Author's response to reviews

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Upstream therapeutic strategies of Valsartan and Fluvastatin on Hypertensive patients with non-permanent Atrial Fibrillation (VF-HT-AF): study protocol for a randomized controlled trial

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Abstract

**Background:** Previous studies regarding rhythm control in patients with atrial fibrillation (AF) could not demonstrate the enough efficacy of available anti-arrhythmic drugs. The “upstream therapy” has emerged as a potential strategy for the prevention and treatment of AF. The use of angiotensin II receptor blockers (ARBs) and statins have been suggested to decrease new-onset AF in previous studies, but which have remained inadequately explored. This study was designed to examine whether valsartan and/or fluvastatin can reduce the probability of non-permanent AF in patients with hypertension.

**Methods/design:** The VF-HT-AF study is a multicenter, randomized, open-label, four-arm parallel group study with comparative evaluation of valsartan and fluvastatin, as upstream therapies for the patients with non-permanent AF complicated hypertension. The primary endpoint is the difference in the development of paroxysmal AF into persistent and/or permanent AF, persistent AF into permanent AF, as well as the incidence of overall and persistent AF recurrence, which are evaluated by 7-days ambulatory electrocardiograph monitoring (Holter) and patients’ diaries during 2 years follow-up. The secondary endpoints of this study include: (1) fatal and nonfatal myocardial infarction; (2) heart failure (NYHA III or IV);
(3) cardiogenic shock; (4) serious bleeding which need to be hospitalization; (5) malignant ventricular arrhythmia (including ventricular tachycardia and/or fibrillation); (6) revascularization therapy (CABG/PCI); (7) radiofrequency catheter ablation of AF; (8) the changes of left atrial dimension on ultrasound echocardiography; (9) Stroke; (10) cardiovascular mortality; and (11) all cause mortality. The study will follow 1879 hypertensive patients with non-permanent AF who are treated at 15 medical centers throughout China and will provide available or useful clinical information.

**Discussion:** The proposed study, evaluating the impact of implementing valsartan and/or fluvastatin treatment on non-permanent AF, is the first study in hypertensive patients complicated non-permanent AF in Chinese population. Results of this study will contribute to the upstream therapies of AF.

**Trial registration:** chictr.org, ChiCTR-TRC-12002642. Registered on 3 November 2012.

**Key Words:** Atrial fibrillation, Fluvastatin, Valsartan, 7-day Holter, Randomized control clinical trial
**Background**

Atrial fibrillation (AF), the most common clinically significant cardiac arrhythmia, is associated with increased mortality and morbidity [1, 2], especially in hypertensive patients [3]. In general, hypertension is the most important risk factor for AF. Although many efforts have been made to develop an effective pharmacological treatment, several trials conducted in the US and Europe proved existing traditional anti-arrhythmic drugs failed to improve the prognosis of AF patients [4-7].

Several systematic reviews and meta-analyses have confirmed antiarrhythmic efficacy while raising signals of concern related to adverse events and mortality [8]. In the last several years, a number of trials investigating upstream therapy for prevention of AF have been reported [9]. Upstream therapies are long-term modulators of atrial remodeling regarding structure/function, which may change the molecules expression contributing to the arrhythmic substrate. The renin-angiotensin system (RAS) is an important therapeutic target for atrial remodeling. Angiotensin II receptor blockers (ARBs) have been recently reported to suppress AF recurrence in both paroxysmal and persistent AF in selected patients. However, recent placebo-controlled, double-blind trials with ARBs failed to show convincing results [10, 11]. Statins, as a well-established secondary prevention benefit
for atherosclerotic coronary artery disease, are hypothesized to be beneficial against atrial arrhythmias, yet the data are inconsistent [12-15]. In addition, there has been little prospective and randomized study to evaluate the effectiveness of upstream therapeutic strategies in hypertensive patients with non-permanent AF.

In order to confirm the effectiveness of ARBs and/or statins on AF in hypertensive patients, the Upstream Therapeutic Strategies of Valsartan and Fluvastatin on Hypertensive Patients with Non-permanent AF (VF-HT-AF study) will be conducted in 1879 participants from 15 centers.

**Methods/ Design**

The VF-HT-AF study is designed as a prospective, randomized, open-label, four-arm parallel, and multicenter study. The objective of the proposed study is to test the hypothesis that upstream therapy using the valsartan and/or fluvastatin is more effective in reducing the recurrence of AF and the progress from non-permanent AF to permanent AF in hypertensive patients with non-permanent AF, compared with conventional antihypertensive therapy using the dihydropyridine calcium channel blockers (CCBs). This study will be conducted according to the principles outlined in the Declaration of Helsinki. Written informed consents will be obtained
from all patients prior to the study. The study protocol has been approved by the ethics committee of the Second Hospital of Tianjin Medical University (Clinical ethical review [2012] No. 27) as well as other participating medical centers, which are secondary or tertiary healthcare centers in China, and should provide proofs of laboratory quality control. The study has registered at http://www.chictr.org (ChiCTR-TRC-12002642).

**Patient population and entry criteria**

Patients enrolled into the study need to meet the inclusive recruited criteria: (1) hypertension, defined as an average systolic blood pressure (BP) ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg (but a systolic BP < 180 mmHg and a diastolic BP < 110 mmHg) of the first visit, or requiring any anti-hypertension treatment at enrollment; (2) a history of non-permanent AF within 1 year prior to the enrollment, which has been confirmed by electrocardiograms (ECG), and converted to sinus rhythm; (3) those who haven’t taken ARBs and/or angiotensin-converting enzyme inhibitors (ACEIs) as well as statins in the past 2 weeks, or those who are having ARBs, ACEIs and statins, can accept 2 weeks washout period; (4) ages ranged from 25 to 79 years; and (5) signed the informed consent.
The exclusion criteria are: (1) persistent AF with a duration ≥1 year, and/or permanent AF; (2) serious left main coronary artery disease identified by coronary angiography; (3) heart failure (New York Heart Association (NYHA) III or IV); (4) acute myocardial infarction in 3 months; (5) with surgical/interventional indications of valvular heart disease; (6) uncontrolled thyroid disease (abnormal free T3, free T4, or thyroid stimulating hormone, or requiring any anti-thyroid treatment at enrollment); (7) serious liver/renal dysfunction (ALT > 80 u/L and/or AST > 80 u/L, and/or creatinine > 132 umol/L); (8) history of unstable angina pectoris; (9) stroke or transient ischemic attack (TIA) history within the past 3 months; (10) poor treatment compliance, such as the central nervous system/mental illness, or may not be cooperative in the follow-up period; (11) patients have had ARBs and/or ACEIs and/or statins but can’t accept the washout period for 2 weeks; (12) patients with obvious hyperlipidemia must be treated by statins and/or fibrates; (13) contraindication of statins and/or ARBs; (14) pregnancy or the possibility of pregnancy, or breast feeding; and (15) patient aged younger than 25 or older than 79 years.

**Study design**

The VF-HT-AF study is a randomized, multicenter, open-label, and
four-arm parallel study to evaluate the effectiveness of valsartan, fluvastatin or both of them on recurrent AF in hypertensive patients with non-permanent AF in China. After providing informed consent, patients will be randomly assigned to one of four groups (the valsartan group, the fluvastatin plus dihydropyridine CCBs group, the valsartan plus fluvastatin group, and the dihydropyridine CCBs group) by the School of Public Health of Tianjin Medical University with the computer system, initially in 1:1:1:1 ratio. Physicians who should have qualifications of medical practitioners screen and follow up the patients in hospital outpatient or inpatient clinic. All patients’ data will be collected using a standard case report form and transmitted to the central database at the data center. All centers will be regularly monitored for source data documentation. Missing or questionable data will be completed and corrected by queries.

If the candidate patients did not take ARBs, ACEIs and/or statins in the past at least 14 days, they will be directly enrolled and randomized. If the candidate patients have taken ARBs, ACEIs and/or statins, they will be randomized after 14 days washout period. Baseline data will be collected after washout period.

The initial dose of fluvastatin will be 40 mg/day at night, and valsartan will be prescribed initially at 80 mg/day. The dose of fluvastatin will be no
less than 40 mg/day and valsartan will be no less than 80 mg/day during the follow-up period. Blood pressures in each group must reach the target BP, which is set at SBP/DBP < 140/90 mm Hg (1 mm Hg = 0.133 kPa).

**Follow-up**

The clinical follow-up using standardized questionnaires will be performed every 3 months during the 2 years follow-up period from the assignment of each patient.

The dosages and types of all other antihypertensive drugs, antihyperlipidemia and antiarrhythmic drugs used during the follow-up will be recorded for each patient. Ultrasound echocardiography will be performed before the patients enter the study and at the end of the follow-up period. A 7-day Holter monitoring will be performed at the baseline, 6th month, 12th month and at the end of the follow-up period. Patients’ diaries, cardiac function of NYHA classification, adverse events during the follow-up will be collected every three months.

Throughout the study, patients should record diaries when they feel discomfort. Arrhythmia-related symptoms are self-evaluated or evaluated by 7-day Holter monitoring, which has 5 poles, is weighted 50g, 2.0*2.7cm, and can record 7 days ECG. The 7-days Holter instruments were manufactured by BORSAM Co. in Shenzhen, Guangdong Province of China,
and provided by sponsor of the study, Tianjin Institute of Cardiology, Tianjin, China. The attending physicians will also record BP and ECG during each follow-up. Unless it is necessary, antiarrhythmic drug therapy will be discontinued during the study according to the attending physicians’ advice for each patient. The design of the present study is shown in Figure 1.

**Primary endpoint**

The VF-HT-AF study will examine whether fluvastatin or valsartan has antiarrhythmic effects on nonpermanent AF besides its lipid-lowering and antihypertensive effects in comparison with dihydropyridine CCBs. Also, it will also confirm if combination of valsartan and fluvastatin have better effects on nonpermanent AF than one of them alone.

Therefore, the primary endpoint is the difference in the development of paroxysmal AF into persistent and/or permanent AF, persistent AF into permanent AF, as well as the incidence of overall and persistent AF recurrence, which will be evaluated by 7-day Holter monitoring and patients’ diaries during the 2 years follow up of the four treatment groups.

**Secondary endpoints**
The secondary endpoints of this study include: (1) myocardial infarction; (2) heart failure (NYHA III or IV); (3) cardiogenic shock; (4) serious bleeding which need to be hospitalization; (5) malignant ventricular arrhythmia (including ventricular tachycardia and/or fibrillation); (6) revascularization therapy (coronary artery bypass grafting/ percutaneous coronary interventions); (7) radiofrequency catheter ablation of AF; (8) the changes of left atrial dimension on ultrasound echocardiography; (9) Stroke; (10) cardiovascular mortality; and (11) all cause mortality.

Definitions

The definitions of AF are made according to 2012 HRS/EHRA/ECAS Expert Consensus [16]. Paroxysmal AF is defined as recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days. Episodes of AF in no more than 48 hours’ duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes. Persistent AF is defined as continuous AF that is sustained beyond 7 days. Episodes of AF in which a decision is made to cardiovert AF electrically or pharmacologically more than 48 hours of AF duration, but less than 7 days, should also be classified as persistent AF episodes.
Permanent AF refers to the patients who have long lasting episode of AF which could be considered by any evidence more than 1 year, or a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means, including catheter ablation or surgery, or lasting episode of AF $\geq$ 1 year, which could be considered by any evidence. Myocardial infarction is defined as a cardiac troponin rise accompanied by typical symptoms, pathological Q waves, ST elevation or depression, or coronary intervention. Heart failure (NYHA III or IV), which requires echocardiographic evidence of reduced left ventricular ejection fraction or a diagnosis of heart failure by a cardiologist. Cardiogenic shock is defined by sustained hypotension with tissue hypoperfusion despite adequate left ventricular filling pressure. Signs of tissue hypoperfusion include oliguria ($<30$ mL/h), cool extremities, and altered level of consciousness.

**Sample size calculation**

The primary endpoint of the study is the difference in the development of paroxysmal AF into persistent and/or permanent AF, persistent AF into permanent AF, as well as the incidence of overall and persistent AF recurrence. Power calculations to provide estimates for the necessary sample
size were conducted concerning primary endpoint. Sample size was estimated based on findings from the 12-month results of J-RHYTHM II study [17], in which incidence of persistent AF is estimated to be 6.8% lower in the valsartan group than in the CCBs group. To ensure 80% power at the 5% significance level, a sample size of at least 1404 needs to be included. Considering a rejection rate of 20%, about 1879 patients need to be approached.

**Statistical analysis**

All analyses will be performed based on the intention-to-treat principle with differences assumed to be significant at a 2-sided $P$ value < 0.05.

Baseline characteristics and follow-up information will be collected for each group through the questionnaire. Absolute values for each question will be used to calculate the mean value, standard deviation, median value, percentile, number of cases, and percentages, per group. The statistical significance will be evaluated by analysis of variance or Kruskal-Wallis rank sum test for continuous variables and chi-squared test for categorical variables, respectively. Kaplan-Meier curves will be used to describe time-dependent occurrence of events, and Log-rank test will be performed to compare survival distributions for the four groups. To adjust for possible
baseline imbalances between groups, Cox proportional hazards model will be used. Hazard ratio will be calculated. In addition, subgroup analyses will be performed corresponding to the nature of the data. All statistical analyses will be performed using SPSS statistical software (version 17.00, Chicago, IL).

**Quality Assurance**

**Steering committee**

The intervention of steering committee includes general practices training, practice visits, to develop and monitor the implementation of the protocol. Telephone support is delivered by intervention team with assistance from the principle investigators. The quality of the intervention process will be monitored and assured by a steering committee using multiple strategies, including a standardized selection, training and performance assessments of the intervention team, evaluation of the general practices training, record of practice visits kept by the intervention team, and ongoing feedback by practice staff on the intervention during 24-month period, which should be supported by a statistician, and is responsible for ensuring the timely publication of this study results.

**7-Day Holter diagnosis committee**
This committee will determine the rhythm of the recorded 7-Days Holter without knowing the patients’ conditions and will be responsible for the diagnosis of the recorded ECGs in 7-Days Holter before the analysis of the primary and secondary endpoints.

**Safety monitoring board**

Safety monitoring board will be responsible for monitoring patient safety and will recommend premature stop of the trial if an increase in unpredicted adverse events.

**Discussion**

Paroxysmal AF often progresses to persistent/permanent AF when the former increases in frequency and duration, which accounts for approximately 5.5% of all patients with paroxysmal AF per year [18]. One consistent fact that emerges from studies is that conventional antiarrhythmic agents such as class I antiarrhythmics do not improve survival rates[19], and their efficacy in preventing progression of paroxysmal AF to persistent AF is limited because they do not exert any potential benefits on electrical or structural remodeling, which contributes to the pathophysiological basis of AF[20].

Preventing new-onset and recurrent AF with upstream therapies is of great
interest, but current data are conflicting. Further studies are needed to optimize rhythm control by antiarrhythmic drugs and targeted catheter ablation to specific patient population at an earlier stage. There is little data on valsartan and fluvastatin treatment in patients with hypertension and non-permanent AF.

**Stains: fluvastatin** During recent years, statins have emerged as one of the most effective treatment to reduce the burden of cardiovascular disease worldwide. Owing to their remarkably good safety profile and declining costs, there has been some interest in the potential use of statins as direct antiarrhythmic or anti-inflammatory drugs [21]. Meta-analysis demonstrated that the use of statins was significantly associated with a decreased risk of AF in patients with sinus rhythm [12,15,22,23]. Statins could be considered for patients with intermediate risk factors [24] as a secondary prevention of AF [23]. These results provided some evidences for the benefit of statins beyond their lipid-lowering activity [21].

The potential mechanisms involved in AF reduction associated with statin therapy are not fully clear. One possible pathway involves inflammation, which has been recognized as an accomplice and a potential trigger for AF [25]. Bellosta et al [26] have suggested that statins have pleiotropic properties, and their anti-inflammatory effects are associated with reduction
in the expression of cytokines, intercellular adhesion molecules, and interleukins. Statins reduced the incidence of paroxysmal AF with a concomitant decrease in C-reactive protein (CRP) levels [27], which are believed to be a risk factor for AF. Statins treatment reduced inflammatory biomarkers, which might also explain a potentially beneficial effect of statins against AF [28]. More recently, antioxidative actions have been hypothesized to prevent electrical remodeling [29]. Administration of statins significantly decreased generation of reactive oxygen species in vitro and in vivo [30]. Statins prevented the development of AF by modulating extracellular remodeling. Statins modified extracellular components by regulating the expression of matrix metalloproteinases or their inhibitors [31]. Additionally, statins may downregulate the RAS and modulate autonomic nervous system-induced increases in sympathetic activity, which has been shown to promote atrial remodeling. Other potential mechanisms of action include modification of the atherosclerotic plaque [32], improvement of endothelial function [33], as well as alteration of membrane fluidity and ion channel conductance [34].

Some clinical and experimental studies have suggested the use of statins to protect against AF [35]. However, insufficient data are available to allow recommending statins for the prevention of AF [36]. STOP AF trial [28]
showed that high dose atorvastatin did not reduce the recurrence of AF after cardioversion. Lee et al [37] have suggested that statin therapy in patients with paroxysmal AF may be limited to the prevention of incident AF, but it does not appear to inhibit the progression of paroxysmal AF to permanent AF.

Although some studies [38] established diverse results from their different end points, they concur that statins are beneficial in decreasing the frequency of paroxysmal AF. We are, however, unable to conclude whether a benefit exists with the use of statins in inhibiting the progression of paroxysmal to persistent AF, due in part to the limited data available.

Interestingly, fluvastatin was able to confer benefit, despite having the lowest potency. An advantage of fluvastatin is a long-acting formation, which the DECREASE study investigators stated could serves as a “bridge” during the post-operative period when patients were not receiving oral medications. For practice to reflect clinical trials, atorvastatin would be selected before PCI and CABG, whereas fluvastatin would be selected before noncardiac surgical procedures [39]. Therefore, we select fluvastatin as the treatment drug of statin in our study. Because it is not clear whether the effects of statin use on AF depend on the underlying lipid levels, we will enroll the patients without severe hyperlipidemia.
**ARBS: valsartan** The VALUE trial [3] found that the incidence of persistent AF was 1.35% with valsartan and 1.97% with amlodipine [unadjusted hazard ratio 0.683 (95% CI: 0.525, 0.889), P=0.0046]. As VALUE trial results, valsartan-based treatment reduced the development of new-onset AF, particularly sustained AF in hypertensive patients, compared with amlodipine-based therapy. These findings suggest that ARBs may result in greater benefits than calcium antagonists in hypertensive patients at risk of AF. This leads to the question of whether or not the RAS is an underlying mechanism that can be targeted to prevent AF. Several mechanisms have been proposed to explain the effects of RAS blockade on prevention of AF, including decreased atrial stretch, lowered end-diastolic left ventricular pressure and left atrial pressure, prevention of atrial fibrosis, modification of sympathetic tone, alteration in potassium currents and atrial refractoriness, and direct antiarrhythmic effects [40-43]. However, recent J-RHYTHM II study[11] have found that there were no significant differences between an ARB (candesartan) and a CCB (amlodipine) groups in the development of persistent AF in the treatment of paroxysmal AF associated with hypertension.

Therefore, large-scale, prospective, randomized clinical trials are urgently needed to establish whether statins or ARB bring a similar benefit and are an
appropriate therapeutic option in the hypertensive patients for the management of AF.

**7-days Holter**  The Holter monitor has been recently developed, which can continuously record ECG of cardiac rhythm without the need for removal during exercise or sleeping. However, the 24 hours Holter can not record the arrhythmia more than one day. In older to monitor AF consistently, we use 7-days Holter and patients’ diary to record AF firstly in Chinese population.

The VF-HT-AF study, is a prospective, randomized, open-labeled and multicenter trial designed to provide novel data necessary to comprehensively assess the efficiency of valsartan and fluvastatin on AF prevention in patients with hypertension and non-permanent AF.

**Expected implications**

The VF-HT-AF study will determine the antiarrhythmic effects of the ARB and statin on the recurrence of non-permanent AF associated with hypertension. It will also examine the mortality, morbidity, and perpetuation of the arrhythmia under valsartan, fluvastatin, dihydropiridine CCBs or combined treatment.

Particularly, prevention of persistent and permenant AF would be
expected to reduce the hospitalization of heart failure, stroke, the morbidity and mortality in patients with hypertension. This study will provide data to health care policymakers and the authors of clinical guidelines regarding the appropriate use of upstream therapy in the hypertensive patients with AF and provide directions for future research.

Therefore, the results of this study will emphasize the role of upstream therapies in prevention of AF in a Chinese hypertensive population and assist in the design of an optimal therapy for such patients.

However, one important limitation that may be present in this study is that it is an open-label trial, because we don’t have enough funds to make the drugs in blind. The drugs which the patients used in our study are all prescribed in the hospitals or drugstores. The patients and doctors know the drugs they used. Another limitation is that the control group is not blank, so we do not test the fluvastatin effect alone. Because the patients in our study are hypertensive patients, they must be treated with antihypertensive therapy according to the ethics. We choose the dihydropyridine CCBs as the control group, compared with the dihydropyridine CCBs plus fluvastatin group. If the recurrence of AF in dihydropyridine CCBs plus fluvastatin group is less than the dihydropyridine CCBs group, it will be proved that fluvastatin can reduce the probability of non-permanent AF in patients with hypertension.
There may be some combined effects of dihydropyridine CCBs plus fluvastatin, but we have to use the antihypertensive drugs.

**Trial status**

The trial is currently in the recruitment phase.

**Abbreviations**

AF, atrial fibrillation; ARBs, angiotensin II receptor blockers; ECG, electrocardiograms; Holter, ambulatory ECG monitoring; RAS, renin-angiotensin system; CCBs, calcium channel blockers; ACEIs, angiotensin-converting enzyme inhibitors; TIA, transient ischemic attack.

**Competing interests**

The authors declare that they have no completing interests.

**Author’s contributions**

WQ participated in study design, drafted the manuscript, obtained ethical approval, planned the statistical analysis, and revised the manuscript. TL participated in study conception and design, and contributed to revising the manuscript. GX participated in study conception and design. LL participated in study conception and design. YL is the head of the Steering Committee.
LY participated in the study design and is the head of the 7-Day Holter diagnosis committee. GL, as the principal investigator, conceived of the study, drafted the manuscript, obtained ethical approval, and reviewed the manuscript. All authors read and approved the final manuscript.

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**Figure 1. Flow-process diagram**