

## Statin Therapy for Primary Prevention of Atrial Fibrillation: Guided by CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>VASc Score

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Atrial fibrillation (AF) is the most common arrhythmia and is associated with increased cardiovascular morbidity and mortality. The antiarrhythmic effect of statins on AF prevention appears to be highly significant in most clinical studies. However, some discrepancies do exist among different clinical studies. Different clinical settings and types of statins used may explain these differences between trials. The CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scoring systems have been used for stroke risk stratification in AF patients. The recent study suggested that these scores can also be used to guide statin therapy for AF prevention. Patients with higher scores had a higher risk of developing AF and gained more benefits from statins therapy than those with lower scores. This review article focused on the ability of these scores to predict AF prevention by statins. (**Korean Circ J 2014;44(4):205-209**)

**KEY WORDS:** Hydroxymethylglutaryl-CoA reductase inhibitors; Atrial fibrillation; Primary prevention.

### Introduction

Atrial fibrillation (AF) is the most common clinically significant arrhythmia and it is associated with increased hospitalization, all-cause mortality, and health care costs.<sup>1-5</sup> The chief hazard of this arrhythmia is ischemic stroke and heart failure, which might cause hemodynamic compromise and lead to further morbidity and mortality.<sup>2</sup> Risk factors for AF include old age, male gender, congestive heart failure, hypertension, diabetes mellitus, vascular disease, pulmonary disease, valvular heart disease, and chronic kidney disease.<sup>2,3,6-8</sup> Because of the rising prevalence of these co-morbidities and the increasing elderly population, the overall economic burden from AF is likely to increase in the following decades. Therefore, there is an urgent need to identify preventive measures in the occurrence

of new-onset AF.<sup>9</sup>

Classical antiarrhythmic drugs are often characterized by several adverse effects and relative inefficacy.<sup>5</sup> Safer and more efficacious therapeutic agents are needed for AF prevention.<sup>9</sup> It has been shown that "upstream therapies", which aim at reversal of atrial substrate derangement, could be used for AF prevention. Accordingly, the current focus has been shifted to non-antiarrhythmic drugs such as statins, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and omega-3 polyunsaturated fatty acids. An increasing number of animal experiments and clinical studies have investigated the beneficial role of statins in AF prevention,<sup>10,11</sup> and meta-analyses showed that the use of statins was significantly associated with a decreased risk of AF.<sup>12-14</sup> In addition, a recent guideline suggests that statins could be used for AF prevention in those with heart failure or undergoing cardiac surgery.<sup>15</sup> However, whether statins may prevent AF in patients other than these subgroups remains a subject of debate. This review article focused on the ability of cardiovascular co-morbidity scoring systems in predicting AF prevention by statins.

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### Heterogeneity Across Studies

Despite increasing evidence supporting the concept of using statins for AF prevention, clinical studies yielded conflicting results.<sup>16-19</sup>

Meta-analyses of randomized controlled trials and observational studies reveal that statin therapy is useful for primary prevention of AF,<sup>12-14</sup> but significant heterogeneity exists across these studies.<sup>14(20)</sup> For example, in a recent meta-analysis by Fauchier et al.,<sup>21</sup> the most significant benefits of statins appear to be the prevention of postoperative AF and secondary prevention of AF. Other meta-analyses are also in agreement,<sup>13(22)</sup> and Bang et al.<sup>23</sup> assumed that the AF prevention effect of statins may be diverse in different clinical settings. These findings suggest that underlying co-morbidities may play an important role in selecting suitable patients for statin therapy.<sup>13</sup>

Consequently, the AF preventive effect of statins might be inconsistent in different clinical setting.<sup>11</sup> Therefore, recent studies have used co-morbidities scoring systems to identify patients who may benefit most from statin therapy for AF prevention. The CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, prior Stroke or transient ischemic attack) and CHA<sub>2</sub>DS<sub>2</sub>VASc (Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, prior Stroke or transient ischemic attack, Vascular disease, Age 65–74 years, Sex category) scores include many cardiovascular co-morbidities, which were reportedly important risk factors for the development of AF. Recent studies show that high CHADS<sub>2</sub> scores are associated with an increased risk of new-onset AF,<sup>24-26</sup> AF recurrence after ablation,<sup>27</sup> and the electroanatomical remodeling of the left atrium.<sup>28</sup> Moreover, the findings of our recent nationwide cohort studies suggest that the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc score can be used to guide the upstream therapy of AF.<sup>29(30)</sup>

### CHADS<sub>2</sub>/CHA<sub>2</sub>DS<sub>2</sub>VASc Score to Predict Atrial Fibrillation Prevention Outcome

The CHADS<sub>2</sub> scoring system, which was initially developed for the risk stratification of strokes in patients with AF, is a convenient way to evaluate the complexity of cardiovascular co-morbidities. Our recent study shows that this score may help in identifying the patients who could benefit most from statin use for AF prevention.<sup>29</sup> The nationwide cohort, which included 27002 elderly hypertensive patients, demonstrates that CHADS<sub>2</sub> score is useful for predicting the effectiveness of statins. Patients with a CHADS<sub>2</sub> score  $\geq 2$  had a 31% risk reduction of AF, but those with CHADS<sub>2</sub> score of 1 gained no significant benefits.<sup>29</sup> Another cohort study, which included 171885 patients aged  $\geq 50$  years, show identical results. Statin therapy provided no obvious beneficial effect in those with a CHADS<sub>2</sub> score of 0 and had the best effect for those with a CHADS<sub>2</sub> score of 2.<sup>30</sup> Those with higher CHADS<sub>2</sub> score have a higher risk of AF, and gain more benefits from statins therapy than those with a lower CHADS<sub>2</sub> score. This implies that the CHADS<sub>2</sub> score could be

used to guide the upstream therapy for AF prevention.

The CHA<sub>2</sub>DS<sub>2</sub>VASc scoring system was recently developed for stroke risk stratification in AF patients. Our study shows that patients with a CHA<sub>2</sub>DS<sub>2</sub>VASc score  $\geq 1$  benefit from statin use, especially those with score  $\geq 3$ .<sup>30</sup> Those with score of 1 gain 20% AF risk reduction from statin therapy, while those with score of 2 gain 30%, and those with score  $\geq 3$  gain 40%. In contrast, the therapy provides no obvious beneficial effect in those with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 0. From this point of view, CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scores are not only clinical predictors for stroke risk stratification, but are also useful scoring systems for predicting the effectiveness of statin in AF prevention. However, the role of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc score in upstream therapy for AF requires further study.

### Possible Mechanisms of Atrial Fibrillation Prevention by Statin

Atrial fibrillation is a progressive disease that depends on the electrophysiological and anatomical remodeling of atrial substrates.<sup>4(31)</sup> Several mechanisms including myocardial inflammation, oxidative stress, endothelial dysfunction, and alternation in ion channel conductance might contribute to atrial substrate remodeling and AF development.<sup>32</sup> Therapeutic approaches aiming at antagonizing atrial remodeling could be of some benefit in the prevention of AF.<sup>33(34)</sup> Recent evidence emphasizes a role for systemic inflammation in the development and persistence of AF,<sup>35(36)</sup> linking inflammatory markers, such as C-reactive protein (CRP), to this arrhythmia.<sup>37(38)</sup> Moreover, there are several possible mechanisms by which statins can act on atrial remodeling, such as anti-inflammatory and antioxidant properties, modulation of endothelial function, and alteration of ion channel conductance.<sup>11(39-45)</sup> These beneficial effects of statins are partly attributed to their anti-inflammatory property,<sup>46(47)</sup> which might be unrelated to their lipid lowering effect.<sup>13(43)46-48</sup> Clinical studies<sup>49-53</sup> indicate that statin treatment can reduce inflammation, which may explain the potential beneficial effect of statins for AF prevention. These concepts suggest that the anti-arrhythmic effect of statins tend to be more pronounced in patients with more systemic inflammation and damaged atrial tissue. Patients with no systemic inflammation or those with normal atrial substrate are unlikely to benefit from statin therapy for AF prevention.

Recent studies demonstrate that CHADS<sub>2</sub> score is useful for predicting CRP levels, left atrium thrombus formation, and the prognosis in patients with AF.<sup>54(55)</sup> This relation between CHADS<sub>2</sub> score and CRP has potential implications for predicting the effect of statin on AF prevention. Evidence from the Justification for the Use of statins in primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial hint at this mechanism.<sup>18</sup> In the JUPITER trial, patients

with high-sensitivity CRP had a better AF protective effect from statin therapy. Therefore, we proposed that those with higher CHADS<sub>2</sub> scores have more severe inflammation, and the anti-inflammatory effect of statins may be more obvious in these patients. Furthermore, female gender and vascular disease, differential factors between CHA<sub>2</sub>DS<sub>2</sub>-VASc and CHADS<sub>2</sub> scores, are also related to increasing systemic inflammation.<sup>56-58</sup> Therefore, patients with higher CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores may have a more severe inflammation, and the anti-inflammatory effect of statin may be more obvious in these patients. The current data and JUPITER trial support the statin anti-inflammatory hypothesis and provide an explanation of statin's AF prevention effects in patients with high CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.

### Effect of Statin Type and Gender in Atrial Fibrillation Prevention by Statin

In addition to the effect of patient characteristics, previous meta-analyses show that there is a type-dependent efficacy of statin in reducing the risk of new-onset AF.<sup>13</sup> A recent nationwide propensity score-matched study from Denmark also indicate that different statins have diverse effect in preventing new-onset AF.<sup>19</sup> In a meta-analysis by Fang et al.,<sup>13</sup> the beneficial effect was noted in the atorvastatin and simvastatin subgroup, but not in pravastatin or rosuvastatin subgroup. Our recent study, on 135275 Taiwanese patients, shows that the level of efficacy in reducing the risk of new-onset AF is related to the type of statin.<sup>59</sup> The study used the defined daily dose, as recommended by the World Health Organization guidelines for assuming average maintenance dose per day of a drug,<sup>30,60</sup> as statins dosage equivalency (simvastatin 30 mg, lovastatin 45 mg, pravastatin 30 mg, fluvastatin 60 mg, atorvastatin 20 mg, and rosuvastatin 10 mg). The results show that fluvastatin and pravastatin provide no significant AF risk reduction. Lovastatin has the strongest AF preventive effect, followed by simvastatin, rosuvastatin, and atorvastatin. A meta-analysis by Wang et al.<sup>22</sup> and a clinical study by Komatsu et al.<sup>16</sup> (atorvastatin 10 mg/day vs. pravastatin 10 mg/day, no significant difference in lipid profile between groups) also show that atorvastatin is more effective than pravastatin. Therefore, the heterogeneity across studies is partially caused by the type of statin used.

Another interesting finding in our recent nationwide cohort study is the effect of gender.<sup>59</sup> Male and female patients gain different AF preventive effect from different statins. Male patients gain obvious beneficial effects from rosuvastatin and atorvastatin (high-potency statins), whereas female patient gain these benefits from lovastatin and simvastatin (lipophilic statins). This finding is comparable to the result of subgroup analysis from the JUPITER trial,<sup>19</sup> which show

that females do not benefit from the AF preventive effect of rosuvastatin, while males do. Different statins show divergent potency in regression of atherosclerosis,<sup>61</sup> as well as anti-inflammatory and anti-oxidant effects.<sup>62-64</sup> Males and females are also different in the distribution of cardiovascular diseases and metabolic syndrome,<sup>59,65</sup> inflammatory and oxidative status.<sup>66-68</sup> Therefore, the distinct efficacy of different statins between genders might be attributable to a complex mechanism involving atherosclerotic, and inflammatory status.<sup>59</sup> Female patients gain the AF preventive effect from lipophilic statins *via* modulation of inflammatory and metabolic abnormality, and male patients gain the AF prevention effect from high-potency statins *via* deceleration the progression of atherosclerotic diseases. The implications of these findings warrant further investigation.

### Conclusion

Statin therapy is significantly associated with a decreased risk of AF in selected population. Recent studies suggest that those with higher CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores will benefit most from statin use for the prevention of AF. Statins provide limited benefits in primary prevention of AF in patients with low CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. The CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring systems are useful for identifying the patients who will benefit most from statins for AF prevention. While these clinical evidences mainly come from retrospective cohort studies, more randomized prospective trials are necessary to further support these conclusions.

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