Antihyperglycemic drugs use and new-onset atrial fibrillation in elderly patients

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ABSTRACT

Background Antihyperglycemic drugs have been linked to new-onset atrial fibrillation (NAF). However, the effect of the different classes of antihyperglycemic drugs on the development of NAF in elderly patients has not been well studied. In this study, we investigated the association between different classes of antihyperglycemic drugs and NAF in elderly patients.

Materials and methods This was a nested case–control study performed using the database of National Health Insurance programme in Taiwan. Each participant aged 65 years and older who were NAF from 2005 to 2012 were assigned to the NAF group, whereas case was sex-, age-, diabetes duration-, index date-matched, and Charlson Comorbidity Index score-matched randomly selected participant without NAF were assigned to the non-NAF group. Multivariable logistic regression model was used for the estimation of odds ratios (ORs) and 95% confidence intervals (CIs) of NAF associated with use of different classes of antihyperglycemic agents. Nonusers served as the reference group.

Results We identified 1958 cases and 7832 controls. The risk of NAF after adjusting for sex, age, comorbidities and concurrent medication was higher among the users of insulin than among the nonusers (OR, 1.58; 95% CI, 1.37–1.82). Patients who took dipeptidyl peptidase 4 inhibitors were at lower risk of developing NAF than the nonusers (OR, 0.65; 95% CI, 0.45–0.93).

Conclusions In this population, use of dipeptidyl peptidase 4 inhibitor was associated with a low risk of NAF. Insulin use was associated with a significant increase in the risk of NAF during the long-term follow-up.

Keywords Antihyperglycemic drugs, dipeptidyl peptidase 4 inhibitors, nested case–control study, new-onset atrial fibrillation.


Introduction

Atrial fibrillation is a common arrhythmia [1] that has been associated with an increased risk of all-cause mortality in population-based studies [2–4]. Concerns about the prevalence of atrial fibrillation, especially new-onset atrial fibrillation (NAF), are gradually increasing worldwide [5,6]. Some recent studies on diabetes mellitus (DM) led to a debate about whether the use of antihyperglycemic drugs is associated with NAF in treated DM patients [7–10]. It seems obvious that cardiovascular risk is higher when DM and atrial fibrillation coexist than when the two conditions stand alone; however, current reports on the effect of various antihyperglycemic drugs on the risk of NAF are conflicting. Data from these studies comparing large groups of patients who receive more than two classes of drugs are lacking [10]. Of particular note, it is not completely clear whether certain antihyperglycemic drug classes are associated with a higher risk of NAF when compared with other antihyperglycemic drug classes in patients with DM. Therefore, we conducted a retrospective cohort study to explore the relationship between all antihyperglycemic drugs and NAF in a general population of Taiwan. We aimed to determine whether insulins, metformins, acarbose, glinides, sulfonylureas, thiazolidinediones (TZD) and dipeptidyl peptidase 4 (DPP4) inhibitors were independently associated with NAF.
Materials and methods

Study population
Our data were taken from claim forms provided to National Health Insurance (NHI) programme in Taiwan from January 2000 to December 2012. The Taiwan NHI programme has been operating since 1995 and representing about 99% of the Taiwan’s population. The NHI database stores information from the claim forms in two tables: a visit table and a prescription table. Visit tables contain information on patient identification numbers, sex, age, three diagnostic codes, dose of drug, and medical expenditures as well as hospital and physician information. The prescription table contains the quantity and expenditure for all drugs, operations and treatments. The details of the programme have been well recorded in previous published article [11,12].

Data collection and endpoints
We used the International Classification of Diseases, Ninth Revision (ICD-9) Clinical Modification code to define atrial fibrillation (ICD-9 codes 427/C131) and diabetes mellitus (ICD-9 codes 250). Prescriptions for antihyperglycemic drug in patients with new diagnosed DM before the index date were retrieved from a prescription database between January 2005 and December 2012. Diabetic patients with an atrial fibrillation diagnosis during the 5-year period prior to 1 January 2005 were excluded.

Finally, a total of 1958 participants aged 65 and older who were newly diagnosed with atrial fibrillation from 2005 to 2012 were assigned to the NAF group, whereas 7832 sex-matched, age-matched, DM duration-matched, index date-matched and Charlson Comorbidity Index score [11]-matched randomly selected participants without NAF served as the non-NAF group (Fig. 1). The index date was the development of NAF, which was defined as the first time that an atrial fibrillation code appeared in the outpatient claim records. We identified all prescriptions for antihyperglycemic drugs administered to patients with NAF within an 8-year period before the date NAF was diagnosed. In Taiwan, all antihyperglycemic drugs are available only by prescription during the time period studied. Patients who had used one class of antihyperglycemic drug continuously before 12 months of the date NAF was diagnosed were categorized according to the antihyperglycemic drug class that they took: insulins, metformins, acarbose, glinides, sulfonylureas, TZDs and DPP4 inhibitors. This study was approved by the ethics committee of the China University Hospital (CMUH104-REC3-112).

Statistical analysis
The central tendency and variability of continuous variables in this study are presented as mean ± standard deviation (SD).

Depending on the attributes of variables, the associations of each independent variable with dependent variable were examined by either the unpaired Student’s t-test or chi-square test. SAS 9.3 was performed to analyse all statistical tests. This study was designed to reveal whether antihyperglycemic drug classes of diabetic patients are association with incident of NAF. In terms of univariate analysis, logistic regression analysis was applied to examine whether the odds ratio (OR) of NAF group is differ from that of non-NAF group. Additional adjusted multivariate logistic regression models including sex, age, comorbidity and concurrent medication were implemented. A P-value of <0.05 was considered statistically significant.

Results
Table 1 demonstrates the distributions of sex, age, diabetes duration, baseline comorbidities and concurrent medication between the NAF group and non-NAF group. There were no significant difference in sex, age and diabetes duration between these two groups of patients (P > 0.05). Men comprised more than half (5,081, 51.9%) of the sample population. Approximately 8.2% (805) of the patients took insulins, 51.6% (5,055) took metformins, 12.2% (1,198) took acarbose, 8.2% (798) took glinides, 55.9% (5,474) took sulfonylureas, 14.3% (1,396) took
Table 1 Baseline characteristics of all patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group n = 7832</th>
<th>NAF group n = 1598</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year (SD)</td>
<td>73.1 (10.8)</td>
<td>73.1 (10.9)</td>
<td>0.98</td>
</tr>
<tr>
<td>DM duration, year (SD)</td>
<td>8.1 (4.1)</td>
<td>8.0 (4.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3767 (48.1)</td>
<td>942 (48.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>Male</td>
<td>4065 (51.9)</td>
<td>1016 (51.9)</td>
<td></td>
</tr>
<tr>
<td>Antihyperglycemic drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulins (%)</td>
<td>604 (7.7)</td>
<td>201 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Metformins (%)</td>
<td>4364 (51.6)</td>
<td>1151 (51.6)</td>
<td></td>
</tr>
<tr>
<td>Acarbose (%)</td>
<td>943 (12.0)</td>
<td>255 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Glinides (%)</td>
<td>615 (7.9)</td>
<td>183 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas (%)</td>
<td>4336 (55.4)</td>
<td>1158 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones (%)</td>
<td>1100 (14.0)</td>
<td>296 (15.1)</td>
<td></td>
</tr>
<tr>
<td>DPP4 inhibitors (%)</td>
<td>260 (3.3)</td>
<td>52 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>6507 (83.1)</td>
<td>1772 (90.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>3900 (50.9)</td>
<td>1415 (72.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD (%)</td>
<td>695 (8.9)</td>
<td>307 (15.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperthyroidism (%)</td>
<td>204 (2.6)</td>
<td>65 (3.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>1249 (15.9)</td>
<td>461 (23.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OSA (%)</td>
<td>56 (0.7)</td>
<td>22 (1.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>1098 (14.0)</td>
<td>769 (39.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PAOD (%)</td>
<td>982 (12.5)</td>
<td>338 (17.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Concurrent medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins (%)</td>
<td>3321 (42.4)</td>
<td>865 (44.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>ACEIs (%)</td>
<td>4424 (56.5)</td>
<td>1345 (68.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARBs (%)</td>
<td>3515 (44.9)</td>
<td>1133 (57.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alpha-blockers (%)</td>
<td>2492 (31.8)</td>
<td>725 (37.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>4614 (58.9)</td>
<td>1390 (71.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CCBs (%)</td>
<td>5631 (71.9)</td>
<td>1640 (83.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>5126 (65.4)</td>
<td>1580 (80.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SD, standard deviation; DM, diabetes mellitus; DPP4, dipeptidyl peptidase-4; CAD, coronary artery disease; CKD, chronic kidney disease; OSA, obstructive sleep apnoea; PAOD, peripheral artery occlusive disease; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.

TZDs and 3.2% (312) took DPP4 inhibitors. Significant differences were observed regarding comorbidities except hyperthyroidism (P = 0.08) and obstructive sleep apnoea (P = 0.07) between two groups of subjects (P < 0.0001). No significant differences were observed regarding concurrent therapies of statins between these two groups of patients except there was a significant difference in the concurrent therapies of use diuretics, calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and alpha-blockers between two groups of patients (P < 0.0001).

The overall risk of NAF using logistic regression model was neutral effect [OR, 0.93; 95% confidence interval (CI), 0.83–1.04] between two groups of subjects (Fig. 2a). The crude risk estimate of NAF for users of metformins (OR, 0.83; 95% CI, 0.72–0.96) was lower (P < 0.05) than for nonusers. Acarbose (OR, 1.03; 95% CI, 0.87–1.21), glinides (OR, 1.16; 95% CI, 0.97–1.39), and significant difference in the concurrent therapies of use diuretics, calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and alpha-blockers between two groups of patients (P < 0.0001).
thiazolidinediones (OR, 1.02; 95% CI, 0.88–1.20) and DPP4 inhibitors (OR, 0.76; 95% CI, 0.49–1.18) were not associated with increased risk of NAF (P > 0.05). However, insulins (OR, 1.33; 95% CI, 1.11–1.59) and sulfonylureas (OR, 1.21; 95% CI, 1.05–1.39) had the highest risk estimates of NAF (P < 0.05) (Fig. 2a).

Finally, the risk estimate of NAF after adjusting for sex, age, diabetes duration, comorbidities and concurrent medication for users of insulin (OR, 1.58; 95% CI, 1.37–1.82) was higher (P < 0.05) than for nonusers. Metformins, acarbose, glinides, sulfonylureas, and thiazolidinediones were not associated with increased risk of NAF (P > 0.05). However, DPP4 inhibitors (OR, 0.65; 95% CI, 0.45–0.93) had a lower risk estimate of NAF (P < 0.05) (Fig. 2b).

Discussion

In this nested case–control study, based on health insurance claims database, we found that the use of DPP4 inhibitors was associated with a lower risk of NAF, while metformin, acarbose, glinides, sulfonylureas, and thiazolidinediones were not associated with an increase in the risk of NAF. Insulin was associated with a significant increase in the risk of NAF during the long-term follow-up. Our findings provide some support for the hypothesis that there are differences in the risk of developing NAF among the different classes of antihyperglycemic drugs in diabetic patients.

Insulin is the most commonly used second-line antihyperglycemic drug for patients with a poor glycemic control [13]. In this study, insulin was found to be associated with a high risk of NAF in outpatients with type 2 diabetes. No studies have reported that insulin is associated with increased risk of NAF. Previous studies have reported that the duration of diabetes and glycemic control is related to the development of NAF [14–17]. Dublin et al. [14] found that there was an association between HbA1c levels and risk of NAF in a population-based cohort study. They indicated that 1% higher HbA1c level was associated with a 14% (OR, 1.14, 95% CI, 0.96–1.35) risk of developing NAF. A potential explanation for the association between insulin therapy and NAF may be related to long duration of diabetes (more than 8 years) and poor glycemic control in our study.

Some studies have reported that atrial fibrillation is an inflammatory process involving arrhythmia, and it has been shown to increase oxidative stress and induce structural remodelling in atrial myocytes [18–20]. Previous studies have also reported that metformin is associated with a lower risk of NAF development that would be attenuated by evidence of an anti-inflammatory response and oxidative stress in diabetic patients [10,21–23]. In contrast to previous findings, metformin was not associated with a low risk of NAF in our study.

The differences between our finding and that reported by Chang et al. [10] may be attributable to old age (75 vs. 58 years old) in our study.

Acarbose, glinides and sulfonylureas were not associated with risk of NAF in the current study. Several studies have reported that DM is one of the independent risk factors for the development of NAF [24]. The reason for these findings in our study was unclear, but it may be attributable to innate character of patients with diabetes. These findings emphasize the need for further investigation of the mechanistic links between these antihyperglycemic drugs and NAF.

Thiazolidinediones may decrease NAF risk by several mechanisms. They may have a positive effect on anti-inflammatory and antioxidant activities by reducing atrial fibrosis, inflammatory response and oxidative stress; suppressing atrial fibrillation inducibility; and reducing atrial structure remodeling in a different animal model [8,24–27]. Therefore, previous studies have reported that use of thiazolidinediones was independently associated with a decreased risk of NAF [9,28]. In an observational clinical study, Chao et al. [9] reported that the use of thiazolidinediones is associated with decreased risk of developing NAF. In that cohort study, the relative risk for NAF in individuals taking a thiazolidinedione after adjustment for age, underlying diseases, and baseline medication compared with those not taking a thiazolidinedione was 0.69 (95% CI 0.49–0.91). The differences between our finding and that reported by Chao et al. [9] may be attributable to younger age and exclusion of patients with few clinical risk factors from their study sample. However, our result is similar to those reported by the RECORD study [29] and the PROactive study [30], which enrolled high-risk patients with type 2 diabetes and did not show a reduction in NAF in the thiazolidinedione group compared with the nonuser group.

In this study, DPP4 inhibitors were found to be associated with a lower risk of NAF in outpatients with DM. No studies have reported that DPP4 inhibitors are associated with decreased risk of NAF. To the best of our knowledge, our study is the first to show that DPP4 inhibitors are associated with a lower risk of NAF. Previous studies have reported that old age and diabetes-associated comorbidities have an increased risk for NAF in diabetic patients [18,31–34]. The reason for this finding in our study was unclear, but it may suggest that a potential explanation for the association between DPP4 inhibitor therapy and NAF is baseline patient’s age and comorbidity.

This study has several strengths. First, to our knowledge, it is the first large observation study with a long (8-year) duration that was to investigate the association between different classes of antihyperglycemic drugs and NAF in elderly patients. Second, to the best of our knowledge, our study is the first to show that DPP4 inhibitors are associated with a lower risk of NAF in elderly patients. Third, this finding shows the importance of
investigating the mechanistic links between antihyperglycemic drugs and NAF in the future.

Some limitations in this study need to be emphasized. First, the present study was based on a retrospective review of prescription records, which quite naturally were not adequate source of information for specifically looking at atrial fibrillation. Hence, it is quite likely that atrial fibrillation was under-reported at the time of inclusion. Therefore, caution must be exercised in interpreting our data. Second, all cases in this study were collected from claim datasets of primary care clinics and diagnoses were based on physician reporting only in Taiwan; therefore, our findings cannot be generalized to patients in different areas. Third, all patients in our study sample had received a diagnosis of DM or atrial fibrillation, and all received treatment with antihyperglycemic agents. However, dosing, treatment adherence and severity of DM may have differed across patients who used different antihyperglycemic drugs. Thus, the association between antihyperglycemic agent therapy and risk for NAF may not reflect the effect of prescribed drugs, but rather the severity of the patient’s disease and treatment adherence. Future research is needed to confirm our findings.

In conclusion, our results show that use of dipeptidyl peptidase 4 inhibitor was associated with a low risk of NAF. Insulin use was associated with a significant increase in the risk of NAF during the long-term follow-up. Based on current evidence, practitioners should recognize that varying antihyperglycemic drug characteristics can influence atrial fibrillation incidence rates. These findings have potential clinical implications and emphasize the need for further investigation of the mechanistic links between antihyperglycemic drugs and NAF.

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