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Candesartan versus imidapril in hypertension: a randomised study to assess effects of anti-AT1 receptor autoantibodies

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ABSTRACT

Background Anti-angiotensin II receptor subtype 1 (AT1 receptor) autoantibodies have previously been shown in sera of hypertensive patients. This study assessed whether anti-AT1-receptor autoantibody in serum is correlated with the efficacy of an AT1-receptor blocker (ARB; candesartan)-based regimen in hypertensive patients after 8 weeks of treatment.

Design The Study of Optimal Treatment in Hypertensive Patients with Anti-AT1-Receptor Autoantibodies is a multicentre, randomised, blinded endpoint, open-label, parallel-group comparison clinical trial conducted in five centres in Wuhan, China. Treatment is designed as stepwise added-on therapy to reduce blood pressure (BP) <140/90 mm Hg. 512 patients with moderate to severe primary hypertension were randomly assigned to an 8-week treatment with either ARB (candesartan)-based regimen (n=257) or ACE inhibitor (imidapril)-based regimen (n=255).

Results Systolic and diastolic BP was reduced significantly in both treatment groups. The candesartan-based regimen achieved a significantly greater systolic BP reduction than imdapril (30.8±10.3 vs 28.8±10.3 mm Hg, p=0.023). In those anti-AT1 receptor autoantibody-positive hypertensive patients, the mean systolic BP at baseline was higher than in the anti-AT1 receptor autoantibody-negative group (160.5±16.5 vs 156.2±17.7 mm Hg; p=0.006). The mean BP reduction was greater in the candesartan-based regimen than the imidapril-based regimen (−35.4±9.8/16.9±6.9 vs −29.4±9.8/14.2±6.9 mm Hg; p=0.000 and 0.002, respectively), and more patients on imidapril required add-on medications to achieve BP control (94% vs 86%; p=0.03). No correlation was observed between the titre of anti-AT1 receptor autoantibody and the efficacy of candesartan-based therapy. In those anti-AT1 receptor autoantibody-negative patients similar BP lowering was reached in the candesartan and the imidapril-based regimens.

Conclusions An ARB-based regimen is more effective in BP lowering than an ACE inhibitor-based regimen in the presence of anti-AT1 receptor autoantibodies.

Trial registration number This trial has been registered at http://www.register.clinicaltrials.gov/ (identifier: NCT00360763).

The pathogenesis of hypertension is multifactorial. Patients with different underlying mechanisms may respond differently to standard antihypertensive therapy. Therefore, a tailored therapy is needed to improve outcome. Hitherto the immune system has been assumed to be involved in hypertension.[1 2] For instance, autoantibodies against α_1-adrenergic receptor and angiotensin II receptor subtype 1 (AT1 receptor) were previously described by Fu and colleagues[3 4] in patients with malignant hypertension. Moreover, we have demonstrated anti-AT1 receptor autoantibodies in approximately 42.9% of patients with refractory hypertension.[5] Furthermore, the experimental studies in vitro and in vivo showed that AT1 autoantibodies were able to exert a stimulatory effect similar to angiotensin II and this effect could be blocked by AT1-receptor blockers (ARB).[6] Being similar to angiotensin II, AT1 autoantibodies may initiate a chain of signalling events including the proliferation of vascular smooth muscle cells[7] and vascular remodelling[8] and then promote end-organ damage, contributing to the development of hypertension. In an earlier pilot clinical trial,[9] we found that ARB lowering blood pressure (BP) were superior to ACE inhibitors in those AT1 autoantibody-positive patients with refractory hypertension (n=26) for 6 months, in which the mean reduction of BP was 12.8±4.3 mm Hg in the ARB group and 7.2±3.5 mm Hg in the ACE inhibitor group, p<0.05. Therefore, the present study was designed to confirm in a larger population whether ARB are more effective in lowering BP in the presence of AT1 autoantibodies.

MATERIALS AND METHODS

Study objective

The objective of the Study of Optimal Treatment in Hypertensive Patients with Anti-AT1-Receptor Autoantibody (SOT-AT1) was to assess whether the AT1 autoantibodies in serum were the influencing factor of ARB (candesartan)-based therapy. The primary analysis of SOT-AT1 was to assess whether the endpoint of BP were to achieve the goal in both ARB (candesartan)-based and ACE inhibitor (imidapril)-based regimens after 8 weeks of treatment. The secondary analysis of SOT-AT1 was to assess whether the AT1 autoantibodies in serum were the influencing factor in ARB (candesartan)-based therapy.

Study design

The SOT-AT1 study was a multicentre, randomised, blinded endpoint, open-label, parallel-group comparison clinical trial conducted in five centres in Wuhan, China. The Institute of Cardiology, Union Hospital, Tongji Medical College, Huazhong

University of Science and Technology was responsible for developing the study protocol and case report forms, and data management was maintained in the Institute of Clinical Pharmacology, Tongji Medical College, Huazhong University of Science and Technology. The protocol was approved by the medical ethics committees of Tongji Medical College. Informed written consent was obtained from each patient before the trial. The first participant was enrolled on 1 September 2006, and the last participant completed the study on 28 February 2008.

Inclusion criteria

1. Age 18 years or older, either sex.
2. Moderate to severe essential hypertension defined as the following: subjects who meet with one of the following three categories were eligible for the study:
   i. patients with moderate to severe essential hypertension (sitting systolic BP ≥160 mm Hg, diastolic BP ≥100 mm Hg, or both) who were untreated;
   ii. patients who had previous treatment with other antihypertensive drugs such as diuretics, calcium antagonists or β-blockers (but not renin–angiotensin system inhibitors) before enrolment still having high BP (sitting systolic BP >140 mm Hg, diastolic BP >90 mm Hg, or both).
3. Patients who had been treated either by ACE inhibitors or ARB entered a washout period of up to 7 days, and then the BP was greater than 140/90 mm Hg.

Exclusion criteria

1. Known secondary hypertension.
2. Sensitivity or contraindication to any of ACE inhibitors or ARB.
3. Life-threatening arrhythmia, heart failure (New York Heart Association class II–IV), severe coronary heart disease.
4. Clinically significant valvular heart disease or congenital cardiovascular disease.
5. Cerebrovascular event, myocardial infarction, cardiac revascularisation procedure including coronary angioplasty and coronary bypass surgery within 3 months before study recruitment.
6. Active hepatic disease: aspartate aminotransferase or alanine aminotransferase value more than two times (alanine aminotransferase >70 U/l, aspartate aminotransferase >80 U/l), history of hepatic encephalopathy or portal hypertension.
7. Renal insufficiency: serum creatinine level higher than 195 μmol/l (2.2 mg/dl), history of haemodialysis, nephritic syndrome.
8. Serum potassium outside normal range (3.5–5.3 mmol/l).
9. Type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus (glycated haemoglobin >8.0%).
10. Drug or alcohol abuse within the past 2 years.
11. Psychiatric disorders or dementia.
12. Low likelihood of compliance with protocol.
13. Current participation in another clinical trial.
14. Woman of childbearing age not able to use a reliable method of birth control (such as condom or prevenception utensil), pregnancy, lactation.
15. Severe systemic or malignant disease within the past 5 years.
16. Other contraindications for safety reasons.

Measurements of BP and heart rate

For each patient, BP was measured in the same arm by the same physician throughout the trial. BP was measured by standard sphygmomanometers with appropriately sized cuffs in the seated position at all visits after a minimum of 5 min at rest. Phase 1 and 5 of the Korotkoff sounds were considered to represent systolic and diastolic BP, respectively. The mean of three readings taken 1–2-min apart was used as BP at visit. Heart rate was determined by a 60 s count before the BP measurement. BP and heart rate were measured at each visit, 24 h after the dose for once-daily administration of candesartan or imidapril.

ELISA assay of AT1 autoantibodies

AT1 autoantibodies were determined by the ELISA method as described previously.[5] AT1 autoantibody is reported as titres at 1:40, 1:80 and 1:160 dilutions.

Data collection

Baseline characteristics were recorded during the run-in period. Each patient underwent routine laboratory testing and 5 ml venous blood samples were collected in tubes containing heparin sulphate before treatment. After centrifugation at 4°C, plasma was immediately frozen and stored at −80°C until analysis. All AT1 autoantibody assays were performed at the cardiovascular immunological laboratory of Union Hospital and were done blindly to treatment at the end of the study. According to the AT1 autoantibody assays, patients were further divided into a positive or negative subgroup.

Therapy procedure

The BP goal for all participants was less than 140/90 mm Hg. At the beginning of the study, allocation numbers were associated with treatment groups created by a computerised random number generator; an investigator transferred allocations to opaque envelopes, which were numbered in sequence; these envelopes were then held and opened in the order of the sequence number by a certain member of the research team in every centre. According to this scheme, patients randomly received open-label candesartan 8 mg or imidapril 5 mg once a day for 2 weeks, and then they were seen at 2-week intervals thereafter until the 8-week visit. During each follow-up visit, adverse events, concomitant medication and compliance with study medication were recorded. The regimen was stepwise combination therapy according to the protocol during subsequent visits. If the BP was higher than the target level, additional drugs were prescribed in three further steps: adding hydrochlorothiazide 12.5 mg/day at the second visit (step 2); adding felodipine 5 mg/day at the third visit (step 3) and adding metoprolol 50–100 mg/day at the fourth visit (step 4) when necessary.

Safety assessment

The safety and tolerability of drugs were evaluated based on clinical adverse events, laboratory abnormalities, changes from baseline in standard safety laboratory analysis, and changes in physical examinations. A serious adverse event was an adverse event that was fatal, life-threatening, or permanently disabling and that required or prolonged inpatient hospitalisation, or was a clinically significant disease such as cancer. All randomly assigned subjects who received at least one dose of medication were included in the analyses. The incidence of adverse events was tabulated by treatment group, according to severity and to relationship to study drug. Differences in the frequency of adverse events were analysed with the χ^2 test.

Statistical methods

Data management and analysis were performed using SPSS 10.0 software. The intent-to-treat (ITT) population included all

patients who were randomly assigned to the study. For this approach, last-observation-carried-forward methods were applied for the replacement of missing values. The per-protocol (PP) population included all patients who completed the study and had no major protocol deviation. The statistical analyses for efficacy were performed on an ITT basis unless otherwise indicated. Treatment groups and subgroups designated as AT1 autoantibody positive or negative were analysed using the analysis of covariance model including treatment as fixed effect and baseline BP as covariate. Because both systolic and diastolic BP were compared between the two treatment groups, to allow for two primary efficacy parameters, a Bonferroni correction was prespecified and a significance level of 0.025 was assigned for each endpoint. Baseline characteristics were compared between the subgroups using χ^2 tests for categorical variables or the unpaired t test for continuous variables. A general linear model was used to identify the relevant interactions between treatment and serum AT1 autoantibody titres. All of the statistical tests were two-sided with an α level of 0.05 except when mentioned above.

The sample size calculation was based on the ability to detect a 5 mm Hg difference in office cuff systolic BP between the subgroups after 8 weeks. With a two-tailed α of 0.05 and a SD of 12 mm Hg, 99 patients per subgroup provided 80% power to detect such a difference. Assuming a dropout rate of 10%, a tentative sample size of 440 patients (110 in each subgroup) was calculated.

RESULTS

Patient participation

Of the 530 recruited patients, 512 patients meeting all inclusion criteria were randomly assigned: 257 in the candesartan-based regimen and 255 in the imidapril-based regimen (ITT database). Nine patients randomly assigned to the candesartan-based regimen and five patients randomly assigned to the imidapril-based regimen were lost during follow-up. In addition, five patients randomly assigned to the candisartan-based regimen and 14 patients randomly assigned to the imidapril-based regimen discontinued because of side effects. As a result, 243 remained in the candesartan-based regimen and 236 in the imidapril-based regimen (PP database). All randomly assigned participants underwent serum evaluation for AT1 autoantibodies. According to the results of the AT1 autoantibodies, patients were further divided into four subgroups: (1) AT1 autoantibody-positive candesartan subgroup (ITT 132, PP 123); (2) AT1 autoantibody-positive imidapril subgroup (ITT 115, PP 106); (3) AT1 autoantibody-negative candesartan subgroup (ITT 125, PP 120); (4) AT1 autoantibody-negative imidapril subgroup (ITT 140, PP 130) (figure 1).

Baseline characteristics

Table 1 summarises the characteristics of patients at baseline. There were no differences in terms of the clinical parameters.

Study outcomes

Primary analysis: systolic and diastolic BP was reduced significantly in both treatment groups. At the last visit attended, a systolic BP of less than 140 mm Hg and a diastolic BP of less than 90 mm Hg was achieved in 82% of the candesartan group and 74% of the imidapril group (p=0.02). The mean BP in the candsartan and imidapril groups at the last visit were 127.7±10.8/78.4±7.4 mm Hg and 129.2±10.9/79.0±8.3 mm Hg, respectively. Systolic BP was reduced by 30.8±10.3 mm Hg in the candesartan group and 28.8±10.3 mm Hg in the imidapril group (difference 2.0 mm Hg; p=0.023); diastolic BP was reduced by 16.0±7.4 mm Hg and 15.0±7.4 mm Hg, respectively (difference 1.0 mm Hg; p=0.119) see table 2.

Secondary analysis: in those AT1 autoantibody-positive hypertensive patients, the mean systolic BP was higher than that in the AT1 autoantibody-negative group at random entry (160.5±16.5 vs 156.2±17.7 mm Hg; p=0.006). In the AT1 autoantibody-positive group, the mean systolic BP was reduced by 35.4±9.8 mm Hg and diastolic BP by 16.9±6.9 mm Hg from

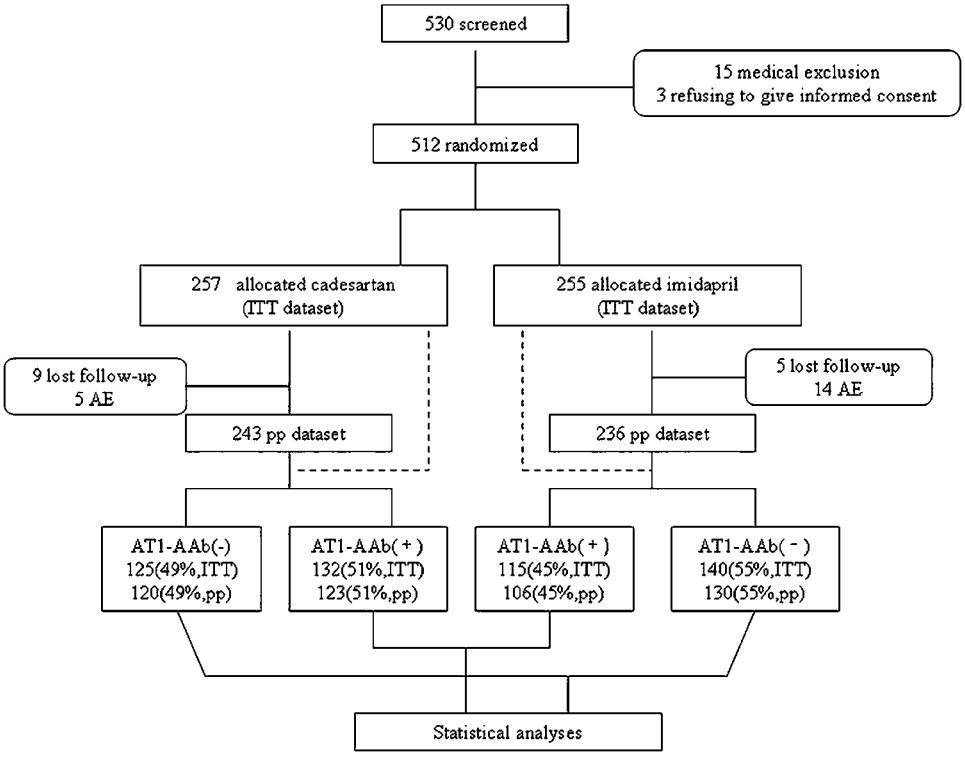

Figure 1 Trial profile. AAb, autoantibodies; AE, adverse events; ITT, intent to treat; PP, per protocol.

Table 1 Baseline characteristics of trial participants

Baseline characteristics	Candesartan		Imidapril	
	AT1 autoantibody (+) n=132	AT1 autoantibody (−) n=125	AT1 autoantibody (+) n=115	AT1 autoantibody (−) n=140
Women (%)	59 (44.7)	48 (38.4)	65 (56.5)	66 (47.1)
Age, years	57.0±13.5	57.4±13.4	58.5±11.9	58.9±12.3
BMI, kg/m^2*	24.9±3.1	24.5±3.1	25.0±2.7	24.5±3.0
SBP, mm Hg	161.1±16.5	157.9±17.1	159.7±16.4	154.7±18.1
DBP, mm Hg	95.0±11.8	95.3±11.8	93.1±11.3	93.6±11.1
Heart rate, bpm	76.4±9.1	78.6±9.8	78.2±9.8	78.6±9.9
Current smokers (%)	23 (17.4)	17 (13.6)	17 (14.8)	25 (17.9)
Severe hypertension† (%)	39 (29.5)	33 (26.4)	24 (20.9)	30 (21.4)
Type 2 diabetes mellitus (%)	7 (5.3)	5 (4.0)	9 (7.8)	7 (5.0)
Cerebrovascular events‡ (%)	8 (6.1)	6 (4.8)	5 (4.3)	8 (5.7)
Cardiac events§ (%)	11 (8.3)	5 (4.0)	8 (7.0)	5 (3.6)
Peripheral atherosclerosis (%)	3 (2.3)	4 (3.2)	2 (1.7)	2 (1.4)
On antihypertensive medication (%)	98 (74.2)	87 (69.6)	92 (80.0)	100 (71.4)

Data are shown as the no of patients (%) or the mean±SD.
*BMI (body mass index) was calculated as weight in kilogrammes divided by height in metres squared.
†Severe hypertension was systolic blood pressure (SBP) ≥180 mm Hg or diastolic blood pressure (DBP) ≥110 mm Hg.
‡History of cerebrovascular events includes cerebral haemorrhage, cerebral infarction and transient ischaemic attack.
§History of cardiac events includes left ventricular hypertrophy, angina pectoris and myocardial infarction.

baseline in the candesartan subgroup, whereas in the imidapril subgroup systolic BP was reduced by 29.4±9.8 mm Hg and diastolic BP by 14.2±6.9 mm Hg. Obviously, both systolic BP and diastolic BP reductions were greater in the candesartan subgroup than that in the imidapril subgroup (p=0.000 and p=0.002, respectively). However, in those AT1 autoantibody-negative subjects BP lowering was similar between the candesaran subgroup and the imidapril subgroup (p=0.156 and p=0.507, respectively) see table 3.

A factor that may influence the interpretation of this study is the number of subjects who required add-on medication to achieve optimal BP control. Fourteen per cent of the subjects in the candesartan subgroup and 6% of those in the imidapril subgroup remained on monotherapy throughout the study. In other words, the percentage of the AT1 autoantibody-positive imidapril-treated patients who required concomitant medication with other antihypertensive drugs was larger than that of the AT1 autoantibody-positive candesartan-treated patients (94% and 86%, respectively; p=0.03).

The AT1 autoantibody-positive subjects in the candesartan-based treatment group were divided into two subgroups according to the titre of AT1 autoantibodies: low titre subgroup (titre of 1:40) and high titre subgroup (titres of 1:80 and 1:160). BP was 161.0±19.1/94.7±11.2 mm Hg at baseline and 125.1±10.2/77.3±7.4 mm Hg after 8 weeks for the low titre subgroup. BP was 161.2±14.1/95.3±12.4 mm Hg at baseline and 125.3±10.5/77.4±7.6 mm Hg after 8 weeks for the high titre subgroup. The mean BP reductions were similar between the two subgroups (35.9±10.0/17.6±7.0 mm Hg vs 36.0±10.0/17.6±7.0 mm Hg, p=0.888 and p=0.975, respectively). The statistical test for interaction between AT1 autoantibody titre and treatment indicates no titre–drug interaction for systolic BP and diastolic BP (p=0.763 and p=0.797, respectively).

Table 2 BP changes between treatment groups throughout the study

Variable	Candesartan	Imidapril
SBP, mm Hg		
Baseline	159.6 (16.8)	156.9 (17.5)
Final visit (mean±SD)	127.7 (10.8)	129.2 (10.9)
Δ from baseline (mean±SD)*	−30.8 (10.3)	−28.8 (10.3)
Difference between groups* †	−2.0	
97.5% CI for difference	−4.1, −0.1	
p Value	0.023	
DBP, mm Hg		
Baseline	95.2 (11.8)	93.4 (11.2)
Final visit (mean±SD)	78.4 (7.4)	79.0 (8.3)
Δ from baseline (mean±SD)*	−16.0 (7.4)	−15.0 (7.4)
Difference between groups* †	−1.0	
97.5% CI for difference	−2.5, 0.5	
p Value	0.119	

*Data were adjusted for the baseline values.
†The mean difference is significant at the 0.025 level.
BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Adverse events

During the study, patients treated with imidapril-based regimens were intolerant of the study drug more often (14 patients, 5.5%) than patients treated with the candesartan-based regimen (five patients, 2%). There was a significant difference between treatment groups in the percentage of patients requiring withdrawal from the study drug because of side effects (p=0.03). In the case of the imidapril group, one patient died from causes unrelated to the study medication; one patient required admission to hospital because of acute myocardial infarction; one patient from each treatment group experienced gingival hyperplasia due to calcium antagonists and discontinued the treatment. The other side effects are listed in table 4.

DISCUSSION

The SOT-AT1 study is the first multicentre clinical trial studying the efficacy of antihypertensive therapy in patients with an underlying autoimmune disorder. We have demonstrated that the ARB candesartan is more effective in lowering BP than the ACE inhibitor imidapril in AT1 autoantibody-positive, moderate to severe, hypertensive patients.

A statistically significant difference occurred in systolic BP between two treatment groups. The systolic BP was reduced by 30.8±10.3 mm Hg in the candesartan group and 28.8±10.3 mm Hg in the imidapril group (difference 2.0 mm Hg; p=0.023). On this basis, further analysis of the results showed that in AT1 autoantibody-positive hypertensive patients, both systolic and diastolic BP reductions were lower in

Table 3 BP changes throughout the study in ITT and PP population

	BP at final visit mean (SD)	Δ from baseline mean (SD)*	Difference between groups* †	97.5% CI for difference	p Value
BP changes throughout the study in ITT population					
AT1 autoantibodies(+)					
SBP					
Candesartan	125.2 (10.3)	−35.4 (9.8)	−6.0	−8.9 to −3.2	0.000
Imidapril	130.9 (10.6)	−29.4 (9.8)			
DBP					
Candesartan	77.4 (7.5)	−16.9 (6.9)	−2.8	−4.8 to −0.8	0.002
Imidapril	79.7 (7.4)	−14.2 (6.9)			
AT1 autoantibodies(−)					
SBP					
Candesartan	130.3 (10.6)	−26.2 (10.3)	−1.8	−4.7 to 1.0	0.156
Imidapril	127.9 (11.0)	−28.0 (10.3)			
DBP					
Candesartan	79.4 (7.2)	−15.1 (7.7)	−0.6	−2.7 to 1.5	0.507
Imidapril	78.5 (8.9)	−15.7 (7.7)			
BP changes throughout the study in PP population					
AT1 autoantibodies(+)					
SBP					
Candesartan	124.8 (9.1)	−35.9 (9.2)	−6.0	−8.8 to −3.3	0.000
Imidapril	130.4 (10.3)	−29.9 (9.2)			
DBP					
Candesartan	77.1 (7.2)	−17.1 (6.7)	−3.1	−5.1 to −1.1	0.001
Imidapril	79.9 (7.3)	−14.0 (6.7)			
AT1 autoantibodies(−)					
SBP					
Candesartan	129.8 (10.4)	−25.4 (9.8)	−2.1	−4.9 to 0.7	0.094
Imidapril	126.8 (9.4)	−27.5 (9.8)			
DBP					
Candesartan	79.4 (7.2)	−15.6 (7.3)	−1.1	−3.2 to 0.9	0.231
Imidapril	78.0 (8.1)	−16.7 (7.3)			

*Data were adjusted for the baseline values.
†The mean difference is significant at the 0.025 level.
BP, blood pressure; DBP, diastolic blood pressure; ITT, intent-to-treat; PP, per-protocol; SBP, systolic blood pressure.

the candesartan-based regimen than the imidapril-based regimen (−35.4±9.8/16.9±6.9 vs −29.4±9.8/14.2±6.9 mm Hg; p=0.000 and 0.002, respectively). In contrast, in AT1 autoantibody-negative patients, the BP response was equal in the two treatment regimens, indicating that an important difference between the two treatment regimens was the impact of AT1 autoantibodies. It was consistent with our previous pilot study that ARB lowering BP is superior to ACE inhibitors in AT1 autoantibody-positive hypertensive patients.[9]

Table 4 Number of patients with adverse events probably related to therapy

	Candesartan (n=257)	Imidapril (n=255)
Withdrawal	5 (2%)	14 (5.5%)*
Death	0	1 (0.4%)
Hospitalisation for AMI	0	1 (0.4%)
Gingival hyperplasia	1 (0.4%)	1 (0.4%)
Allergy	1 (0.4%)	0
Dizziness	2 (0.8%)	0
Nausea and vomiting	0	1 (0.4%)
Cough	0	8 (3.2%)
Fatigue	0	1 (0.4%)
Hypotension	1 (0.4%)	0
Elevated creatinine level	0	1 (0.4%)

Data reported as n (%).
*p=0.03 versus cadesartan-based regimen.
AMI, acute myocardial infarction.

It is well recognised that most of the known functions of angiotensin II are related to AT1 receptor activation. The AT1 receptor-directed autoimmune mechanism has been assumed to be involved in hypertension.[10] For instance, the autoantibodies against AT1 receptor were previously described in patients with hypertension.[4 5] Furthermore, experimental studies in vitro and in vivo showed that AT1 autoantibodies were able to display stimulatory effects similar to angiotensin II and that this effect could be blocked by ARB.[6] These AT1 autoantibodies bound to the second extracellular loop of the AT1 receptor, which is known to exert agonist-like activity. Thus activated AT1 receptors in AT1 autoantibody-positive hypertensive patients could be induced by two potential mechanisms, one is angiotensin II and another is AT1 autoantibodies. It seems that the AT1 autoantibody is competitive with angiotensin II for AT1 receptor binding sites. In addition, angiotensin II-induced signal transduction by the AT1 receptor is often accompanied by rapid desensitisation, that is attenuation of the cellular response upon prolonged or repeated stimulation by ligands. However, Fu *et al*[4] demonstrated that AT1 autoantibodies stimulated the proliferation of vascular smooth muscle cells without desensitisation of the AT1 receptor despite sustained stimulation, suggesting that AT1 autoantibodies could induce a prolonged stimulatory effect while angiotensin II could not.

Theoretically, the antihypertensive effectiveness of ACE inhibitors is dependent on reductions in the production of angiotensin II, whereas ARB directly inhibits the AT1 receptor.

Therefore, when an ACE inhibitor was used, a decreased level of angiotensin II leads to less competitive inhibition of AT1 autoantibodies in AT1 autoantibody-positive hypertensive patients. These consequently result in sustained overstimulation of AT1 receptors. However, when ARB was used and AT1 receptors were already occupied by ARB, AT1 autoantibodies were unable to bind to AT1 receptors in AT1 autoantibody-positive hypertensive patients. Our findings add weight to the above hypothesis.

There was a statistically significant difference in systolic BP between the AT1 autoantibody-positive and AT1 autoantibody-negative groups (160.5±16.5 and 156.2±17.7 mm Hg, respectively; p=0.006), suggesting that the autoimmune response mediated by AT1 autoantibodies is perhaps one of the important pathophysiological factors in hypertension. The exact underlying mechanisms at the molecular and cellular level remain to be defined. In a previous paper, Wang *et al*[8] found that AT1 autoantibodies caused hypertrophy of vascular smooth muscle cells and interstitial collagen deposition, and led to structural alterations in the peripheral vasculature in rats immunised by AT1 receptor peptide. Mechanisms underlying these cellular effects seem to occur at the post-receptor level and appear to be associated with hyperactivity of AT autoantibody-stimulated G protein-coupled phospholipases,[6 11] tyrosine kinase,[7] and mitogen-activated protein kinase-dependent pathways,[12] as well as with oxidative stress.[13]

We are aware of that our study is a short-term observation and is not powered for the study of hard endpoints. However, it is believed that our study is hypothesis generating for further large-scale clinical trials.

In summary, an ARB-based regimen is more effective in BP lowering than an ACE inhibitor-based regimen in the presence of AT1 autoantibodies. Therefore, circulating AT1 autoantibodies is a useful biomarker for targeted antihypertensive therapy in those patients with an underlying autoimmune disorder. Moreover, this may further enable us to obtain a better understanding of the role of AT1 autoantibodies in hypertension and develop novel therapeutic targets in hypertension.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the medical ethics committees of Tongji Medical College.

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Heart

Candesartan versus imidapril in hypertension: a randomised study to assess effects of anti-AT1 receptor autoantibodies

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