out, adjusting for the imbalance in any such characteristics.

In addition to the primary analysis of AER, two secondary, supportive analyses were carried out. The first included randomized patients with a baseline AER of $<$20 μg/min. The second was a last observation carried forward analysis that included all randomized subjects except those with an AER of $<$20 μg/min. Thus the primary analysis included data from all subjects who returned an AER result within a very broad window of time around the week 20 visit, with the exception of patients who had normal albumin excretion at baseline ($<$20 μg/min) and were prospectively excluded from the primary analysis. The two prospective supportive analyses put potentially excluded data back into the analysis simply to gauge the effect of that data on the results. This approach is similar to that used in the analysis of AER data in both the CALM Ref.[27] and COOPERATE[20,21] studies.

Changes from baseline in SeSBP and SeDBP at week 20 were also analyzed using analysis of covariance to compare the ramipril plus irbesartan and ramipril plus placebo groups. The analysis model consisted of treatment as the main effect and baseline value as covariate. The covariate-adjusted difference between treatment groups was tested at the two-sided 5% significance level.

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Conflict of interest: GB and MW have served as consultants and speakers for Bristol-Myers Squibb and sanofi-aventis. LR has served as a consultant and speaker for Bristol-Myers Squibb. FL has received honoraria for lectures and grants for drug registrations studies from Bristol-Myers Squibb and sanofi-aventis.

Clinical trials registry: This study has been registered on the clinicialtrials.gov website (Identifier: NCT00095290).

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