

國立臺灣大學公共衛生學院流行病學與預防醫學研究所

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比較非維生素 K 拮抗劑口服抗凝血劑與 warfarin 在心房
顫動和糖尿病患者中對糖尿病相關併發症及嚴重低血糖
風險的影響

Comparative Effectiveness of Non-Vitamin K Antagonist
Oral Anticoagulants and Warfarin on the Risks of Diabetes-
related Complications and Serious Hypoglycemia in Patients
with Atrial Fibrillation and Diabetes Mellitus

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論文英文題目：Comparative Effectiveness of Non-Vitamin K Antagonist Oral Anticoagulants and Warfarin on the Risks of Diabetes-related Complications and Serious Hypoglycemia in Patients with Atrial Fibrillation and Diabetes Mellitus

本論文係 黃暉凱 君（學號 D08849020）在國立臺灣大學流行病學與預防醫學研究所完成之博士學位論文，於民國 113 年 01 月 29 日承下列考試委員審查通過及口試及格，特此證明。

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摘要



引言：

心房顫動和糖尿病是全球性的重要公共衛生問題，隨著人口老化，其盛行率和發病率皆不斷上升。患有心房顫動的病人，尤其又同時患有糖尿病的病人，有相當高的中風發生風險，因此往往需要長期使用口服抗凝血藥物來預防中風。先前有研究指出，維生素 K 可能對於改善胰島素敏感性和葡萄糖耐受性有所助益。亦有研究進一步指出，非維生素 K 拮抗劑口服抗凝血劑（non-vitamin K antagonist oral anticoagulants, NOAC）和維生素 K 拮抗劑華法林（warfarin），對維生素 K 功能抑制與否之不同，可能導致其使用者，在葡萄糖耐受性和糖尿病控制方面存在差異。然而，目前有關 NOAC 與 warfarin 的使用，對於心房顫動和糖尿病病患其各種糖尿病相關併發症發生風險的潛在影響，臨床證據仍然不足。此外，先前曾有研究指出，warfarin 與某些糖尿病藥物之間可能有潛在的藥物交互作用，併用時可能增加低血糖風險，但關於 NOAC 與 warfarin 的使用對於低血糖風險影響之比較，相關證據仍相當缺乏。在心房顫動和糖尿病病患中，選擇適當的口服抗凝血藥物以最小化糖尿病併發症和低血糖的風險，是重要的臨床問題，然而相關研究證據有限，仍需要進一步探討。

研究目的：

我們的第一項研究旨在探討心房顫動和糖尿病病患使用 NOAC 相較於 warfarin，對糖尿病各項相關併發症和死亡風險的影響。我們的第二項研究旨在探討病患在使用各種糖尿病藥物時，併用 NOAC 相較於併用 warfarin，對於嚴重低血糖風險的影響。

方法：

我們使用台灣全人口健保資料庫，進行回顧性世代研究。我們納入了健保資料庫中曾診斷有心房顫動和糖尿病，並有使用 NOAC 或 warfarin 的患者。在研究中，我們使用目標試驗模擬設計，比較 NOAC 與 warfarin 使用者在糖尿病相關併發症（包含

大血管併發症、小血管併發症和血糖急症)和死亡風險的差異。我們使用穩定治療權重倒數機率(stabilized inverse probability of treatment weighting, IPTW),來建立一個在不同治療組之間具有相似患者特性的假想族群進行分析。我們採用Cox比例風險模型來估計風險比(hazard ratio, HR)。在研究二中,我們使用泊松回歸模型估計嚴重低血糖的發生率比(incidence rate ratio, IRR)。同樣使用穩定治療權重倒數機率來平衡治療組之間的特徵,以進行分析比較。

結果：

在研究一中,共有19847名NOAC使用者和10372名warfarin使用者被納入分析。與使用warfarin的病患相比,使用NOAC的病患在發展大血管併發症(HR=0.84, 95% CI: 0.78-0.91, $p<0.001$)、小血管併發症(HR=0.79, 95% CI: 0.73-0.85, $p<0.001$)、血糖急症(HR=0.91, 95% CI: 0.83-0.99, $p=0.043$)和死亡(HR=0.78, 95% CI: 0.75-0.82, $p<0.001$)的風險皆顯著較低。針對個別NOAC(dabigatran, rivaroxaban, apixaban, and edoxaban)的分析顯示,與warfarin相比,各NOAC的使用者在併發症和死亡風險方面,都有一致的減少趨勢。各項敏感性分析和負對照指標的分析,也都支持我們的研究發現。

在研究二中,我們共納入56774名診斷有心房顫動和糖尿病且有併用糖尿病藥物和口服抗凝血劑之患者進行分析。總體而言,與糖尿病藥物併用warfarin相比,併用NOAC其嚴重低血糖風險顯著較低(IRR=0.73, 95% CI: 0.63–0.85, $p<0.001$)。在根據不同糖尿病藥物的次族群分析中,發現在服用糖尿病藥物二甲雙胍(metformin)(IRR=0.73, 95% CI: 0.59–0.89, $p=0.002$)、二肽基肽酶-4抑制劑(dipeptidyl peptidase-4 inhibitor, DPP-4i)(IRR=0.73, 95% CI: 0.59–0.92, $p=0.007$)或磺脲類藥物(sulfonylurea)(IRR=0.68, 95% CI: 0.56–0.81, $p<0.001$)的次族群患者中,併用NOAC者其嚴重低血糖風險顯著較併用warfarin者低。

結論：

在患有心房顫動和糖尿病之患者中，與 warfarin 相比，使用 NOAC 與較低的糖尿病相關併發症（例如大血管併發症、小血管併發症、血糖急症）和死亡風險相關。與糖尿病藥物同時使用時，NOAC 使用者也比 warfarin 使用者有顯著較低的嚴重低血糖風險。因此，對於需要使用口服抗凝血劑治療的心房顫動和糖尿病患者而言，NOAC 可能是一個比 warfarin 更好的治療選擇，以降低這些糖尿病相關併發症和死亡風險。

關鍵字：心房顫動、糖尿病、非維生素 K 拮抗劑口服抗凝血劑、華法林、併發症、低血糖、世代研究

Abstract



Introduction:

Atrial fibrillation (AF) and diabetes mellitus (DM) are significant public health issues, with rising prevalence and incidence in the aging population worldwide. Patients with AF, particularly those with DM, are more likely to experience stroke during their lifetime, necessitating long-term oral anticoagulant use for stroke prevention. Previous evidence suggests that vitamin K may play a beneficial role in improving insulin sensitivity and glucose tolerance. Some studies have further indicated potential differences in glucose tolerance and diabetes control between non-vitamin K antagonist oral anticoagulants (NOACs) use and warfarin use due to their varying effects on vitamin K function. However, current clinical evidence regarding the potential effects of NOACs versus warfarin on the risks of developing various diabetes-related complications in patients with AF and DM remains limited. Furthermore, a few previous studies have suggested potential drug-drug interactions between warfarin and some specific antidiabetic drugs, which may increase the risk of hypoglycemia, but evidence comparing NOACs and warfarin on this issue is scarce. Identifying an optimal oral anticoagulant to minimize the risk of diabetes complications and hypoglycemia in patients with AF and DM is a critical clinical concern, yet relevant evidence is limited and requires further investigation.

Study Aims:

Our first study aimed to investigate the risk of diabetes-related complications and mortality in patients with AF and DM taking NOACs compared to those taking warfarin. In our second study (Study 2), we aimed to specifically investigate the risk of serious hypoglycemia when taking various antidiabetic medications with concurrent NOACs compared to those with concurrent warfarin.



Methods:

We conducted retrospective cohort studies using nationwide data from Taiwan's National Health Insurance Research Database (NHIRD). Patients with AF and DM taking either NOACs or warfarin in the NHIRD were identified. In Study 1, we investigated the risks of diabetes-related complications (macrovascular complications, microvascular complications, and glycemic emergencies) and mortality in NOAC versus warfarin users using a target trial emulation framework. Stabilized inverse probability of treatment weighting (IPTW) was used to create a pseudo-population with balance patient characteristics between treatment groups for analyses. Cox proportional hazard models were employed to estimate hazard ratios (HRs). In Study 2, we estimated the incidence rate ratios (IRRs) of serious hypoglycemia using Poisson regression models. Stabilized IPTW was also utilized to balance characteristics between treatment groups for comparisons. Various sensitivity analyses were further performed in both Study 1 and Study 2.

Results:

In Study 1, a total of 19847 NOAC users and 10372 warfarin users were included. Patients taking NOACs had significantly lower risks of developing macrovascular complications (HR=0.84, 95% CI: 0.78-0.91, $p<0.001$), microvascular complications (HR=0.79, 95% CI: 0.73-0.85, $p<0.001$), glycemic emergency (HR=0.91, 95% CI: 0.83-0.99, $p=0.043$), and mortality (HR=0.78, 95% CI: 0.75-0.82, $p<0.001$) than those taking warfarin. The analyses for individual NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) revealed a consistent trend of decreased complication and mortality risks for NOAC users compared to warfarin users. Several sensitivity analyses and the analyses for negative control outcomes also supported our study findings.

In Study 2, a total of 56,774 patients with AF and DM taking antidiabetic drugs with concurrent use of NOACs or warfarin were included for analyses. Overall, concurrent use of NOACs with antidiabetic drugs had a significantly lower risk of serious hypoglycemia than concurrent use of warfarin with antidiabetic drugs (IRR=0.73, 95% CI: 0.63–0.85, $p<0.001$). In the subgroup analyses according to different antidiabetic drugs, the significantly lower risk of serious hypoglycemia associated with concurrent NOAC use was found in patients taking metformin (IRR=0.73, 95% CI: 0.59–0.89, $p=0.002$), DPP-4i (IRR=0.73, 95% CI: 0.59–0.92, $p=0.007$), or sulfonylurea (IRR=0.68, 95% CI: 0.56–0.81, $p<0.001$).

Conclusions:

Among patients with AF and DM, NOAC use was associated with lower risks of diabetes-related complications (e.g., macrovascular complications, microvascular complications, glycemic emergencies) and mortality compared with warfarin use. Patients taking antidiabetic drugs with concurrent use of NOACs also had a significantly lower risk of serious hypoglycemia than those with concurrent use of warfarin. Therefore, NOAC may be a better therapeutic choice than warfarin for decreasing these complications and mortality in diabetic AF patients requiring oral anticoagulant treatment.

Keywords: atrial fibrillation; diabetes mellitus; non-vitamin K antagonist oral anticoagulants; warfarin; complication; hypoglycemia; cohort study

Abbreviation list



ACEI: angiotensin-converting enzyme inhibitors

AF: atrial fibrillation

AGI: alpha-glucosidase inhibitors

ARB: angiotensin II receptor blockers

ATC: Anatomical Therapeutic Chemical

ATE: average treatment effect in the whole population

CKD: chronic kidney disease

COPD: chronic obstructive pulmonary disease

CHA2DS2-VASc score: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category score

DM: diabetes mellitus

DPP-4i: dipeptidyl peptidase-4 inhibitors

ESRD: end-stage renal disease

GLP-1RA: glucagon-like peptide-1 receptor agonists

HWDC: Health and Welfare Data Science Center

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification

INR: international normalized ratio

NHIRD: National Health Insurance Research Database

NOAC: non-vitamin K antagonist oral anticoagulant

NSAID: nonsteroidal anti-inflammatory drugs

SGLT-2i: sodium-glucose cotransporter-2 inhibitors

TZD: thiazolidinediones

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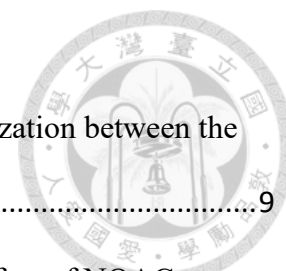


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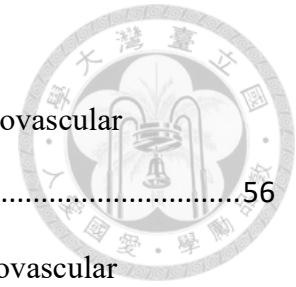
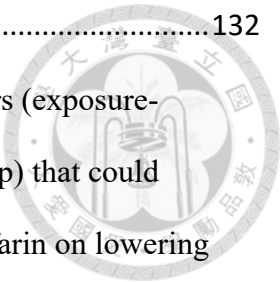


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Chapter 1. Introduction

1.1 Diabetes mellitus

Diabetes mellitus (DM), a chronic metabolic disorder characterized by persistent hyperglycemia, is a major public health concern globally.¹ It arises from defects in insulin secretion, insulin action, or both, leading to complications that impact various organ systems. The two primary types of diabetes are type 1 DM and type 2 DM. Type 1 DM is primarily due to pancreatic β -cell destruction leading to insulin deficiency, often due to an autoimmune process. In contrast, type 2 DM, which accounts for the majority of diabetes cases, is characterized by insulin resistance and relative insulin deficiency. More than 90% of DM cases are attributed to type 2 DM.¹

The prevalence of DM has been increasing steadily, making it a global epidemic. According to the 2021 report from the International Diabetes Federation in the 10th edition of the IDF Diabetes Atlas,² there are currently 537 million adults aged 20 to 79 living with diabetes, representing 1 in 10 adults globally. This figure is projected to increase to 643 million by 2030 and 783 million by 2045. In 2021, diabetes was accountable for 6.7 million deaths, equating to one death every 5 seconds. The financial burden is also substantial, with diabetes-related healthcare costs reaching at least USD 966 billion, a 316% rise in the past 15 years. Additionally, 541 million adults are currently experiencing impaired glucose tolerance, placing them at a high risk of developing type 2 DM.² This rise of prevalence is attributed to various factors, such as aging populations, increasing prevalence of obesity, and sedentary lifestyles. The global burden of diabetes is significant, not only in terms of healthcare costs but also in terms of loss of productivity, reduced quality of life, and increased mortality.¹⁻⁵

The pathophysiology of DM involves complex interactions between genetic,

environmental, and lifestyle factors. The genetic predisposition to type 2 DM involves multiple genes, each contributing a small amount to the overall risk. The inheritance pattern is polygenic, meaning several genes are involved, which may influence insulin secretion, insulin action, or both. Environmental influencers, such as exposure to certain viruses, toxins, or a diet high in calories, can trigger or exacerbate the development of insulin resistance and β -cell dysfunction. Lifestyle factors are perhaps the most significant contributors to the development of type 2 DM. These include obesity, physical inactivity, and poor dietary choices. Obesity is a major risk factor for the development of insulin resistance. Adipose tissue, especially visceral fat, secretes various substances that can impair insulin signaling, leading to insulin resistance. Additionally, physical inactivity and diets high in refined carbohydrates and saturated fats can exacerbate insulin resistance and β -cell dysfunction. The development of type 2 DM is thus a multifactorial process, where genetic predisposition interacts with environmental and lifestyle factors, leading to insulin resistance and β -cell dysfunction.⁵⁻⁸

Diabetes management mainly focuses on glycemic control to prevent or delay the onset of complications. This management often requires a multifaceted approach, including lifestyle modifications and diabetes medications. Despite advances in diabetes management, many individuals with diabetes still experience suboptimal glycemic control, thus remaining at risk for various complications.^{9,10}

1.2 Diabetes-related macrovascular complications, microvascular complications, and glycemic emergency

Over time, persistent hyperglycemia in diabetes can lead to a spectrum of diabetes-related complications, resulting in considerable health risks for the patients.

These complications are broadly categorized into macrovascular and microvascular complications, each associated with significant morbidity and mortality.^{11,12} The complications associated with type 2 DM were prevalent. A previous study spanning 28 countries across Asia, Africa, South America, and Europe showed that about half of the patients with type 2 DM presented with microvascular complications, while 27% were affected by macrovascular complications.¹³

Macrovascular complications refer to diseases of the large blood vessels and are primarily related to atherosclerotic cardiovascular disease.¹¹ They include coronary artery disease, peripheral vascular disease, and cerebrovascular disease. The pathogenesis of these conditions in diabetes is complex, involving chronic hyperglycemia, dyslipidemia, hypertension, and inflammation that accelerates atherosclerosis.

Microvascular complications are the result of damage to small blood vessels and capillaries, leading to conditions such as diabetic retinopathy, nephropathy, neuropathy, and foot/toe amputation.¹¹ Diabetic retinopathy, a significant cause of blindness, arises from the damage to the retinal blood vessels. Diabetic nephropathy, one of the leading causes of end-stage renal disease, is characterized by albuminuria and declining renal function. Diabetic neuropathy, which includes various nerve disorders, can result in pain, loss of sensation, and foot ulcers, potentially leading to the need for foot/toe amputation if the wound worsens and becomes uncontrollable.

Apart from macrovascular and microvascular complications, diabetes can lead to acute glycemic emergencies. These include diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and severe hypoglycemia. DKA is characterized by hyperglycemia, ketosis, and metabolic acidosis. It results from a severe deficiency of insulin, leading to increased breakdown of fats and production of

ketone bodies, which cause the blood to become acidic. HHS presents with extreme hyperglycemia and hyperosmolarity without significant ketosis or acidosis. It evolves over a longer period and is often triggered by an illness or infection. Both DKA and HHS can be life-threatening if not quickly recognized and treated effectively ¹².

Severe hypoglycemia is also a critical condition often encountered in diabetes management, as introduced in the following section.

1.3 Severe hypoglycemia: a dangerous side-effect of antidiabetic medications

In patients with DM, it's not just high blood glucose levels that can harm their health; low blood glucose levels can also be detrimental. Severe hypoglycemia, characterized by critically low blood glucose levels requiring assistance from another person for treatment, is one of the most dangerous side effects of antidiabetic medications. This condition is particularly associated with the use of insulin and sulfonylureas, which are potent in lowering blood glucose.¹⁴ It occurs more frequently in patients with poorly controlled or progressed diabetes ^{15,16}. Severe hypoglycemia can lead to neurological deficits, convulsions, loss of consciousness, and in extreme cases, can be fatal. Hypoglycemia could also affect cardiac autonomic tone and cause abnormal repolarization, which may further lead to cardiac arrhythmias and sudden cardiac death.^{17,18} Therefore, in patients undergoing diabetes treatment, preventing the occurrence of severe hypoglycemia as well as promptly managing low blood sugar levels is an important clinical issue.

1.4 Atrial fibrillation

Atrial fibrillation (AF) is a most common and clinically significant cardiac arrhythmia characterized by an irregular and often rapid heart rhythm that originates in the atria, leading to ineffective contractions and reduced blood flow. AF can cause a variety of symptoms including palpitations, fatigue, and shortness of breath, although it can also be asymptomatic.

As a result of its rising prevalence and incidence among aging populations worldwide, atrial fibrillation has emerged as a significant public health concern ^{19,20}. A previous nationwide study in Taiwan demonstrated that the incidence of AF was 1.51 per 1,000 person-years in 2011. It is projected that the prevalence of AF will reach 4.0% by the year 2050, resulting in an anticipated total of around 730,431 patients with AF in Taiwan.²¹

AF is a significant contributor to the incidence of thromboembolic events, especially stroke; it is associated with a three- to five-fold increased risk of ischemic stroke. Globally, it is estimated that AF accounts for approximately 15% of all strokes ^{22,23}. The irregular heart rhythm in AF leads to stasis of blood in the atria, particularly in the left atrial appendage, increasing the risk of blood clot formation. When a blood clot dislodges, it can travel to the brain, causing a cardioembolic stroke.

The management of AF typically includes two primary principles: stroke/systemic embolism prevention and symptom management through either rate control or rhythm control strategies. Rhythm/rate control involves medical therapy or procedural interventions to restore and maintain normal sinus rhythm or heart rate.²⁴ The primary focus of stroke prevention involves the long-term use of anticoagulation therapy to minimize the risk of thromboembolic events.²⁵

1.5 Diabetes mellitus and atrial fibrillation

Previous research has indicated that DM is a major risk factor for the development of AF. This is due to the metabolic and structural changes in the heart caused by prolonged high blood sugar levels, which in turn, can affect the electrical system of the heart, leading to AF. These changes include myocardial fibrosis, increased fatty deposits around the heart,²⁶ and a general thickening of the heart muscle,²⁷ all of which can disrupt the normal electrical impulses and lead to arrhythmias such as AF.

On the other hand, in individuals with AF, the presence of diabetes, particularly when accompanied by poor glycemic control, increases the risk of complications such as stroke, thromboembolism, and cardiovascular mortality.²⁸⁻³¹ This increased risk may be attributed to the synergistic effects of both conditions. Poor glycemic control in DM can lead to endothelial dysfunction, increased inflammation, and hypercoagulability,³²⁻³⁴ thereby predisposing individuals to thrombotic events, which are the primary causes of stroke in AF patients. This dual burden of DM and AF underlines the imperative need for effective management strategies. Effective control of DM is essential to mitigate the risks of both AF and DM complications, improve patient outcomes, and reduce the burden on healthcare systems.

1.6 Oral anticoagulant use in patients with atrial fibrillation

Oral anticoagulants play a crucial role in the management of patients with AF, primarily for the prevention of stroke and systemic embolism. The use of oral anticoagulants in patients with AF is guided by risk stratification scores like CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score, which includes clinical factors such as congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack, vascular

disease, and sex.³⁵ Based on these scores, anticoagulation therapy is recommended for patients with moderate to high risk of stroke.

While oral anticoagulants are effective in reducing the risk of thromboembolic events in patients with AF, they are not without risks. The most significant complication associated with these medications is bleeding. This risk is particularly heightened in cases of over-anticoagulation or in the presence of other risk factors such as advanced age, concurrent use of antiplatelet drugs, or a history of major bleeding.³⁶ Regular monitoring and careful dose adjustment are required, especially with agents like warfarin, to minimize the bleeding risk.

1.7 Oral anticoagulant types – warfarin and NOACs

Oral anticoagulants can be divided into two main types depending on whether they inhibit vitamin K function: vitamin K antagonists and non-vitamin K antagonist oral anticoagulants (NOACs).

Warfarin, a vitamin K antagonist, has been the mainstay of oral anticoagulation therapy for decades. It functions by inhibiting the synthesis of vitamin K-dependent clotting factors, thus preventing blood clot formation. Despite its effectiveness, warfarin therapy poses challenges due to its narrow therapeutic range, requiring frequent monitoring of the international normalized ratio (INR) to ensure therapeutic efficacy while minimizing the risk of bleeding. Additionally, warfarin interacts with many drugs and is affected by dietary Vitamin K, and thus may need regular adjustments in dosing.^{37,38}

NOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, represent significant advancements in anticoagulation therapy. These agents directly inhibit specific clotting factors: dabigatran is a direct thrombin inhibitor, while rivaroxaban,

apixaban, and edoxaban are factor Xa inhibitors. NOACs offer several advantages over warfarin, including a rapid onset of action, fewer dietary and drug interactions, and unnecessary routine INR monitoring. This convenience, combined with their potential favorable safety and efficacy profiles, has led to their increasing use in clinical practice.^{38,39}

Table 1 provides a summary of the clinical characteristics and a comparison between the use of NOACs and warfarin for patients with AF.^{40,41}

Table 1. Comparative summary of the clinical characteristics and utilization between the use of NOACs and warfarin for patients with AF

Feature	NOACs	Warfarin
Indications or preferences	<ul style="list-style-type: none"> - Stroke prevention in AF - Preferred in non-valvular AF 	<ul style="list-style-type: none"> - Stroke prevention in AF - Indicated for mechanical heart valves, severe rheumatic mitral stenosis, recent bioprosthetic valve implantation, and when NOACs are contraindicated
Contraindications or non-preferences	<ul style="list-style-type: none"> - Active, clinically significant bleeding - Severe bleeding diathesis - Avoided or used with caution in patients with severe renal impairment - Not recommended for mechanical heart valves, severe rheumatic mitral stenosis, and specific drug interactions (e.g., P-glycoprotein inducers, chronic antiviral agents) 	<ul style="list-style-type: none"> - Active, clinically significant bleeding - Severe bleeding diathesis - Should be careful as it interacts with numerous medications
Dosing considerations	<ul style="list-style-type: none"> - Fixed dosing, no routine INR testing, minimal dietary interactions - Specific dosing adjustments for renal function and drug interactions 	<ul style="list-style-type: none"> - Requires regular INR monitoring with adjustments to maintain the targeted INR level - Affected by diet and drug interactions.
Cost and accessibility	<ul style="list-style-type: none"> - Generally higher cost than warfarin - May impact choice in resource-limited settings 	<ul style="list-style-type: none"> - Lower cost compared to NOACs - May be more accessible in resource-limited settings
Clinical efficacy and	<ul style="list-style-type: none"> - Shown to have similar or lower 	<ul style="list-style-type: none"> - Long-standing use with a well-

safety	rates of ischemic stroke and major bleeding compared to warfarin	understood profile. - Requires careful management to balance stroke prevention and bleeding risk
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When drugs were introduced and covered by Taiwan's National Health Insurance	<ul style="list-style-type: none"> - Dabigatran: June 2012 - Rivaroxaban: January 2012 - Apixaban: June 2014 - Edoxaban: September 2016 	- Warfarin: March 1995
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Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant

1.8 Vitamin K, warfarin, and glucose metabolism

In addition to its role in coagulation, previous studies have suggested that vitamin K may also play a beneficial role in improving insulin sensitivity and glucose tolerance, as well as in reducing the risk of developing DM.⁴²⁻⁴⁴ These effects may be mediated through various mechanisms. For instance, vitamin K could improve insulin sensitivity via the metabolism of osteocalcin, which is a vitamin K-dependent protein. Osteocalcin stimulates the expression of *Cyclin D1* and *Insulin* in β -cells and *Adiponectin* (an insulin-sensitizing adipokine) in adipocytes, resulting in β -cell proliferation and improving insulin secretion and sensitivity.⁴² Furthermore, vitamin K may also suppress inflammatory responses by inactivating the NF- κ B signaling pathway and exhibit lipid-lowering effects, which may help to improve insulin resistance^{42,43}. In addition to in vitro and in vivo studies, clinical trials have also suggested that vitamin K supplementation can improve glycemic status and slow the progression to insulin resistance.^{45,46} A large-scale prospective cohort study further demonstrated that high dietary intake of vitamin K was associated with a reduced risk of developing DM.⁴⁷ Given the aforementioned beneficial effects of vitamin K on glucose metabolism, the inhibition of vitamin K by warfarin, but not by NOACs, may potentially result in reduced insulin sensitivity and impaired glucose tolerance, leading to poorer diabetes control. These hypotheses are further supported by two recent real-world cohort studies which reported that NOACs were associated with a lower risk of developing diabetes compared to warfarin in non-diabetic AF patients^{48,49}. However, whether the choice of NOAC or warfarin would influence diabetes control or the risk of diabetes complication development in patients already having DM is still undetermined due to currently limited evidence.

1.9 NOACs, inflammation and atherosclerotic plaque formation

Inflammation and coagulation are closely interconnected. According to available data, coagulation proteases, including factor Xa and thrombin, are involved in non-hemostatic cellular activities, such as inflammation. Factor Xa has been shown to exhibit pro-inflammatory activity in vitro, inducing the expression of IL-6, IL-8, and monocyte chemoattractant protein 1 in endothelial cells and leukocytes, thereby contributing to the inflammatory process⁵⁰. Thrombin-induced pro-inflammatory activities include upregulating leukocyte adhesion molecules and P-selectin onto platelets and endothelial cells, stimulating pro-inflammatory cytokines (e.g., IL-6 and IL-8 by monocytes) and chemokine production, and stimulating the release of histamine^{50,51}.

Inflammation is widely acknowledged as a significant contributor to the pathophysiology of atherosclerosis and atherothrombosis. Recent evidence suggests that coagulation proteases, including factor Xa and thrombin, contribute to the progression of atherosclerotic plaques, in addition to involving thrombus formation after plaque rupture. This may be partly due to their involvement in the inflammatory process mentioned above^{50,52}.

Dabigatran is a direct thrombin inhibitor, while rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors. Inhibition of factor Xa or thrombin by NOACs may have additional benefits beyond anticoagulation; for instance, they may block several pro-inflammatory mechanisms and increase the stability of atherosclerotic plaques as previously mentioned.⁵⁰ Nevertheless, compared with warfarin, whether the use of NOACs could reduce the risk of inflammation- or atherosclerosis-related diseases (e.g., several diabetes complications) in patients with DM is still needed further exploration.

Chapter 2. Literature review and study aims



2.1 Potential effect of NOACs versus warfarin on development of diabetes-related complications

As aforementioned, vitamin K may play a beneficial role in improving insulin sensitivity/glucose tolerance and thus, warfarin, a vitamin K antagonist, may potentially result in poorer diabetes control than NOACs. Additionally, some preclinical studies suggested potential effects of NOACs on suppressing the inflammation and atherosclerotic plaque formation, which were related to the mechanisms of developing several diabetes complications. Therefore, in patients with AF and DM, NOAC use may theoretically lead to lower risks of various diabetes complications and better clinical outcome than warfarin use. Nevertheless, the available evidence remains limited, particularly in terms of research on non-macrovascular complications and studies evaluating Asian populations.

2.1.1 Preexisting evidence on macrovascular complications

A previous post hoc analysis of the ARISTOTLE trial indicated that apixaban, in comparison to warfarin, displayed similar trends in reducing the risk of stroke or systemic embolism in AF patients, regardless of their diabetes status.⁵³ However, this trend was not statistically significant in the subgroup with diabetes (HR = 0.75, 95% CI: 0.53–1.05). Additionally, there was no notable difference in the risk of myocardial infarction between apixaban and warfarin (HR = 1.02, 95% CI: 0.62–1.67) in the diabetes subgroup.⁵³ A retrospective claims analysis using US Truven MarketScan data from 2012 to 2017 showed that, among patients with AF and DM, rivaroxaban was linked to lower risks of major adverse cardiovascular events (defined as ischemic

stroke or myocardial infarction) compared to warfarin (HR = 0.75, 95% CI: 0.59–0.96).⁵⁴ Another recent retrospective cohort study, using Medicare data in the United States, demonstrated that NOACs were associated with a significantly reduced risk of stroke or systemic embolism when compared to warfarin (HR = 0.37, 95% CI: 0.25–0.56).⁵⁵ Furthermore, a previous meta-analysis pooling data from four major warfarin-controlled phase 3 AF trials (e.g., RE-LY,⁵⁶ ROCKET AF,⁵⁷ ARISTOTLE,⁵³ and ENGAGE AF-TIMI trials⁵⁸) assessed the effects of NOACs (including dabigatran, rivaroxaban, apixaban, and edoxaban) specifically in diabetes subgroups.²⁹ This meta-analysis revealed that in the diabetes subgroup of AF patients, NOAC users had a lower risk of stroke/systemic embolism than those using warfarin (RR = 0.80, 95% CI: 0.69–0.93).²⁹ However, although some existing studies have explored these issues, most have focused on Western populations, leaving evidence pertaining to Asian populations insufficient.

A previous retrospective study in Taiwan found that among diabetic AF patients, there was no significant difference in the risks of stroke or myocardial infarction between NOACs (dabigatran and rivaroxaban) and warfarin users.⁵⁹ However, that study was restricted to patients participating in Taiwan's diabetes pay-for-performance program and had a relatively small sample size (322 dabigatran users and 320 rivaroxaban users), which may not adequately represent the broader patient population in Taiwan. Therefore, further research is necessary.

2.1.2 Preexisting evidence on microvascular complications

To date, only a few real-world studies have investigated renal outcomes with different oral anticoagulants specifically in patients with AF and DM. A previous retrospective cohort analysis in the United States indicated that NOACs, particularly

dabigatran and rivaroxaban, might be linked to lower risks of a $\geq 30\%$ decline in eGFR in AF patients with baseline diabetes (dabigatran vs. warfarin: HR = 0.51, 95% CI: 0.33-0.76; rivaroxaban vs. warfarin: HR = 0.68, 95% CI: 0.53-0.86).⁶⁰ However, the study found no significant difference in the risk of kidney failure (defined as eGFR < 15 ml/min per 1.73 m², kidney transplant, or long-term dialysis) between NOACs and warfarin users. It is noteworthy that the mean on-treatment follow-up period in this study was relatively short, at only 10.7 months.⁶⁰ Another retrospective claims analysis, utilizing data from the United States IBM MarketScan, revealed that in patients with AF and DM, rivaroxaban was associated with a lower risk of developing Stage 5 CKD or receiving hemodialysis, compared to warfarin (HR = 0.82, 95% CI: 0.70–0.96).⁶¹ Additionally, a retrospective claims analysis using US Truven MarketScan data suggested that rivaroxaban was associated with a lower risk of major limb amputation compared to warfarin (HR = 0.20, 95% CI: 0.06–0.69).⁵⁴

However, currently, there is scarce evidence comparing the risks of retinopathy and neuropathy among patients with AF and DM who are taking NOACs versus warfarin. Moreover, the aforementioned studies did not focus on Asian populations. Research exploring NOAC vs. warfarin in patients with AF and DM, specifically regarding microvascular complications in Asians, is still lacking.

2.1.3 Preexisting evidence on glycemic emergencies

To our knowledge, only a previous study has compared the risk of hypoglycemia between NOAC and warfarin users, and it observed no significant difference in hypoglycemic risk between the two medications among patients with type 2 diabetes.⁶² Research comparing the risks of DKA and HHS between NOAC and warfarin is still lacking. Due to this paucity of evidence, whether there are different

risks of glycemic emergencies associated with NOAC and warfarin in both Western and Asian populations remains unknown.



2.1.4 Preexisting evidence on mortality

Several studies have observed an overall lower mortality risk associated with NOAC use compared to warfarin in both the general and older AF populations.^{63,64} In patients with diabetes and AF, some evidence has also suggested a lower all-cause mortality risk for NOAC users than for warfarin users. A recent retrospective cohort study using Medicare data in the United States showed that NOACs were associated with a significantly lower risk of all-cause mortality compared to warfarin (HR = 0.78, 95% CI: 0.66–0.87).⁵⁵ Another retrospective study in Taiwan, which enrolled patients in Taiwan's diabetes pay-for-performance program, found that among diabetic AF patients, significantly lower all-cause mortality was observed with dabigatran (HR = 0.27, 95% CI: 0.12–0.62) but not with rivaroxaban (HR = 1.41, 95% CI: 0.60–3.32), compared to warfarin.⁵⁹ However, the relatively small sample size (322 dabigatran users and 320 rivaroxaban users) and the limited number of events in this study make it difficult to draw reliable conclusions on this matter.⁵⁹

2.2 Potential differences in serious hypoglycemia risk between NOAC and warfarin use in patients on antidiabetic drugs

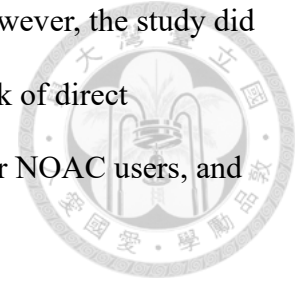
Among patients treated with antidiabetic drugs, serious hypoglycemia can be a dangerous side-effect. Sulfonylureas are primarily metabolized by the cytochrome P450 2C9 hepatic metabolic pathway, which is the same pathway that is mainly responsible for metabolizing warfarin, but not NOACs.⁶⁵ Therefore, there is a potential drug-drug interaction between sulfonylureas and warfarin, which may limit

the rate at which sulfonylureas are metabolized and increase the risk of serious hypoglycemia. Some previous observational studies have evaluated the risk of serious hypoglycemia associated with warfarin use versus non-use in patients taking antidiabetic medications.^{66,67} Those studies suggested an increased risk of serious hypoglycemia in patients taking sulfonylureas with concurrent use of warfarin^{66,67}. However, whether the concurrent use of warfarin with other antidiabetic drugs can also lead to serious hypoglycemia is still debated and inconclusive. Furthermore, whether there are differences in the risk of serious hypoglycemia between NOACs and warfarin in patients taking antidiabetic drugs is still undetermined.

A recent retrospective cohort study in the UK, which focused exclusively on patients taking sulfonylureas, reported an increased risk of severe hypoglycemia in those using both sulfonylureas and warfarin, as compared to sulfonylurea monotherapy (HR = 1.25, 95% CI: 1.16–1.35).⁶² This finding aligns with previous literature.^{66,67} However, the authors noted that residual confounding might be a concern when analyzing the use of warfarin versus non-use, since no significant difference in hypoglycemia risk was found between warfarin and NOACs (HR = 1.01, 95% CI: 0.67–1.52) in their supplementary analyses.⁶² It is noteworthy that only a limited number of severe hypoglycemia events (43 events) were reported in the NOAC group. Therefore, a larger study with more events is needed to draw more definitive conclusions.

Another recent UK cohort study, also focusing on patients taking sulfonylureas, reported that using warfarin concurrently with sulfonylureas was linked to a higher risk of hypoglycemia compared to sulfonylureas alone (HR=1.38; 95% CI: 1.10–1.76).⁶⁸ The study further found that, when comparing the use of NOACs with sulfonylureas against sulfonylureas alone, no statistically significant difference in

hypoglycemia risk was found (HR 0.54; 95% CI: 0.27–1.10). However, the study did not detail the severity of hypoglycemia. It is also limited by a lack of direct comparison between NOAC and warfarin, a small sample size for NOAC users, and the exclusion of other antidiabetic drugs from the analysis.⁶⁸



In addition to the potential drug-drug interactions that may increase the risk of severe hypoglycemia, patients with poorly controlled diabetes are also at a heightened risk of hypoglycemic events^{15,16}. Therefore, theoretically, patients on antidiabetic drugs who take NOACs may have a lower risk of hypoglycemia compared to those taking warfarin. Nevertheless, there is limited evidence comparing the effects of NOACs versus warfarin on serious hypoglycemia risk in patients taking antidiabetic drugs⁶². No studies have evaluated this issue by considering various antidiabetic drugs concurrently used with NOAC or warfarin; however, this is crucial as hypoglycemia can be a short-term adverse event of antidiabetic agents, and the underlying mechanisms may be related to potential drug–drug interactions.

2.3 Study aims

Since AF and DM commonly co-exist in aging populations and many patients need to take antidiabetic drugs and anticoagulants concurrently, choosing an optimal oral anticoagulant that reduces the risks of diabetes-related complications and serious hypoglycemia in patients with AF and DM becomes a crucial clinical issue. As aforementioned, clinical evidence on the potential effects of NOAC versus warfarin on the risk of developing diabetes-related complications remains limited. Comprehensive research that examines various diabetes-related complications, particularly in Asian populations, is still lacking. Further, none of the previous studies have compared the hypoglycemia risk between NOAC and warfarin considering

various and time-varying concurrent antidiabetic drugs. Our studies aimed to address these knowledge gaps.

The aim of our first study (Study 1) was to investigate the overall risks of various diabetes-related complications, such as macrovascular complications, microvascular complications, glycemic emergencies, and mortality in patients with AF and DM who are taking NOACs compared to those taking warfarin.

In our second study (Study 2), we aimed to specifically investigate the risk of serious hypoglycemia when taking various antidiabetic medications with concurrent NOACs compared to those with concurrent warfarin.

Chapter 3. Methods

3.1 Methods of Study 1

3.1.1 Data source

This nationwide retrospective cohort study was conducted using data from the National Health Insurance Research Database (NHIRD) in Taiwan. The National Health Insurance program is a mandatory single-payer program administered by the Taiwanese government; it covers more than 99% of the entire population of Taiwan (approximately 23.6 million individuals). The NHIRD contains patient demographic information and medical claims for inpatients, outpatients, and emergency care services in Taiwan.^{69,70}

Our analysis utilized various components of NHIRD; specifically, we accessed data from multiple NHIRD datasets such as the Registry for Beneficiaries, Ambulatory Care Expenditures by Visits, Inpatient Expenditures by Admissions, Expenditures for Prescriptions Dispensed at Contracted Pharmacies, Details of Ambulatory Care Orders, Details of Inpatient Orders, and Details of Prescriptions Dispensed at Contracted Pharmacies. Additionally, we linked the NHIRD data with the Taiwan National Register of Death to obtain mortality information. By associating these datasets with unique personal identification numbers, researchers are able to access comprehensive information at the patient level. The diagnostic and procedure codes in the NHIRD were derived using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes before 2016 and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes since 2016.

The NHIRD is maintained by the Health and Welfare Data Science Center



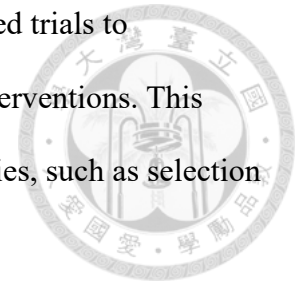
(HWDC), Ministry of Health and Welfare. Accessing the database requires researchers to submit formal applications to Taiwan's Ministry of Health and Welfare. Each application is subjected to a peer-review process by experts to ensure the validity of the data access request. The Ministry established the HWDC as a centralized hub for various health-related databases, including NHIRD and the National Register of Deaths, to oversee their management and analysis. Within HWDC, strict supervision is maintained; researchers or analysts must conduct their analyses onsite through a remote link to the Ministry's servers. Results obtained from analyses at HWDC must be thoroughly reviewed by data custodians to prevent any patient identity disclosures. Additionally, strict rules prohibit the removal or export of individual-level data from the center.

The study protocol has been approved by the Research Ethics Committee of Hualien Tzu Chi Hospital (REC No: IRB107-152-C); informed consent is not required due to the retrospective use of anonymized data.

3.1.2 Target trial emulation

While randomized trials are the gold standard for evaluating intervention effectiveness and safety, they can sometimes be impractical due to high costs, ethical concerns, or lengthy durations. In scenarios where conducting a randomized trial is not feasible, observational studies may serve as an alternative to address similar research questions. However, drawing causal inferences from observational data is fraught with challenges. These studies are inherently susceptible to confounding bias due to non-randomization and can also suffer from biases introduced by incorrect study design choices, such as the timing of follow-up initiation. The target trial emulation framework provides a structured method to use observational data to

emulate a target trial, applying the design principles of randomized trials to observational studies aimed at estimating the causal effects of interventions. This approach helps prevent self-inflicted biases in observational studies, such as selection bias and immortal time bias.⁷¹⁻⁷⁵



Key components of the target trial emulation framework include defining eligibility criteria, treatment strategies, assignment procedures, outcome measurement, follow-up, specific causal contrasts of interest, and analysis plan.^{71,72} Below is a brief introduction to each of these components for emulating a target trial.

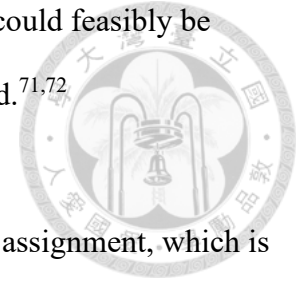
1. Eligibility criteria:

The selection of participants in randomized trials hinges on their characteristics at the time of enrollment. Similarly, it is crucial for researchers to clearly define the eligibility criteria for the target trial, relying only on information available at the initial baseline, without considering any subsequent data after baseline.⁷¹

2. Treatment strategies:

The development of treatment strategies in a target trial should encompass specifying the exact treatments to be assigned to participants. When emulating a target trial with observational data, the focus is often on pragmatic trials, which compare treatment strategies under the usual conditions of application. It is not feasible to emulate a placebo-controlled trial with stringent monitoring and adherence enforcement to study protocol. Notably, comparing individuals who initiate different treatment strategies being studied, often known as the new-user design, is a straightforward method to circumvent biases. These biases may arise when selecting participants who meet eligibility criteria established after starting a treatment strategy (prevalent users), which could potentially be influenced by the strategy itself. Further, comparing current (prevalent) users with never users does

not align with any contrast between treatment strategies that could feasibly be conducted in a randomized trial, and thus is not recommended.^{71,72}



3. Assignment procedures:

Emulation can only mirror target trials that do not have blind assignment, which is typical in pragmatic trial designs. Ideally, in such a target trial, participants who are eligible and enrolled would be assigned randomly to different treatment strategies. However, in observational studies, the data usually represent treatments already administered in regular clinical practice. Therefore, in emulating a target trial, we need to align individuals with treatment strategies that match their existing data. To emulate the initial random assignment of these strategies, it is essential to adjust for all confounding factors. The adjustment can be performed via various methods, such as matching, stratification, regression, and inverse probability weighting (perhaps according to the propensity score). These adjustments ensure comparability (i.e., exchangeability) of the groups defined by the initiation of the treatment strategies. While it is generally not possible to clearly determine if the emulation was unsuccessful due to uncontrolled confounding, some indirect approaches, such as analyzing outcome controls, can provide hints about potential unmeasured confounding.^{71,72}

4. Outcome measurement:

It is essential to clearly define the outcome, for instance, using ICD-10-CM diagnostic codes. If available, it is beneficial to include data on the validity and reliability of the measurement.⁷¹

5. Follow-up:

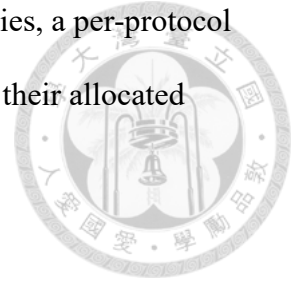
The initiation of follow-up in a study should satisfy three conditions: meeting the eligibility criteria, assignment of treatment strategies, and start of outcome

measurement. While these conditions often coincide naturally in a randomized trial by design, they can easily deviate in an observational study, potentially leading to biases caused by choosing prevalent users or immortal time. In studies using observational data, the best way to emulate the time zero of the target trial is by setting the time zero as the moment when an eligible individual starts a treatment strategy. This means we should synchronize the index date, treatment assignment, and eligibility to prevent using post-index date information for defining treatment groups and thereby avoid immortal time bias.^{71,72} The follow-up period typically continues from the index date until the first occurrence of any of the following: a study outcome, censoring, death, competing events (depending on the effect being estimated), or the designated end of the follow-up period.^{71,72} In cases where the comparison is between treatment and no treatment (rather than using an active comparator) and a grace period for treatment initiation is necessary, the clone-censor-weight target trial emulation approach can be employed to effectively address the issue of immortal time bias.^{72,76}

6. Causal contrast of interest and analysis plan:

In randomized trials, the primary causal contrast is typically the intention-to-treat effect, which is the impact of being assigned to a treatment. For observational studies, a similar effect can be aimed for if there is data on treatment assignment, like prescription information, allowing participants to be analyzed based on the treatment strategy that aligns with their data at baseline. The closest equivalent to intention-to-treat analysis in this context involves comparing individuals who start different treatment strategies, ensuring adequate adjustment for any baseline confounders. Additionally, it is feasible to evaluate the per-protocol effect, which refers to the outcomes observed if there was complete adherence to the assigned

treatment strategy. In both randomized and observational studies, a per-protocol analysis necessitates censoring participants who deviate from their allocated treatment strategy.⁷¹



In the Study 1, we used a target trial emulation framework to emulate a pragmatic randomized controlled trial with observational data. The specification of how we emulate a target trial is shown in Table 2.

Table 2. Specification and emulation of a target trial evaluating the effect of NOAC versus warfarin on hazards of diabetes complications using real-world data from Taiwan's NHIRD

Component	Target trial	Emulated trial using real-world data
Aim	To estimate the relative effect of NOAC versus warfarin on risks of diabetes complications and mortality in AF patients with DM	Same
Eligibility	Adult patients aged ≥ 20 years previously diagnosed with AF and DM without severe valvular heart disease or end stage renal disease No prior use of oral anticoagulants.	Same, but with the exclusion of patients with a previous diagnosis of rheumatic heart disease, congenital heart disease, or who had received valve replacement surgery, because severe valvular heart disease could not be specifically identified by diagnostic codes in NHIRD
Treatment strategies	1. Receiving NOAC treatment 2. Receiving warfarin treatment	Same
Treatment assignment	Eligible patients are randomly assigned to either treatment group (the same probability of treatment assignment between the two groups)	Using propensity score approaches to generate a study population with similar probability of treatment assignment to NOAC/warfarin between the two groups.
Follow-up	Follow-up begins at treatment assignment and ends at occurrence of diabetes complications, at death, at loss to follow-up, or on 31 December 2018, whichever occurs first	Same (the assignment and initiation of the treatment occur at the same time in the real-world scenario)
Outcome	Macrovascular complications, microvascular complications, glycemic emergency, and mortality	Same

Causal contrast	Primary analysis: ITT effect (i.e., effect of being assigned to NOAC versus warfarin at baseline, regardless of whether patients continue following the assigned treatment after baseline)	Same (using as-started analysis, analog of ITT)
	Sensitivity analysis: per-protocol effect (i.e., effect of following the treatment strategies in the study protocol at baseline and after baseline)	Same (using on-treatment analysis, analog of per-protocol)
Statistical analysis	Cox proportional hazards model	Same

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulant; IPTW, inverse probability of treatment weighting; ITT, intention-to-treat

3.1.3 Study population and exposure

We collected data on adult patients aged 20 years or older who have been diagnosed with both AF and DM and treated with oral anticoagulants between 2012 and 2017. AF diagnosis was based on the ICD-9-CM code 427.31 or ICD-10-CM codes I48.0, I48.1, I48.2, and I48.91, and diabetes diagnosis by ICD-9-CM code 250 or ICD-10-CM codes E08-E13, applied at least once in an inpatient service or twice in an outpatient service. Patients were divided into NOAC and warfarin groups based on the type of oral anticoagulant they receive in their first prescription. The "time zero" (index date) was defined as the first day of receiving the NOAC or warfarin, and follow-up began on this date. This approach used a "as-started" design, which is similar to an intention-to-treat analysis and aimed to emulate a target trial to strengthen causal inference from observational data.⁷³

We excluded patients who were initially diagnosed with AF or DM after the index date. Patients receiving any oral anticoagulants in 2011 were excluded to increase the likelihood of capturing patients with newly initiated oral anticoagulant treatment since 2012 (when NOACs were introduced in Taiwan). Patients with rheumatic heart disease, congenital heart disease, valve replacement surgery, or end-stage renal disease (ESRD) at baseline were excluded since they were more likely to be treated with warfarin than with NOAC based on current clinical guidelines; the exclusion criteria helped minimize the possible confounding by indication.⁷⁷ Patients with ESRD were defined as those who received a Catastrophic Illness Certificate of ESRD. Patients with index dates in 2018 were excluded to ensure at least one year of follow-up. Notably, for each study outcome analysis (which will be introduced in subsequent sections), we further excluded patients with any recorded instance of the corresponding outcome event prior to the index date. As a result, the final number of

patients included for analysis may differ across the various outcome analyses.



3.1.4 Study outcomes, comparison, and follow-up

This study aimed to evaluate four primary outcomes: (1) macrovascular complications (ischemic heart disease, stroke, and peripheral vascular disease), (2) microvascular complications (retinopathy, neuropathy, receiving dialysis, and lower extremity amputations), (3) glycemic emergency (diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, and hypoglycemia), and (4) all-cause mortality. Secondary outcomes included individual components of the composite outcomes, cardiovascular and non-cardiovascular mortality. The comparisons for each study outcome were made between patients taking NOACs and those taking warfarin.

Outcome events were defined as diagnoses or corresponding procedures during the follow-up period, using diagnostic or procedure codes summarized in Table 3. Specific outcome events (ischemic heart disease, stroke, peripheral vascular disease, diabetic retinopathy, and diabetic neuropathy) were defined as inpatient diagnoses or at least three outpatient diagnoses, with the first-time diagnosis assigned as the event date. Diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, and hypoglycemia were identified using only inpatient or emergency department diagnoses. Mortality information was obtained from the National Register of Deaths. Patients with outcome events before the index date were excluded from the analyses of those corresponding outcomes. Individuals were followed from the index date until the corresponding outcome, death, or December 31, 2018, whichever comes first. In each outcome analysis, patients were followed up until that corresponding outcome was observed without censoring for other earlier outcomes.

Table 3. Diagnosis and procedure codes for each study outcome

Diseases	ICD-9-CM codes	ICD-10-CM codes	Procedure codes
Coronary artery diseases	410–414	I20–I25	
Stroke	430–438	I60–I69	
Peripheral vascular disease	250.7, 443.9, 440.2	E08.5, E10.5, E11.5, E13.5, I73.9, I70.2	
Retinopathy	250.5, 362.0	E08.31–E08.35, E08.37 E10.31–E10.35, E10.37 E11.31–E11.35, E11.37 E13.31–E13.35, E13.37	
Neuropathy	250.6, 357.2	E08.4, E10.4, E11.4, E13.4	
Dialysis			Case type: 05 or procedure codes: 58001C, 58002C, 58002CB, 58011AB, 58014C, 58017B, 58018C, 58019C, 58020C, 58021C, 58022C, 58023C, 58024C, 58025C, 58026C, 58027C, 58029C, 58030B in Taiwan's NHIRD
Lower extremity amputation			ICD-9-CM procedure code: 84.1 or ICD-10-CM procedure code: 0Y6
Diabetic ketoacidosis	250.1	E08.1, E10.1, E11.1, E13.1	
Hyperosmolar hyperglycemic state	250.2	E08.0, E11.0, E13.0	
Hypoglycemia	251.0–251.2	E16.0–E16.2 E08.64, E10.64,	

E11.64, E13.64		
Cardiovascular mortality	390–459 (using the primary diagnosis for the cause of death in National Register of Deaths)	I00–I99 (using the primary diagnosis for the cause of death in National Register of Deaths)



Abbreviations: NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification

3.1.5 Covariates and confounders

Baseline demographic and clinical information of patients was obtained from the database. Preexisting comorbidities were defined as medical conditions diagnosed at least once during inpatient care or twice during outpatient visits in the year prior to the index date. The comorbidities included hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), liver cirrhosis, hyperlipidemia, stroke, rheumatoid arthritis, gout, dementia, and malignancy; the diagnostic codes used for identifying these comorbidities are presented in Appendix (see Supplemental Table S1).

In addition to those individual comorbidities, we also calculated the Charlson Comorbidity Index to quantify the overall comorbidity status.^{78,79} The Charlson Comorbidity Index is a widely used method for categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnoses. The Charlson Comorbidity Index encompasses 17 comorbidities, which include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complication, diabetes with chronic complication, hemiplegia or paraplegia, renal disease, any malignancy (including lymphoma and leukemia, except malignant neoplasm of skin), moderate or severe liver disease, metastatic solid tumor, and acquired immune deficiency syndrome/human immunodeficiency virus infection. This index assigns weighted scores to each of these conditions, with each score reflecting the associated risk of mortality. The sum of these scores provides a single numerical estimate of a patient's overall burden of comorbidity, which can be used to predict short- and long-term mortality. The Charlson Comorbidity Index is commonly employed in clinical research to adjust for

patients' baseline comorbidity levels. The comorbidities and diagnostic codes we employed for calculating the Charlson Comorbidity Index were based on the version published by Quan et al. in 2005.⁷⁸ The details of these codes are presented in the Appendix (see Supplemental Table S2).

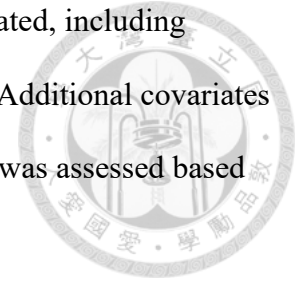


The CHA2DS2-VASc score, which is widely used in clinical practice to assess the risk of stroke and thromboembolic events and to guide the prescription of oral anticoagulants, was also calculated.^{35,80} The factors used to calculate the CHA2DS2-VASc score include congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, and sex; Supplemental Table S3 in Appendix demonstrates how the scores were calculated.

Baseline medications were retrieved, including statins, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), β -blockers, calcium channel blockers, diuretics, nonsteroidal anti-inflammatory drugs (NSAID), corticosteroids, antipsychotics, and proton pump inhibitors. A drug prescribed for at least 30 days within the year before the index date will be defined as a baseline medication. In addition, each type of antidiabetic medication used at baseline was identified based on prescriptions issued within one month before the index date. These medications included metformin, sulfonylurea, meglitinide, alpha-glucosidase inhibitors (AGI), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and Insulin. The Anatomical Therapeutic Chemical (ATC) codes used to identify the prescriptions of medications are listed in the Appendix (see Supplemental Table S4).

Covariates also encompassed the medical specialty of the physician prescribing the oral anticoagulants, such as cardiologists, neurologists, and other specialties, as

well as the hospital level where the oral anticoagulants were initiated, including medical centers, regional hospitals, and district hospitals/clinics. Additional covariates included the index year and the patients' monthly income, which was assessed based on income-related insurance premiums.



The age, Charlson comorbidity index, and CHA2DS2-VASc score were specified as continuous variables; the other covariates (sex, income level, comorbidity, medication use, numbers of diabetes medications, index year, hospital level, and physician specialty) were specified as categorical variables.

3.1.6 Subgroup and stratified analyses

NOAC users will be subclassified into four subgroups (dabigatran, rivaroxaban, apixaban, and edoxaban) based on the first prescribed NOAC type. Each NOAC subgroup will be compared with warfarin users to estimate the relative effect of each NOAC on diabetes complications and mortality risks. Additionally, stratified analysis will be performed according to age (<65 and ≥ 65 years), sex, and hospital level (medical center, regional hospital, and district hospital/clinic) to investigate the potential moderating effects of these factors on the comparisons between NOACs and warfarin.

3.1.7 Propensity score methods

The propensity score methods involve calculating the propensity score for each participant, which is the probability that a participant would receive a specific treatment based on observed characteristics. Researchers can then apply several processes (e.g., matching, weighting, or stratification) to balance the treatment groups on these observed variables. This process makes the study groups more comparable

and subsequently reduces confounding and bias, helping in approximating the conditions of a randomized controlled trial. Propensity score methods are valuable and commonly used in healthcare-related research, where they are used to assess the effectiveness and safety of different treatments and interventions in real-world settings.⁸¹

There are several reasons to support that propensity score methods may be more suitable than traditional regression-based adjustments in retrospective observational studies. Propensity score methods allow one to separate the design of the study from the analysis of the study; this is more similar to the procedure in randomized controlled trials. Using propensity score methods (either matching, weighting, or stratification), the study sample could be constructed without any reference to the outcome.^{81,82} Additionally, propensity score methods can increase flexibility when outcomes (binary or time-to-event in nature) are rare and treatment is common. Previous literature has suggested that for every covariate entered into a regression model, at least 10 outcome events should be observed. Insufficient outcome events may preclude adequate regression-based adjustments for all baseline variables in the study, and an overfitting issue may exist;⁸¹ however, the use of propensity score methods can circumvent this problem.

Table 4 presents a comparative summary of various propensity score methods as well as traditional multivariable regression that could be used for covariate adjustment and confounder control.^{81,83,84}

Table 4. Comparative summary of various propensity score methods as well as traditional multivariable regression that could be used for covariate adjustment and confounder control

Analysis method	Justification of using the method	Limitation
IPTW using propensity score	<ul style="list-style-type: none"> - Retains original cohort population with different weights - Exchangeable weighted population with more balanced covariates for risk comparison - Provides an average treatment effect in the whole study population 	<ul style="list-style-type: none"> - May become unreliable or biased if extreme weights exist - Stabilized weights or weight trimming/truncation should be considered to avoid the extreme weights
Propensity score matching	<ul style="list-style-type: none"> - More straightforward and easy to understand for the most readers - Exchangeable matched population with more balanced covariates for risk comparison - Provides an average treatment effect in a condition of all patients being treated with NOAC 	<ul style="list-style-type: none"> - Exclusion of unmatched patients from the analysis - If too many participants are excluded after matching, it may become unrepresentative of the targeted population
Propensity score stratification	<ul style="list-style-type: none"> - Preserves information from all individuals in the study - Allows for the examination of potential interactions between treatment and propensity score on outcome risk - Can provide estimates of effects across various propensity score strata 	<ul style="list-style-type: none"> - May underperform in datasets with limited outcome events, especially when there is a high number of strata - Might not effectively address strong confounding factors
Propensity score covariate	<ul style="list-style-type: none"> - Retains original cohort population 	<ul style="list-style-type: none"> - More easily affected by residual confounding

adjustment (using propensity score as a covariate in the regression model)	<div data-bbox="1117 190 1412 470" data-label="Image"> </div> - The nature of the relationship between the propensity score and the outcome should be correctly modeled, a requirement that is not necessary when employing other propensity score methods	
Traditional multivariable regression	<ul style="list-style-type: none"> - Retains original cohort population - More commonly used and easy to perform - Easy to understand by most readers 	<ul style="list-style-type: none"> - May be not suitable when there are many covariates with small sample sizes or few outcome events
Abbreviations: IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant		

3.1.8 Propensity score methods used in our analyses

In our study, we calculated the propensity score to estimate the probability of each patient receiving NOAC treatment using a multivariable logistic regression model that includes all covariates listed in Table 5 (including age, sex, income level, Charlson comorbidity index, CHA2DS2-VASc score, comorbidities, baseline diabetes and other medications, numbers of diabetes medications, index year, hospital level, and physician specialty).

In research that compares the effectiveness between two potential treatments (i.e., comparative effectiveness research), the average treatment effect in the whole population (ATE) can be easily estimated and is usually the most useful for clinicians and policymakers in real-world clinical settings.⁸⁵ To estimate the ATE, we used stabilized inverse probability of treatment weighting (IPTW) to generate a comparison set before data analyses for each study outcome and comparison.⁸⁶ The stabilized IPTW helps construct a pseudo-population with balanced patient baseline characteristics between treatment groups. The stabilization of weights mitigates potential unstable weights for subjects with a low probability of receiving the treatment received, as suggested in previous literature.^{81,87} Moreover, employing stabilized weights in the pseudo-population data helps maintain the original data's sample size, ensures accurate estimation of the variance of the main effect, and preserves an appropriate type I error rate.⁸⁸ The stabilized weight for each subject is obtained using the formula:

$$W = \frac{ZPr(Z = 1)}{e} + \frac{(1 - Z)Pr(Z = 0)}{1 - e}$$

Here, Z represents the treatment assignment, with $Z=1$ indicating the use of NOAC and $Z=0$ indicating warfarin. Let X symbolize the vector of observed baseline

characteristics. The propensity score, denoted as e , is the conditional probability $P(Z = 1|X)$ of a participant being assigned to the treatment of interest (NOAC) given their observed baseline characteristics. $Pr(Z = 1)$ and $Pr(Z = 0)$ represent the marginal probabilities of receiving the treatment (NOAC) and control (warfarin) in the overall sample.⁸⁹

In addition to utilizing stabilized IPTW in our main analyses, we also conducted sensitivity analyses to evaluate whether an alternative propensity score method or the absence of such method might influence our results. Specifically, we re-analyzed our data using propensity score matching. Propensity score matching was conducted using a 1:1 nearest-neighbor matching algorithm without replacement, and a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score was adopted. Previous studies suggest that such a setting for matching can minimize the mean squared error of the estimated treatment effect and eliminate bias in several scenarios.^{81,90} To ensure that the index year is similar between the NOAC and warfarin groups, matching was conducted within the stratum of the index year. Furthermore, we employed multivariable regression models to obtain adjusted estimates, without the application of any propensity score methods.

Importantly, the study population included in each analysis and comparison (including different outcome analyses, subgroup analyses, stratified analyses, and sensitivity analyses) may vary due to the application of specific inclusion or exclusion criteria for each. Therefore, in each analysis, we recalculated the propensity score and re-implemented the propensity score methods (e.g., stabilized IPTW or propensity score matching). This approach ensures effective control of confounders in every distinct analysis.

3.1.9 Statistical analyses

The differences in baseline characteristics were evaluated using the standardized difference, with a value of <0.1 indicating a negligible difference. The standardized difference, denoted as d , quantifies the disparity between covariates in experimental and control groups.⁹¹ For continuous variables, it is defined as:

$$d = \frac{|\bar{x}_E - \bar{x}_C|}{\sqrt{(\sigma_E^2 + \sigma_C^2)/2}}$$

For binary variables, the standardized difference is given by:

$$d = \frac{|\hat{p}_E - \hat{p}_C|}{\sqrt{(\hat{p}_E(1 - \hat{p}_E) + \hat{p}_C(1 - \hat{p}_C))/2}}$$

In these formulas, $\bar{x}_E$ and $\bar{x}_C$ represent the mean values of a covariate in the experimental and control groups, respectively, while σ_E and σ_C denote the corresponding standard deviations. For binary variables, $\hat{p}_E$ and $\hat{p}_C$ reflect the proportion of a given category (e.g., female sex, hypertension status) in the experimental and control groups, respectively.⁹¹ The standardized difference is widely used in propensity score-matched/weighted samples to evaluate the balance in baseline covariates between treatment groups. Previous studies have suggested that the standardized difference is preferred over significance testing of covariates (reporting p-values) between experimental and control groups, as it is not confounded by sample size or the statistical power of the test employed.⁹¹⁻⁹³

Cox proportional hazard models were employed to estimate cumulative incidences and hazard ratios (HRs) for each outcome.⁹⁴ We assessed the proportional hazard assumption by incorporating time-dependent covariates to explore potential interactions between the predictors (NOAC/warfarin) and time (log(time)). No significant time-dependent effect was detected, indicating that there was no violation

of the proportionality assumption in our analyses. When estimating HRs, we included shared frailty in the Cox models to account for potential cluster effects and variations among hospitals or clinics, because subjects within the same hospital/clinic may not be independent^{95,96}. The Cox model with shared frailty (random effects) is formulated as follows:

$$h_i(t) = h_0(t) \times \exp(\mathbf{X}_i\beta + Z_j)$$

In this equation, $h_i(t)$ represents the hazard function for the i -th individual at time t . The term $h_0(t)$ is the baseline hazard function, which is common to all individuals. The vector $\mathbf{X}_i$ includes the covariates for the i -th individual, and β is a vector of coefficients corresponding to these covariates. The shared frailty term, Z_j , pertains to the j -th cluster (such as a hospital or clinic) and captures the random effects associated with each cluster, influencing all individuals within that cluster. The shared frailty accounts for the unobserved heterogeneity at the cluster level. It allows for the correlation among individuals within the same cluster due to shared characteristics or environmental factors. Such a model is valuable in survival analysis, where data are clustered, and individuals within the same cluster are likely to share unmeasured characteristics that may influence the outcome of interest.

A two-tailed probability value <0.05 was considered statistically significant. Data management and statistical analyses were performed using SAS version 9.4, R version 4.1.1, or STATA version 15.

3.1.10 Sensitivity analyses

Various sensitivity analyses were performed to assess the robustness of our study findings as follows. First, we applied an on-treatment design (analog of per-protocol) as a sensitivity analysis, which considers the treatment adherence during follow-up⁷³.

In the on-treatment design, censoring will also occur at the time when patients switch the oral anticoagulant type or 90 days after discontinuing the index oral anticoagulant treatment.

Second, we performed a sensitivity analysis limited to patients taking the index oral anticoagulant (the initially prescribed oral anticoagulant) with a high medication possession ratio ($\geq 80\%$) during follow-up. The medication possession ratio was calculated for each patient by dividing the number of days a patient took oral anticoagulants by their follow-up period in days⁹⁷. These two sensitivity analyses addressed potential exposure misclassification that could arise from changes in medications or from lack of medication possession during the follow-up period.

Third, since precise renal function data was not available in our database but impaired renal function may influence physicians' selection of oral anticoagulants, we thus conducted a sensitivity analysis excluding patients with any diagnosis of CKD at baseline.

Fourth, the presence of extreme weights in the IPTW analysis could potentially influence or even bias the results.⁹⁸ Therefore, we performed an analysis with weight truncation, reducing any weight greater than 5 down to this threshold, to ascertain their influence on our outcome estimates.⁸³

Fifth, as mentioned in Section 3.1.8, we utilized an alternative propensity score method (propensity score matching) as well as employed multivariable regression models without propensity score methods to determine if the use or the choice of propensity score methods influenced our study results.

In addition, we calculated E-values to determine the strength required of an unmeasured confounder to negate the observed treatment–outcome relationship (specifically, the relationship between NOAC use and complication risks) if such an

unmeasured confounder truly exists.^{99,100} The E-value is defined as the minimum strength of association, expressed in the scale of the risk ratio, that an unmeasured confounder would require to have with both the treatment (exposure) and the outcome, to fully explain away a specific treatment–outcome association, while also considering the measured covariates.¹⁰⁰ The E-value can serve as an indicator, quantifying the robustness of our results against the influence of potential confounders. We calculated the E-values and illustrated the plots showing a joint relationship between the two sensitivity parameters (exposure-confounder relationship and confounder-outcome relationship) that could potentially explain away the estimated effect using the online E-value calculator: <https://www.evalue-calculator.com>.

Moreover, we analyzed three negative control outcomes (occurrence of cancer, chronic obstructive pulmonary disease, and suicide death) — conditions not expected to have a causal link with different oral anticoagulants — to indirectly assess the presence of potential unmeasured confounders.¹⁰¹

3.2 Methods of Study 2

3.2.1 Data source

We used Taiwan's NHIRD to conducted this nationwide retrospective cohort study. The introduction of NHIRD could be found in '3.1.1 Data source' section. The study protocol has been approved by the Research Ethics Committee of Hualien Tzu Chi Hospital (REC No: IRB110-170-C); informed consent is not required due to the retrospective use of anonymized data.

3.2.2 Study population, exposure, and follow-up time

Data were collected from all adult patients aged ≥ 20 years who have been diagnosed with both DM (ICD-9-CM code 250 or ICD-10-CM codes E08–E13) and AF (ICD-9-CM code 427.31 or ICD-10-CM codes I48.0, I48.1, I48.2, and I48.91) at least once in an inpatient service or twice in outpatient services between 2012 and 2020 in the NHIRD. Our study population was then limited to patients treated with antidiabetic medications concurrently with oral anticoagulants.

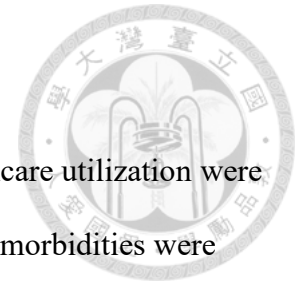
In clinical practice, the use of diabetes medications and anticoagulants may vary over time. Restricting patients to consistent drug use status throughout several years of follow-up in our analyses may not be feasible because our study outcome, the severe hypoglycemia event, is highly correlated with the current antidiabetic drug types used. Moreover, the risk of a hypoglycemia event can be immediately affected by short-term changes in antidiabetic medication. Consequently, we divided each patient's follow-up time (unit of time: day) into distinct periods based on the specific combination of antidiabetic medication and oral anticoagulant types used concurrently. Each period of concurrent use of the same combination of oral anticoagulants and antidiabetic drugs in each patient was serve as the unit of analysis. In other words, each patient's follow-

up time was split into multiple separate periods for analysis according to each specific combination of oral anticoagulant and antidiabetic drug; if the oral anticoagulant or antidiabetic drug changed, the periods before and after the change were treated as different samples for analysis. Each period of concurrent use of oral anticoagulants and antidiabetic drugs was then categorized into the warfarin or NOAC group based on the type of oral anticoagulant prescribed. This design aimed to minimize the likelihood of exposure misclassification for patients who have altered their antidiabetic medications and oral anticoagulants during long-term follow-up.

The follow-up periods without prescriptions for antidiabetic drugs or oral anticoagulants were excluded from the analysis. Other exclusion criteria included those without any diagnosis of AF before the follow-up periods, as well as those with ESRD, rheumatic heart disease, congenital heart disease, or having undergone valve replacement surgery to avoid potential confounding by indications.^{77,102}

3.2.3 Study outcome and comparison

The primary outcome of this study was serious hypoglycemia, which was ascertained when a patient was admitted to the hospital or treated in the emergency department with a diagnosis of hypoglycemia (ICD-9-CM codes: 251.0–251.2 or ICD-10-CM codes: E16.0–E16.2, E08.64, E10.64, E11.64, E13.64), accompanied by prescriptions of intravenous high concentration glucose solution (e.g., 50% glucose solution). If the diagnosis dates for an emergency department visit and a hospital admission coincided, the occurrence was considered as a single hypoglycemia event. We compared the incidence rates of serious hypoglycemia between the periods of NOAC use and warfarin use.



3.2.4 Covariates and confounders

Patient demographics, comorbidities, medications, and healthcare utilization were considered as covariates for each period. Pre-existing baseline comorbidities were determined by medical conditions diagnosed at least once during inpatient visits or twice during outpatient visits within the year before each period. These conditions included hypertension, coronary artery disease, congestive heart failure, COPD, asthma, CKD, cirrhosis, hyperlipidemia, stroke, rheumatoid arthritis, dementia, depression, and malignancy. We calculated the Charlson Comorbidity Index ^{78,79} and CHA2DS2-VASc score ^{35,80}, as detailed in '3.1.5 Covariates and confounders' section and the Supplemental Tables S2 and S3 in the Appendix. We also retrieved baseline medical utilization data, including the number of outpatient visits, emergency room visits, and hospitalizations in the previous year of each period as covariates. Baseline medications were defined as drugs prescribed for at least 30 days within the year prior to the corresponding period. The baseline medications we included in our analysis comprised statins, ACEI or ARB, β -blockers, calcium channel blockers, diuretics, NSAIDs, corticosteroids, antipsychotics, and proton pump inhibitors.

Diabetes medications currently in use during the corresponding period were identified as covariates, including metformin, sulfonylurea, meglitinide, AGI, TZD, DPP-4i, SGLT-2i, GLP-1RA, and Insulin. Additionally, we calculated the number of antidiabetic drugs used. We also considered whether there was a history of serious hypoglycemia within the year before each period as a covariate. Other covariates that were retrieved included the index year, duration of DM and AF diagnosis, monthly income, and hospital level where oral anticoagulants were prescribed.

3.2.5 Subgroup and stratified analyses

In addition to the primary analysis comparing the use of NOACs and warfarin among patients taking any antidiabetic medications, subgroup analyses were conducted according to each type of concurrent antidiabetic drug, including metformin, sulfonylurea, meglitinide, AGI, TZD, DPP-4i, SGLT-2i, GLP-1RA, and Insulin. Periods involving concurrent prescriptions of specific antidiabetic drugs were included in the respective subgroup analyses.

NOACs were categorized into four subgroups: dabigatran, rivaroxaban, apixaban, and edoxaban. The risks of serious hypoglycemia associated with each NOAC was compared to those of warfarin in the subgroup analyses of NOAC types. Stratified analyses were performed based on age (<65 and ≥65 years), sex, and the number of antidiabetic drugs used, further examining the relationships within these subgroups.

3.2.6 Stabilized inverse probability of treatment weighting using propensity score

A propensity score was calculated to estimate the probability of prescribing NOACs for each period using a multivariable logistic regression model that includes all covariates mentioned in the ‘3.2.4 Covariates and confounders’ section. We then applied stabilized IPTW with truncating the extreme weights to construct a weighted dataset with balanced characteristics between treatment groups. Stabilization of weights helps in reducing potential unstable weights for subjects with low probability of receiving the treatment received, preventing sample size inflation, and ensuring accurate variance estimation.^{81,87,88} We reduced any weights greater than 5 down to this threshold to avoid the potential influence of extreme weights on outcome estimates.⁸³ Stabilized IPTW with weight truncation was utilized to generate the

comparison set (weighted dataset) before conducting each analysis, including overall, subgroup, stratified, and sensitivity analyses.



3.2.7 Statistical analyses

Baseline characteristic differences between treatment groups were assessed using the standardized difference, with a value of <0.1 indicating a negligible difference. As the outcome event, serious hypoglycemia, may occur multiple times during each follow-up period within a patient, Poisson regression models were employed to estimate the incidence rate ratios (IRRs) of serious hypoglycemia for patients taking antidiabetic drugs with NOACs versus warfarin. We used an offset to deal with the varied lengths between the different observed periods. The regression models were weighted by stabilized IPTW to control potential confounders, and generalized estimating equations were applied to account for intra-individual correlation since the follow-up periods from the same patient are not entirely independent. The correlation matrix was designed as an exchangeable structure in generalized estimating equations. The risk of serious hypoglycemia during periods prescribed with warfarin served as the reference group. A two-tailed p-value <0.05 will be considered statistically significant. Data management and statistical analyses will be performed using SAS version 9.4, R version 4.1.1, or STATA version 15.

3.2.8 Sensitivity analyses

Various sensitivity analyses were conducted to assess the robustness of our study findings as follows.

First, a sensitivity analysis was conducted by excluding patients with any diagnosis of CKD, as renal function may influence the choice of oral anticoagulants,

but renal function data is unavailable in the claims-based dataset.

Second, although weight truncation in IPTW analysis helps to avoid the potential influence of extreme weights on outcome estimates, it directly changes the population of inference, which may also introduce bias.¹⁰³ Therefore, we conducted a sensitivity analysis applying stabilized IPTW without weight truncation to determine whether truncating weights influences the outcome estimates in our study.

Third, to determine whether analyzing emergency department diagnoses or inpatient diagnoses of hypoglycemia separately would affect our study results, we conducted two sensitivity analyses. One analysis specifically targeted cases of hypoglycemia diagnosed in the emergency department, and the other focused on diagnoses during hospitalization. In line with our main analysis, a diagnosis was required to be accompanied by a prescription for intravenous high-concentration glucose solution to qualify as a severe hypoglycemia event.

Fourth, considering the potential for an incubation period or lagged effect from the start of NOAC or warfarin use to its impact on hypoglycemia risk, we carried out two sensitivity analyses. One analysis excluded observations with a duration of less than 14 days, focusing only on periods of 14 days or more. This aimed to eliminate instances of only brief oral anticoagulant use, ensuring a more prolonged exposure period in the analysis. The other analysis addressed individuals who had switched their oral anticoagulant medications, whether from NOAC to warfarin or vice versa. In this case, we identified the 30 days following the change in medication as a potential overlapping period for drug effects and excluded these periods from the analysis. This helped prevent mistakenly attributing the lag effect of the previous medication to the new one.

In addition, similar to Study 1, we calculated E-values to determine the strength

required of an unmeasured confounder to negate the observed treatment–outcome relationship (the relationship between NOAC use and severe hypoglycemia risk) if such an unmeasured confounder exists.^{99,100} The E-values were calculated using the online E-value calculator: <https://www.evaluate-calculator.com>.

Furthermore, we evaluated four negative control outcomes — the occurrence of conjunctivitis, influenza, urinary tract infection, and suicide death — for which no causal effect is expected, to indirectly investigate the presence of potential unmeasured or unknown confounders.¹⁰¹

Chapter 4. Results

4.1 Results of Study 1

4.1.1 Patient characteristics

The overall initial study population, prior to the application of any propensity score methods, consisted of 30,219 patients (Table 5). For each outcome analysis, we exclude patients who had any records of the corresponding outcome prior to the index date. Consequently, the number of patients ultimately included in each analysis varies across the different outcome analyses. For a detailed description of the patient inclusion and exclusion processes, please refer to Figures 1-4 (Figure 1 for the analysis of macrovascular complications; Figure 2 for the analysis of microvascular complications; Figure 3 for the analysis of glycemic emergencies; Figure 4 for the analysis of mortality).

For analysis of each study outcome, we constructed a pseudo-population by stabilized IPTW; the baseline characteristics of patients for the analysis of macrovascular complications, microvascular complications, glycemic emergencies, and mortality are displayed in Table 6, Table 7, Table 8, and Table 9, respectively.

In the analysis of macrovascular complications, 6,914 patients in the NOAC group and 3,225 in the warfarin group were included in the pseudo-population constructed using stabilized IPTW. The mean age was 72.5 years for the NOAC group and 72.6 years for the warfarin group, with females comprising 47.1% and 47.3% of each group, respectively. All baseline characteristics were appropriately balanced between the two groups, with a standardized difference of less than 0.1, as shown in Table 6. The mean follow-up duration for the macrovascular complication analysis was 2.3 years.



In the analysis of microvascular complications, the pseudo-population included 16,835 patients in the NOAC group and 8,506 in the warfarin group. The mean age was 73.8 years in the NOAC group and 73.9 years in the warfarin group, with females accounting for 45.4% and 45.5% of the respective groups. All baseline characteristics were found to be appropriately balanced between these groups, as indicated in Table 7. The mean follow-up duration for the analysis of microvascular complications was 2.7 years.

In the analysis of glycemic emergencies, the pseudo-population comprised 19,358 patients in the NOAC group and 9,934 in the warfarin group. The average age was 73.7 years for the NOAC group and 73.9 years for the warfarin group, with females representing 45.4% and 45.6% of each group, respectively. All baseline characteristics were well balanced between these groups, as shown in Table 8. The average follow-up period for the glycemic emergency analysis was 2.8 years.

In the mortality analysis, the pseudo-population included 19,909 patients in the NOAC group and 10,300 in the warfarin group. The mean age was 73.8 years in the NOAC group and 73.9 years in the warfarin group, with females constituting 45.7% of each group. The baseline characteristics were balanced between the groups, as detailed in Table 9. The mean follow-up duration for the mortality analysis was 2.9 years.

Table 5. Baseline characteristics of NOAC and warfarin users in the original population before applying propensity score methods

	NOAC (N = 19847)		Warfarin (N = 10372)		SMD [†]
	N	%	N	%	
Age (years) [‡]	74.9 ± 9.7		71.8 ± 10.9		0.292
Sex					
Male	10,651	53.7	5,712	55.1	0.028
Female	9,196	46.3	4,660	44.9	0.028
Income level (NTD)					
Financially dependent	5,779	29.1	2,907	28.0	0.024
15840–29999	9,283	46.8	4,804	46.3	0.009
30000–44999	2,510	12.6	1,576	15.2	0.074
≥ 45000	2,275	11.5	1,085	10.5	0.032
Charlson comorbidity index ^{‡§}	2.8 ± 1.9		2.9 ± 1.9		0.062
CHA2DS2-VASc score ^{‡#}	4.4 ± 1.6		4.3 ± 1.8		0.077
Comorbidities					
Hypertension	15,426	77.7	8,037	77.5	0.006
Coronary artery disease	6,864	34.6	3,795	36.6	0.000
Congestive heart failure	5,199	26.2	3,132	30.2	0.089
COPD	2,856	14.4	1,468	14.2	0.007
Chronic kidney disease	2,595	13.1	1,610	15.5	0.070
Liver cirrhosis	951	4.8	699	6.7	0.084
Hyperlipidemia	7,377	37.2	3,769	36.3	0.017
Stroke	6,152	31.0	3,291	31.7	0.000
Rheumatoid arthritis	148	0.7	81	0.8	0.004
Gout	1,946	9.8	1,170	11.3	0.048
Dementia	1,348	6.8	571	5.5	0.054
Malignancy	1,706	8.6	807	7.8	0.030
Medication use					
Statins	7,521	37.9	3,508	33.8	0.085
ACEI or ARB	12,570	63.3	6,385	61.6	0.037
β blockers	9,118	45.9	4,905	47.3	0.027
Calcium channel blockers	9,215	46.4	4,917	47.4	0.020

	NOAC (N = 19847)		Warfarin (N = 10372)		SMD [†]
	N	%	N	%	
Diuretics	6,087	30.7	3,687	35.5	0.104
NSAID	6,902	34.8	3,486	33.6	0.025
Corticosteroids	1,763	8.9	975	9.4	0.018
Antipsychotics	979	4.9	529	5.1	0.008
Proton pump inhibitors	1,553	7.8	877	8.5	0.023
Baseline diabetes medications					
Metformin	9,896	49.9	4,866	46.9	0.059
Sulfonylurea	6,596	33.2	3,824	36.9	0.076
Meglitinide	1,193	6.0	872	8.4	0.093
AGI	1,646	8.3	1,010	9.7	0.050
TZD	920	4.6	496	4.8	0.007
DPP-4i	5,789	29.2	2,469	23.8	0.122
SGLT-2i	231	1.2	25	0.2	0.111
GLP-1	17	0.1	6	0.1	0.010
Insulin	2,263	11.4	1,432	13.8	0.072
Numbers of diabetes medications					
Without medications	6,192	31.2	2,956	28.5	0.059
1 type	4,787	24.1	2,764	26.6	0.058
2 types	4,438	22.4	2,462	23.7	0.033
≥ 3 types	4,430	22.3	2,190	21.1	0.029
Index year					
2012–2013	2,211	11.1	4,575	44.1	0.793
2014–2015	6,963	35.1	3,787	36.5	0.030
2016–2017	10,673	53.8	2,010	19.4	0.765
Hospital level of OAC initiation					
Medical center	7,945	40.0	3,403	32.8	0.150
Regional hospital	8,838	44.5	4,742	45.7	0.024
District hospital or clinic	3,064	15.4	2,227	21.5	0.156
Physician specialty					

	NOAC (N = 19847)		Warfarin (N = 10372)		SMD [†]
	N	%	N	%	
Cardiologist	13,274	66.9	6,419	61.9	0.104
Neurologist	3,254	16.4	1,415	13.6	0.077
Others	3,319	16.7	2,538	24.5	0.192

Data are presented as percentages unless otherwise noted.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

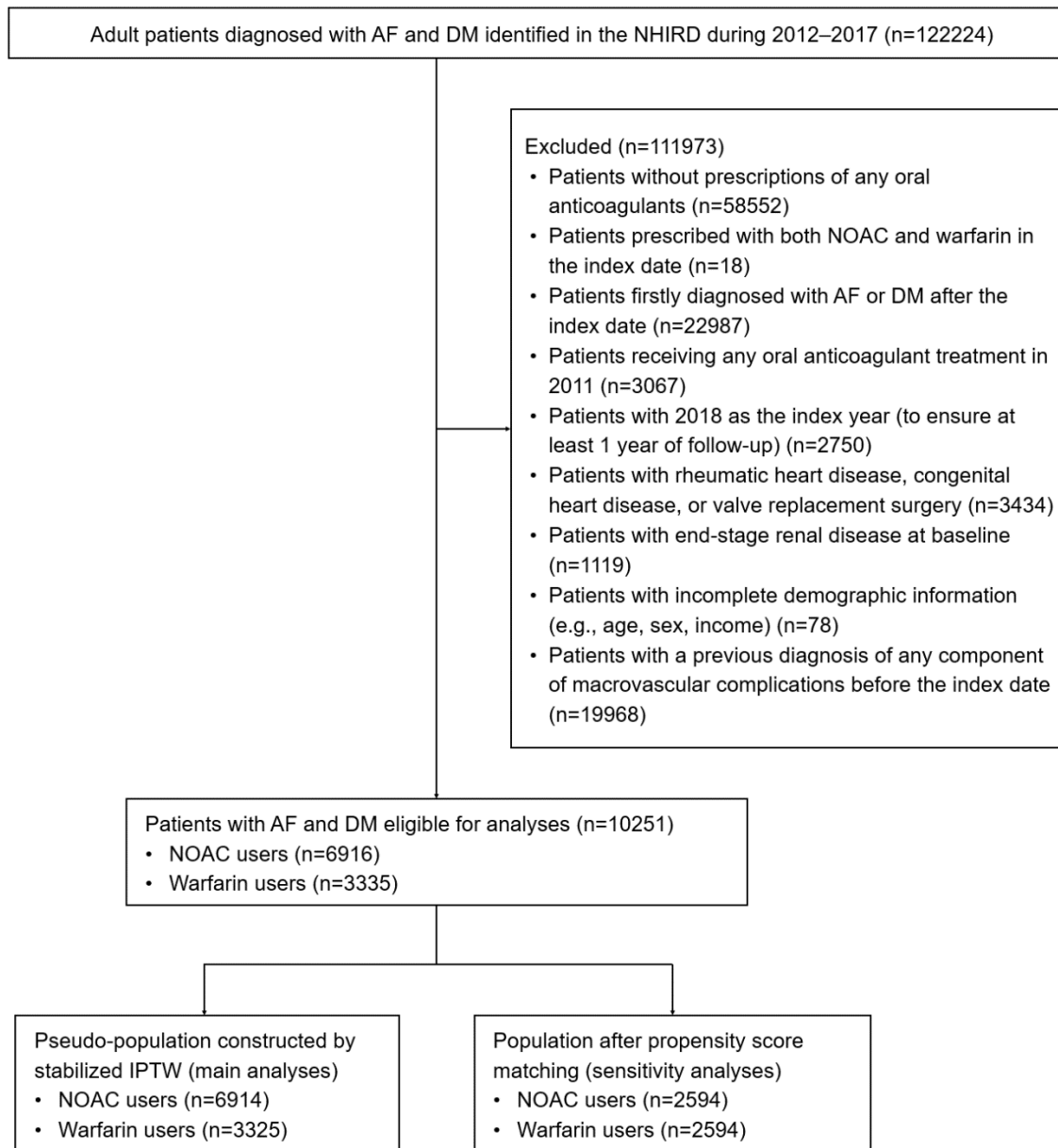


Figure 1. Study flow diagram of patient selection for analysis of macrovascular complications in Study 1

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; IPTW, inverse probability of treatment weighting; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulants

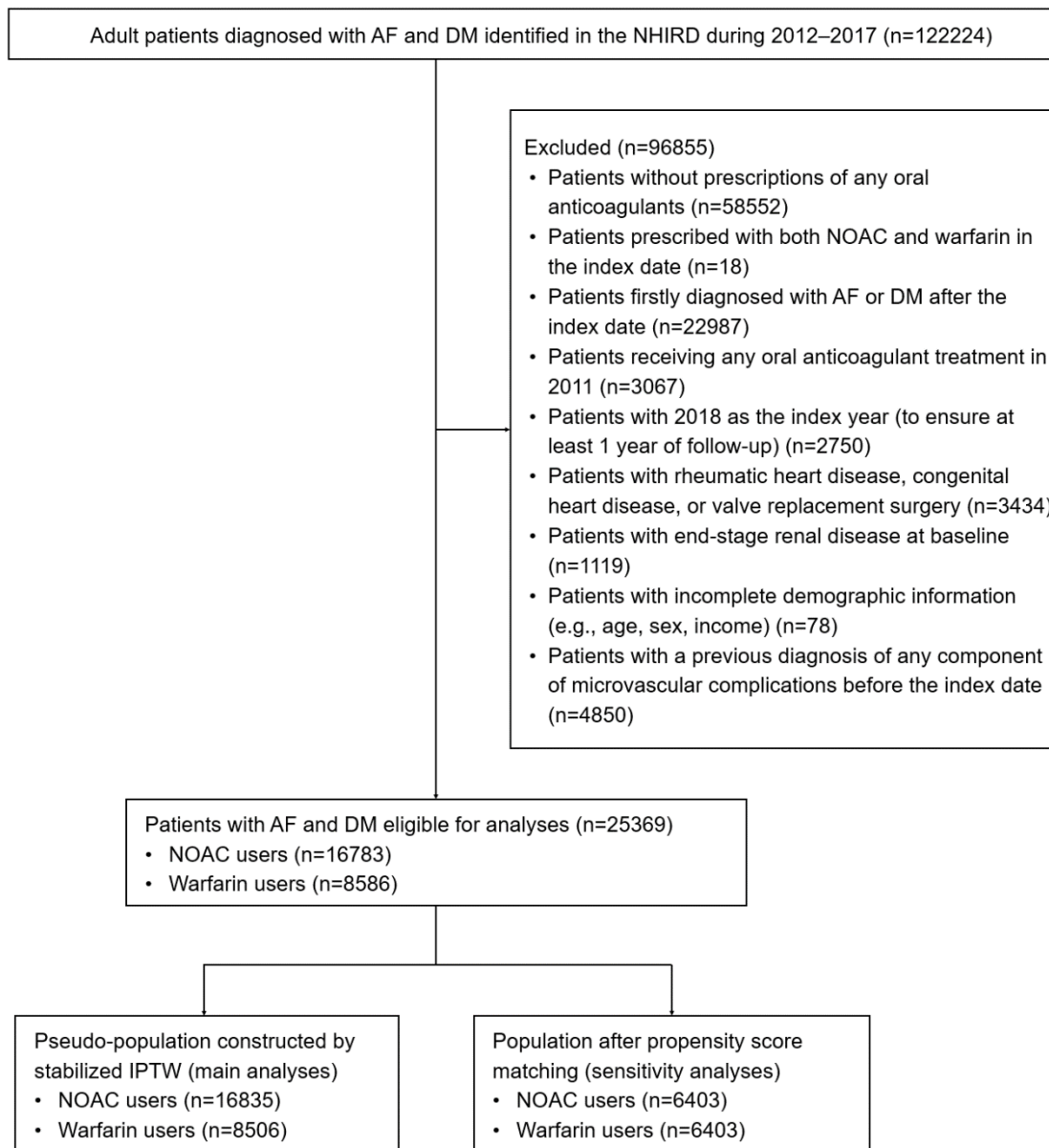


Figure 2. Study flow diagram of patient selection for analysis of microvascular complications in Study 1

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; IPTW, inverse probability of treatment weighting; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulants

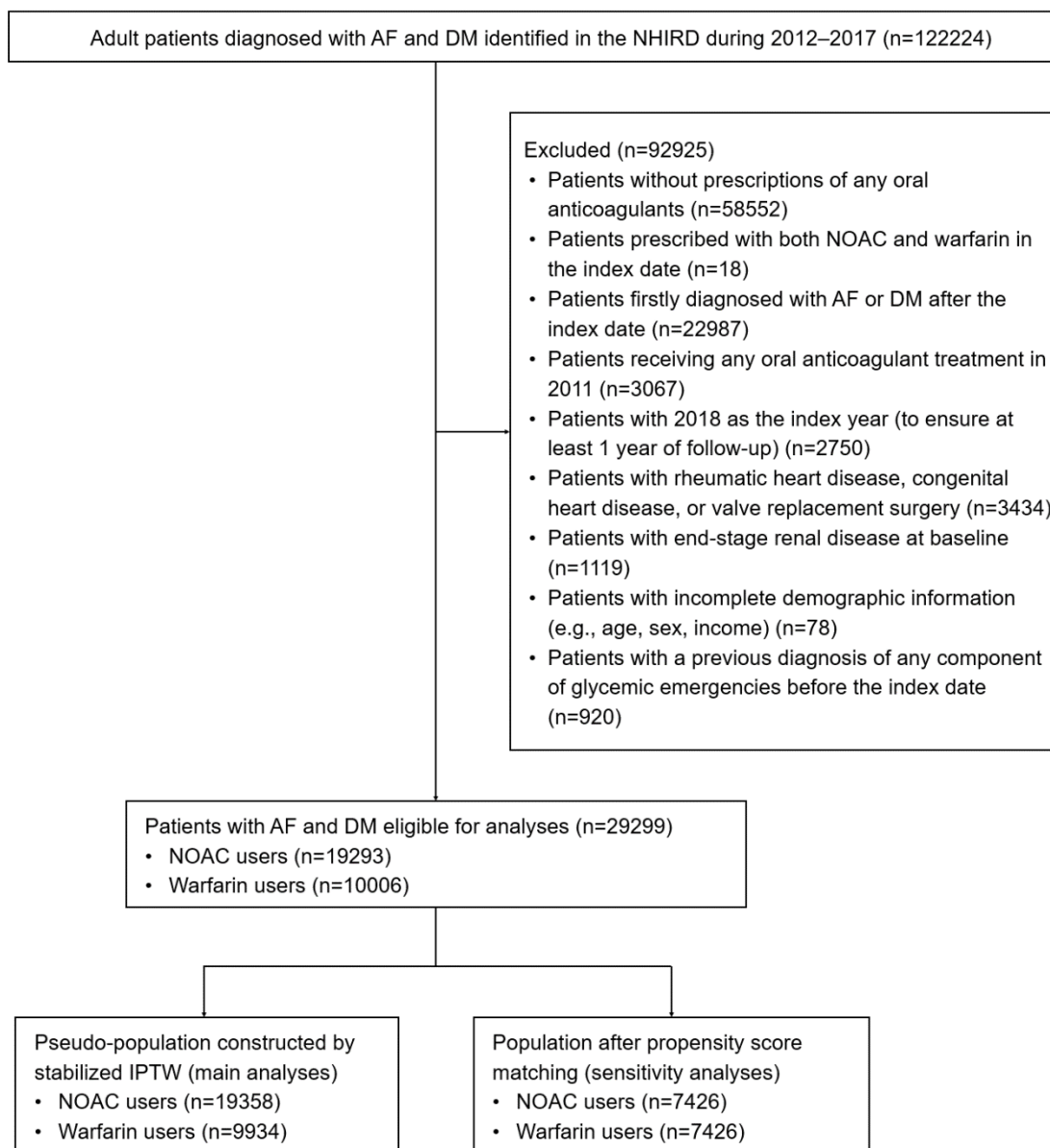


Figure 3. Study flow diagram of patient selection for analysis of glycemic emergencies in Study 1

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; IPTW, inverse probability of treatment weighting; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulants

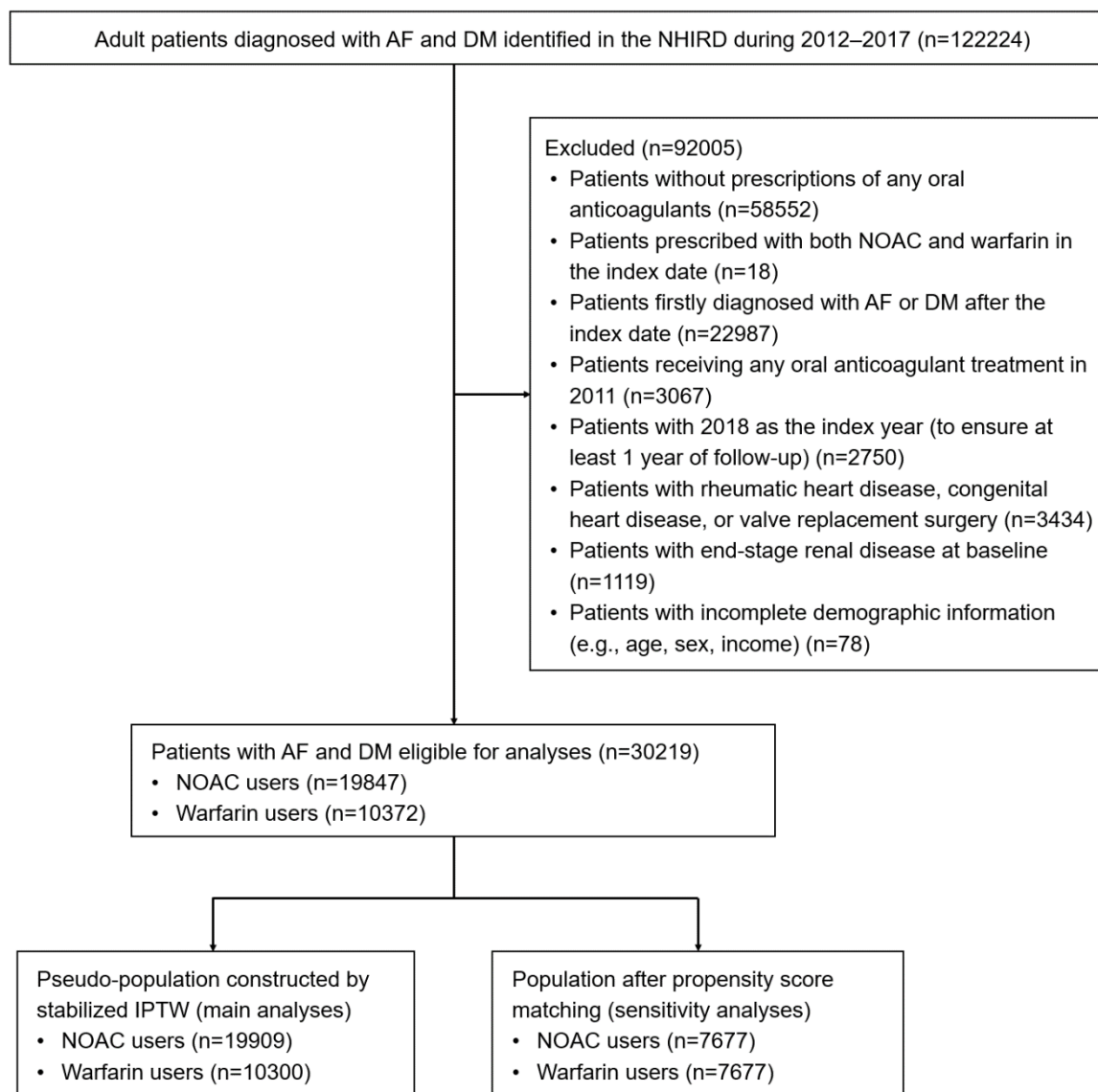


Figure 4. Study flow diagram of patient selection for analysis of mortality in Study 1

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; IPTW, inverse probability of treatment weighting; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulants

Table 6. Baseline characteristics of NOAC and warfarin users in the population after stabilized inverse probability of treatment weighting for the analysis of macrovascular complications

	NOAC (N = 6914)		Warfarin (N = 3325)		SMD [†]
	N	%	N	%	
Age (years) [‡]	72.5 ± 10.2		72.6 ± 11.1		0.009
Sex					
Male	3,656	52.9	1,752	52.7	0.003
Female	3,258	47.1	1,573	47.3	0.003
Income level (NTD)					
Financially dependent	1,882	27.2	894	26.9	0.007
15840–29999	3,215	46.5	1,580	47.5	0.020
30000–44999	1,022	14.8	468	14.1	0.020
≥ 45000	796	11.5	383	11.5	0.001
Charlson comorbidity index ^{‡§}	2.2 ± 1.6		2.2 ± 1.7		0.003
CHA2DS2-VASc score ^{‡#}	3.5 ± 1.3		3.5 ± 1.4		0.021
Comorbidities					
Hypertension	5,036	72.8	2,427	73.0	0.004
Coronary artery disease	0	0.0	0	0.0	0.000
Congestive heart failure	1,656	24.0	851	25.6	0.038
COPD	866	12.5	426	12.8	0.009
Chronic kidney disease	850	12.3	406	12.2	0.002
Liver cirrhosis	400	5.8	190	5.7	0.003
Hyperlipidemia	2,459	35.6	1,182	35.6	0.000
Stroke	0	0.0	0	0.0	0.000
Rheumatoid arthritis	62	0.9	30	0.9	0.000
Gout	707	10.2	348	10.5	0.008
Dementia	263	3.8	107	3.2	0.031
Malignancy	625	9.0	289	8.7	0.013
Medication use					
Statins	2,316	33.5	1,123	33.8	0.006
ACEI or ARB	4,183	60.5	1,998	60.1	0.009
β blockers	2,886	41.7	1,394	41.9	0.004
Calcium channel blockers	3,027	43.8	1,478	44.5	0.014

	NOAC (N = 6914)		Warfarin (N = 3325)		SMD [†]
	N	%	N	%	
Diuretics	2,000	28.9	999	30.1	0.025
NSAID	2,289	33.1	1,104	33.2	0.002
Corticosteroids	574	8.3	276	8.3	0.001
Antipsychotics	247	3.6	109	3.3	0.016
Proton pump inhibitors	490	7.1	222	6.7	0.016
Baseline diabetes medications					
Metformin	3,441	49.8	1,655	49.8	0.000
Sulfonylurea	2,431	35.2	1,160	34.9	0.006
Meglitinide	426	6.2	192	5.8	0.017
AGI	590	8.5	272	8.2	0.013
TZD	377	5.5	175	5.3	0.008
DPP-4i	1,838	26.6	857	25.8	0.018
SGLT-2i	56	0.8	23	0.7	0.012
GLP-1	6	0.1	3	0.1	0.005
Insulin	685	9.9	342	10.3	0.013
Numbers of diabetes medications					
Without medications	2,210	32.0	999	30.0	0.041
1 type	1,623	23.5	908	27.3	0.088
2 types	1,559	22.5	733	22.1	0.012
≥ 3 types	1,522	22.0	685	20.6	0.035
Index year					
2012–2013	1,315	19.0	639	19.2	0.005
2014–2015	2,417	35.0	1,185	35.7	0.015
2016–2017	3,183	46.0	1,500	45.1	0.018
Hospital level of OAC initiation					
Medical center	2,609	37.7	1,239	37.3	0.010
Regional hospital	2,947	42.6	1,426	42.9	0.005
District hospital or clinic	1,358	19.6	660	19.8	0.005
Physician specialty					

	NOAC (N = 6914)		Warfarin (N = 3325)		SMD [†]
	N	%	N	%	
Cardiologist	5,414	78.3	2,606	78.4	0.002
Neurologist	192	2.8	85	2.5	0.014
Others	1,308	18.9	634	19.1	0.004

Data are presented as percentages unless otherwise noted.

All the covariates listed in the table were used to calculate the propensity score for IPTW.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Table 7. Baseline characteristics of NOAC and warfarin users in the population after stabilized inverse probability of treatment weighting for the analysis of microvascular complications

	NOAC (N = 16835)		Warfarin (N = 8506)		SMD [†]
	N	%	N	%	
Age (years) [‡]	73.8 ± 10.1		73.9 ± 11.0		0.010
Sex					
Male	9,194	54.6	4,636	54.5	0.002
Female	7,641	45.4	3,870	45.5	0.002
Income level (NTD)					
Financially dependent	4,779	28.4	2,411	28.3	0.001
15840–29999	7,931	47.1	4,046	47.6	0.009
30000–44999	2,247	13.3	1,127	13.2	0.003
≥ 45000	1,878	11.2	922	10.8	0.010
Charlson comorbidity index ^{‡§}	2.6 ± 1.8		2.6 ± 1.8		0.002
CHA2DS2-VASc score ^{‡#}	4.3 ± 1.6		4.3 ± 1.8		0.007
Comorbidities					
Hypertension	12,944	76.9	6,544	76.9	0.001
Coronary artery disease	5,880	34.9	2,951	34.7	0.000
Congestive heart failure	4,665	27.7	2,422	28.5	0.017
COPD	2,395	14.2	1,230	14.5	0.007
Chronic kidney disease	2,224	13.2	1,120	13.2	0.001
Liver cirrhosis	908	5.4	466	5.5	0.004
Hyperlipidemia	5,983	35.5	2,990	35.2	0.008
Stroke	5,023	29.8	2,516	29.6	0.000
Rheumatoid arthritis	121	0.7	56	0.7	0.007
Gout	1,752	10.4	892	10.5	0.003
Dementia	1,058	6.3	515	6.1	0.010
Malignancy	1,372	8.2	685	8.1	0.004
Medication use					
Statins	5,924	35.2	3,000	35.3	0.002
ACEI or ARB	10,375	61.6	5,233	61.5	0.002
β blockers	7,783	46.2	3,937	46.3	0.001
Calcium channel blockers	7,845	46.6	4,003	47.1	0.009

	NOAC (N = 16835)		Warfarin (N = 8506)		SMD [†]
	N	%	N	%	
Diuretics	5,387	32.0	2,756	32.4	0.009
NSAID	5,664	33.6	2,875	33.8	0.003
Corticosteroids	1,491	8.9	770	9.1	0.007
Antipsychotics	844	5.0	427	5.0	0.000
Proton pump inhibitors	1,309	7.8	639	7.5	0.010
Baseline diabetes medications					
Metformin	7,810	46.4	3,912	46.0	0.008
Sulfonylurea	5,417	32.2	2,771	32.6	0.009
Meglitinide	1,045	6.2	515	6.1	0.006
AGI	1,333	7.9	663	7.8	0.005
TZD	695	4.1	365	4.3	0.008
DPP-4i	4,254	25.3	2,148	25.2	0.000
SGLT-2i	131	0.8	69	0.8	0.004
GLP-1	8	0.0	4	0.1	0.002
Insulin	1,614	9.6	841	9.9	0.010
Numbers of diabetes medications					
Without medications	5,880	34.9	2,784	32.7	0.046
1 type	4,065	24.1	2,282	26.8	0.061
2 types	3,572	21.2	1,841	21.6	0.011
≥ 3 types	3,318	19.7	1,599	18.8	0.023
Index year					
2012–2013	3,747	22.3	1,899	22.3	0.002
2014–2015	5,941	35.3	3,059	36.0	0.014
2016–2017	7,147	42.5	3,548	41.7	0.015
Hospital level of OAC initiation					
Medical center	6,239	37.1	3,063	36.0	0.022
Regional hospital	7,561	44.9	3,916	46.0	0.023
District hospital or clinic	3,035	18.0	1,527	18.0	0.002
Physician specialty					

	NOAC (N = 16835)		Warfarin (N = 8506)		SMD [†]
	N	%	N	%	
Cardiologist	11,145	66.2	5,621	66.1	0.002
Neurologist	2,431	14.4	1,190	14.0	0.013
Others	3,259	19.4	1,695	19.9	0.014

Data are presented as percentages unless otherwise noted.

All the covariates listed in the table were used to calculate the propensity score for IPTW.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Table 8. Baseline characteristics of NOAC and warfarin users in the population after stabilized inverse probability of treatment weighting for the analysis of glycemic emergency

	NOAC (N = 19358)		Warfarin (N = 9934)		SMD [†]
	N	%	N	%	
Age (years) [‡]	73.7 ± 10.0		73.9 ± 10.8		0.012
Sex					
Male	10,566	54.6	5,408	54.4	0.003
Female	8,792	45.4	4,526	45.6	0.003
Income level (NTD)					
Financially dependent	5,537	28.6	2,856	28.8	0.003
15840–29999	9,058	46.8	4,687	47.2	0.008
30000–44999	2,623	13.5	1,320	13.3	0.008
≥ 45000	2,141	11.1	1,070	10.8	0.009
Charlson comorbidity index ^{‡§}	2.8 ± 1.9		2.8 ± 1.9		0.003
CHA2DS2-VASc score ^{‡#}	4.3 ± 1.6		4.3 ± 1.8		0.009
Comorbidities					
Hypertension	15,008	77.5	7,713	77.6	0.003
Coronary artery disease	6,803	35.1	3,456	34.8	0.000
Congestive heart failure	5,295	27.4	2,781	28.0	0.014
COPD	2,731	14.1	1,426	14.4	0.007
Chronic kidney disease	2,687	13.9	1,375	13.8	0.001
Liver cirrhosis	1,064	5.5	560	5.6	0.006
Hyperlipidemia	7,135	36.9	3,648	36.7	0.003
Stroke	5,983	30.9	3,049	30.7	0.000
Rheumatoid arthritis	142	0.7	70	0.7	0.003
Gout	2,009	10.4	1,030	10.4	0.000
Dementia	1,204	6.2	583	5.9	0.015
Malignancy	1,568	8.1	793	8.0	0.004
Medication use					
Statins	7,072	36.5	3,641	36.7	0.003
ACEI or ARB	12,174	62.9	6,243	62.8	0.001
β blockers	9,020	46.6	4,635	46.7	0.001
Calcium channel blockers	9,058	46.8	4,693	47.2	0.009

	NOAC (N = 19358)		Warfarin (N = 9934)		SMD [†]
	N	%	N	%	
Diuretics	6,249	32.3	3,245	32.7	0.008
NSAID	6,633	34.3	3,444	34.7	0.008
Corticosteroids	1,721	8.9	906	9.1	0.008
Antipsychotics	964	5.0	503	5.1	0.004
Proton pump inhibitors	1,542	8.0	768	7.7	0.009
Baseline diabetes medications					
Metformin	9,404	48.6	4,808	48.4	0.004
Sulfonylurea	6,675	34.5	3,456	34.8	0.006
Meglitinide	1,300	6.7	643	6.5	0.010
AGI	1,688	8.7	866	8.7	0.000
TZD	897	4.6	480	4.8	0.009
DPP-4i	5,264	27.2	2,712	27.3	0.003
SGLT-2i	166	0.9	90	0.9	0.005
GLP-1	15	0.1	9	0.1	0.005
Insulin	2,202	11.4	1,138	11.5	0.003
Numbers of diabetes medications					
Without medications	6,089	31.5	2,925	29.4	0.044
1 type	4,688	24.2	2,624	26.4	0.051
2 types	4,337	22.4	2,282	23.0	0.013
≥ 3 types	4,244	21.9	2,103	21.2	0.018
Index year					
2012–2013	4,393	22.7	2,252	22.7	0.000
2014–2015	6,869	35.5	3,584	36.1	0.013
2016–2017	8,096	41.8	4,097	41.2	0.012
Hospital level of OAC initiation					
Medical center	7,237	37.4	3,637	36.6	0.016
Regional hospital	8,659	44.7	4,534	45.6	0.018
District hospital or clinic	3,462	17.9	1,763	17.7	0.004
Physician specialty					

	NOAC (N = 19358)		Warfarin (N = 9934)		SMD [†]
	N	%	N	%	
Cardiologist	12,703	65.6	6,524	65.7	0.001
Neurologist	2,951	15.2	1,474	14.8	0.011
Others	3,704	19.1	1,936	19.5	0.009

Data are presented as percentages unless otherwise noted.

All the covariates listed in the table were used to calculate the propensity score for IPTW.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Table 9. Baseline characteristics of overall NOAC and warfarin users in the population after stabilized inverse probability of treatment weighting for the analysis of mortality

	NOAC (N = 19909)		Warfarin (N = 10300)		SMD [†]
	N	%	N	%	
Age (years) [‡]	73.8 ± 10.0		73.9 ± 10.8		0.011
Sex					
Male	10,820	54.3	5,590	54.3	0.002
Female	9,089	45.7	4,710	45.7	0.002
Income level (NTD)					
Financially dependent	5,708	28.7	2,964	28.8	0.002
15840–29999	9,323	46.8	4,864	47.2	0.008
30000–44999	2,689	13.5	1,368	13.3	0.007
≥ 45000	2,189	11.0	1,105	10.7	0.009
Charlson comorbidity index ^{‡§}	2.9 ± 1.9		2.9 ± 1.9		0.004
CHA2DS2-VASc score ^{‡#}	4.4 ± 1.6		4.4 ± 1.8		0.009
Comorbidities					
Hypertension	15,484	77.8	8,025	77.9	0.003
Coronary artery disease	7,029	35.3	3,600	35.0	0.000
Congestive heart failure	5,528	27.8	2,928	28.4	0.015
COPD	2,835	14.2	1,496	14.5	0.008
Chronic kidney disease	2,828	14.2	1,459	14.2	0.001
Liver cirrhosis	1,102	5.5	584	5.7	0.006
Hyperlipidemia	7,342	36.9	3,776	36.7	0.004
Stroke	6,199	31.1	3,190	31.0	0.000
Rheumatoid arthritis	147	0.7	73	0.7	0.003
Gout	2,073	10.4	1,071	10.4	0.001
Dementia	1,278	6.4	632	6.1	0.012
Malignancy	1,630	8.2	838	8.1	0.002
Medication use					
Statins	7,277	36.6	3,775	36.6	0.002
ACEI or ARB	12,559	63.1	6,497	63.1	0.000
β blockers	9,277	46.6	4,803	46.6	0.001
Calcium channel blockers	9,335	46.9	4,874	47.3	0.009

	NOAC (N = 19909)		Warfarin (N = 10300)		SMD [†]
	N	%	N	%	
Diuretics	6,524	32.8	3,417	33.2	0.009
NSAID	6,840	34.4	3,577	34.7	0.008
Corticosteroids	1,792	9.0	949	9.2	0.007
Antipsychotics	1,026	5.2	541	5.3	0.005
Proton pump inhibitors	1,603	8.1	807	7.8	0.008
Baseline diabetes medications					
Metformin	9,683	48.6	4,982	48.4	0.005
Sulfonylurea	6,922	34.8	3,611	35.1	0.006
Meglitinide	1,393	7.0	698	6.8	0.009
AGI	1,769	8.9	913	8.9	0.001
TZD	931	4.7	503	4.9	0.010
DPP-4i	5,504	27.6	2,854	27.7	0.001
SGLT-2i	169	0.8	92	0.9	0.005
GLP-1	15	0.1	9	0.1	0.005
Insulin	2,455	12.3	1,290	12.5	0.006
Numbers of diabetes medications					
Without medications	6,130	30.8	2,955	28.7	0.046
1 type	4,810	24.2	2,728	26.5	0.054
2 types	4,500	22.6	2,386	23.2	0.013
≥ 3 types	4,469	22.4	2,230	21.7	0.019
Index year					
2012–2013	4,527	22.7	2,341	22.7	0.000
2014–2015	7,063	35.5	3,710	36.0	0.011
2016–2017	8,319	41.8	4,248	41.2	0.011
Hospital level of OAC initiation					
Medical center	7,440	37.4	3,779	36.7	0.014
Regional hospital	8,922	44.8	4,704	45.7	0.017
District hospital or clinic	3,548	17.8	1,818	17.6	0.004
Physician specialty					

	NOAC (N = 19909)		Warfarin (N = 10300)		SMD [†]
	N	%	N	%	
Cardiologist	13,022	65.4	6,733	65.4	0.001
Neurologist	3,044	15.3	1,534	14.9	0.011
Others	3,843	19.3	2,033	19.7	0.011

Data are presented as percentages unless otherwise noted.

All the covariates listed in the table were used to calculate the propensity score for IPTW.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

4.1.2 Distribution of propensity scores and the weights calculated by stabilized IPTW

The distribution of propensity scores showed good overlap between the NOAC and warfarin groups after stabilized IPTW. The distributions of propensity scores, both before and after stabilized IPTW, for each outcome analysis are presented in Figures 5-8 (Figure 5 for the analysis of macrovascular complications; Figure 6 for the analysis of microvascular complications; Figure 7 for the analysis of glycemic emergencies; Figure 8 for the analysis of mortality).

In the macrovascular complication analysis, the overall calculated weights had a mean of 1.00, median of 0.84, IQR of 0.32, maximum of 11.9, and minimum of 0.35. In the microvascular complication analysis, the corresponding figures were a mean of 1.00, median of 0.82, IQR of 0.32, maximum of 11.9, and minimum of 0.35. In the glycemic emergencies analysis, the weights were: mean 1.00, median 0.82, IQR 0.33, maximum 11.4, and minimum 0.35. For the mortality analysis, the weights were: mean 1.00, median 0.81, IQR 0.33, maximum 11.4, and minimum 0.36. The weight distributions for each outcome analysis in the NOAC and warfarin groups are presented in Figure 9-12 (Figure 9 for the analysis of macrovascular complications; Figure 10 for the analysis of microvascular complications; Figure 11 for the analysis of glycemic emergencies; Figure 12 for the analysis of mortality).

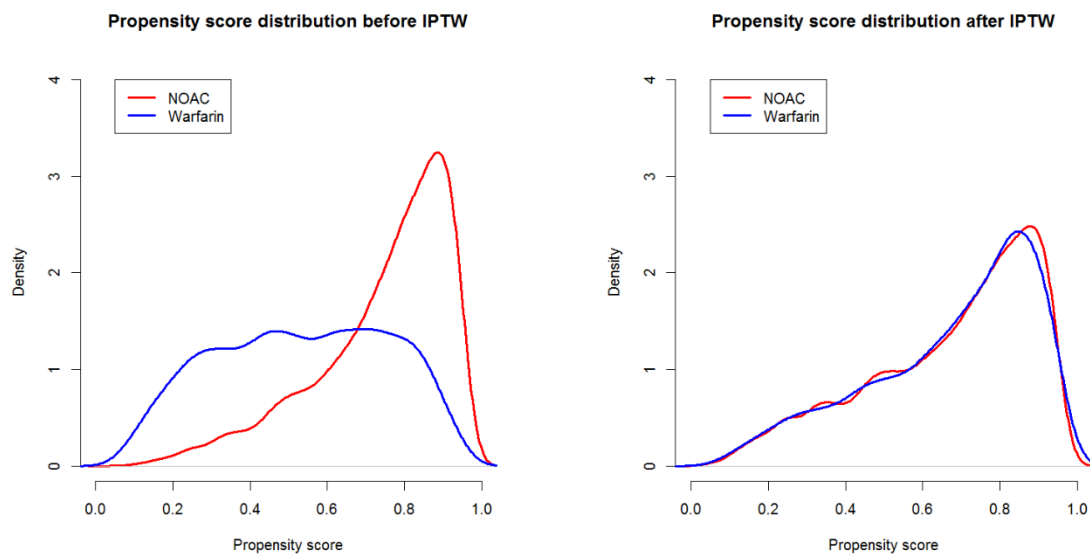


Figure 5. Distribution of propensity scores before and after applying stabilized IPTW for the macrovascular complication analysis in Study 1

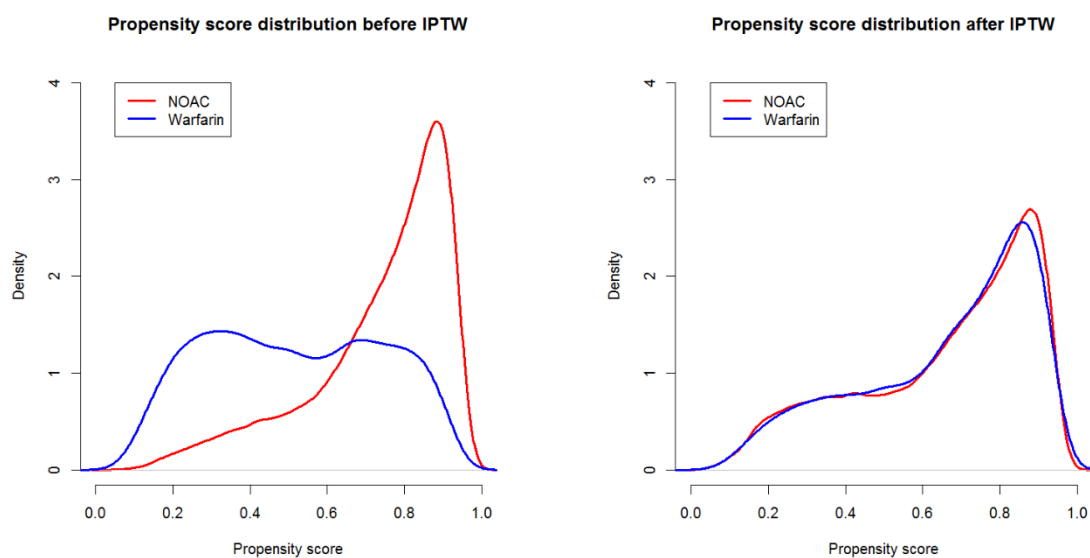


Figure 6. Distribution of propensity scores before and after applying stabilized IPTW for the microvascular complication analysis in Study 1

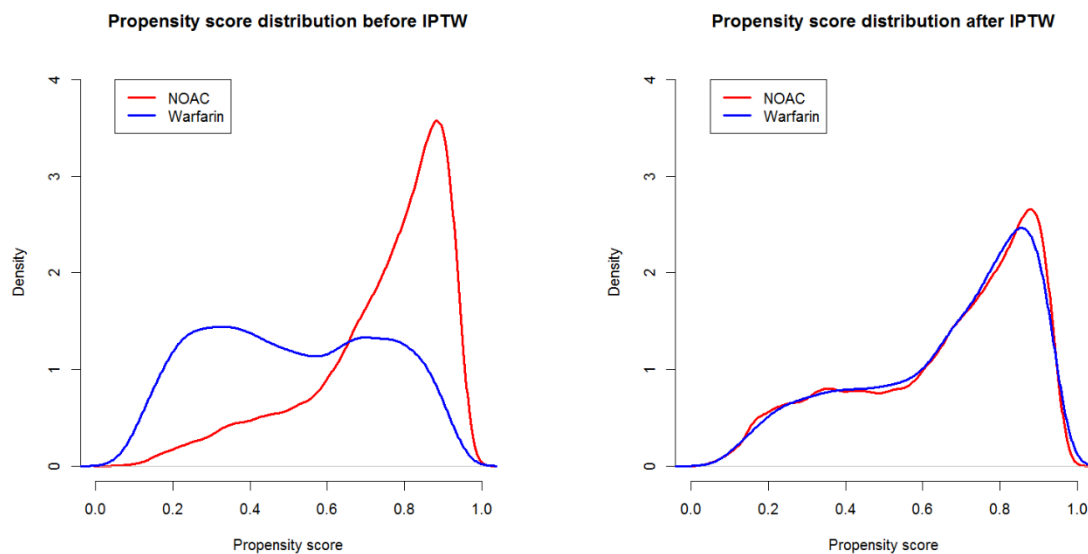


Figure 7. Distribution of propensity scores before and after applying stabilized IPTW for the glycemic emergency analysis in Study 1

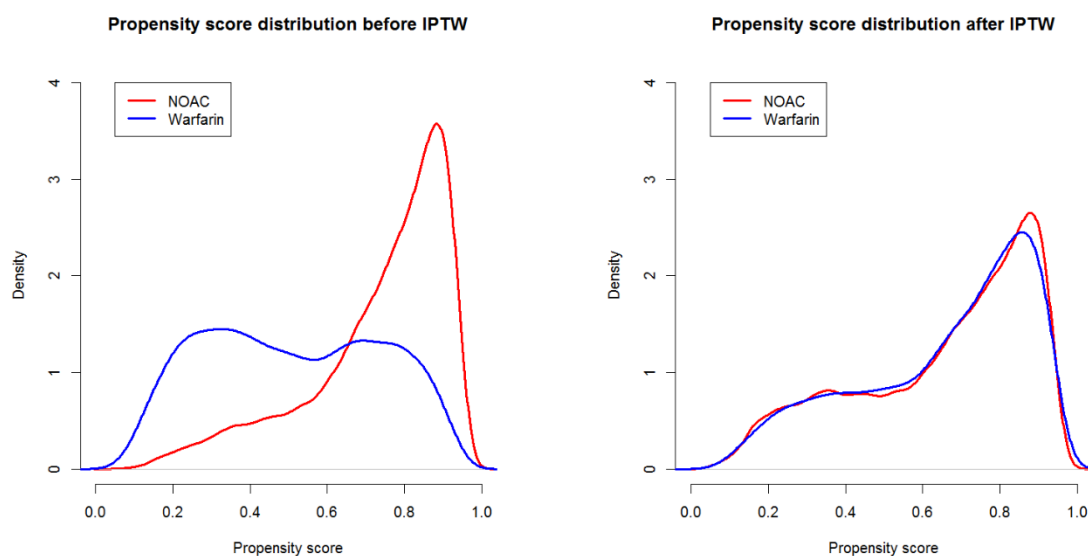


Figure 8. Distribution of propensity scores before and after applying stabilized IPTW for the mortality analysis in Study 1

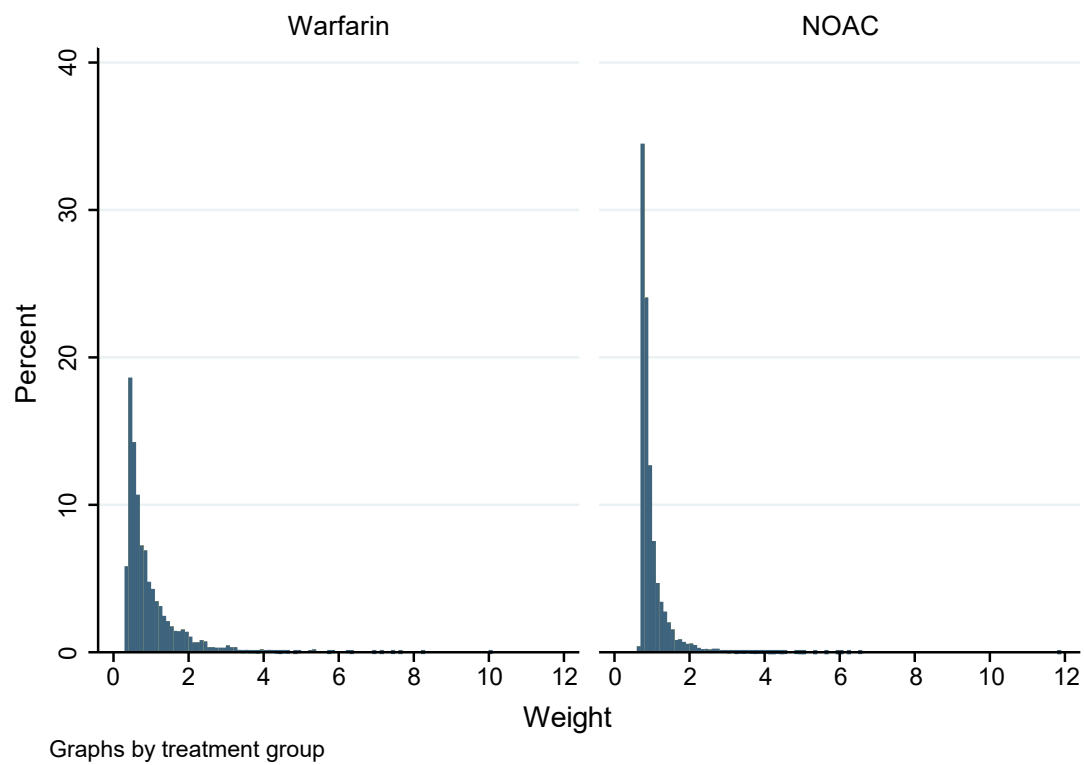


Figure 9. Distribution of weights obtained by stabilized IPTW in the NOAC and warfarin groups for the macrovascular complication analysis in Study 1

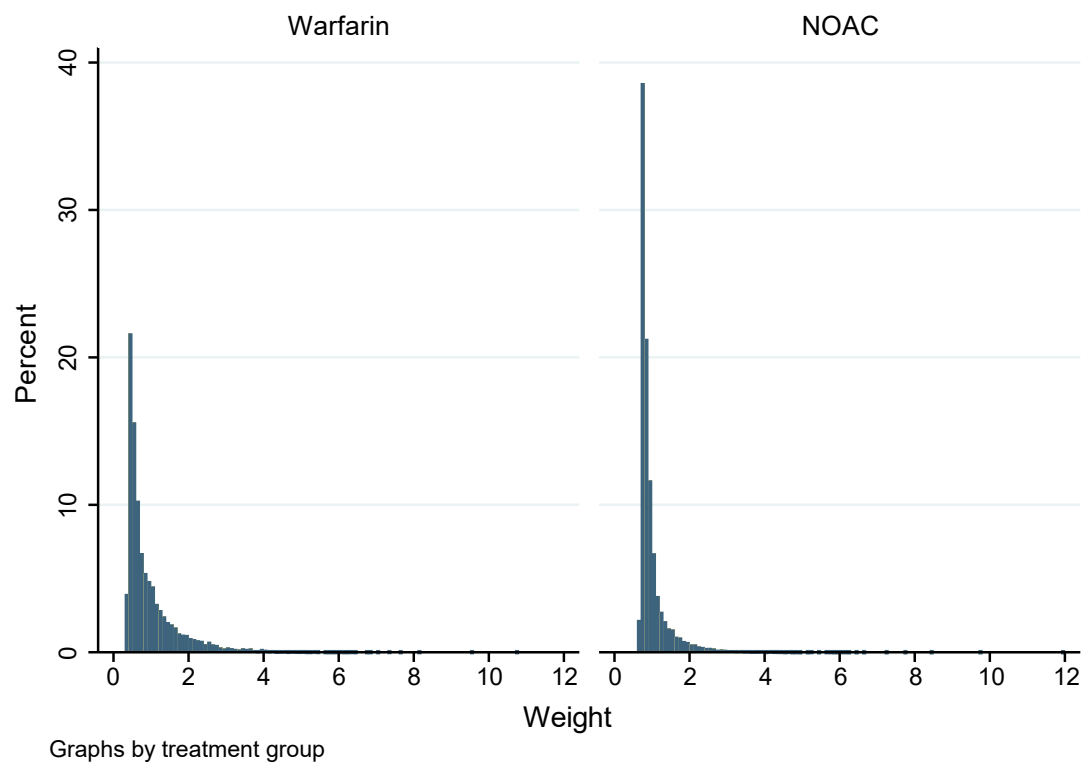


Figure 10. Distribution of weights obtained by stabilized IPTW in the NOAC and warfarin groups for the microvascular complication analysis in Study 1

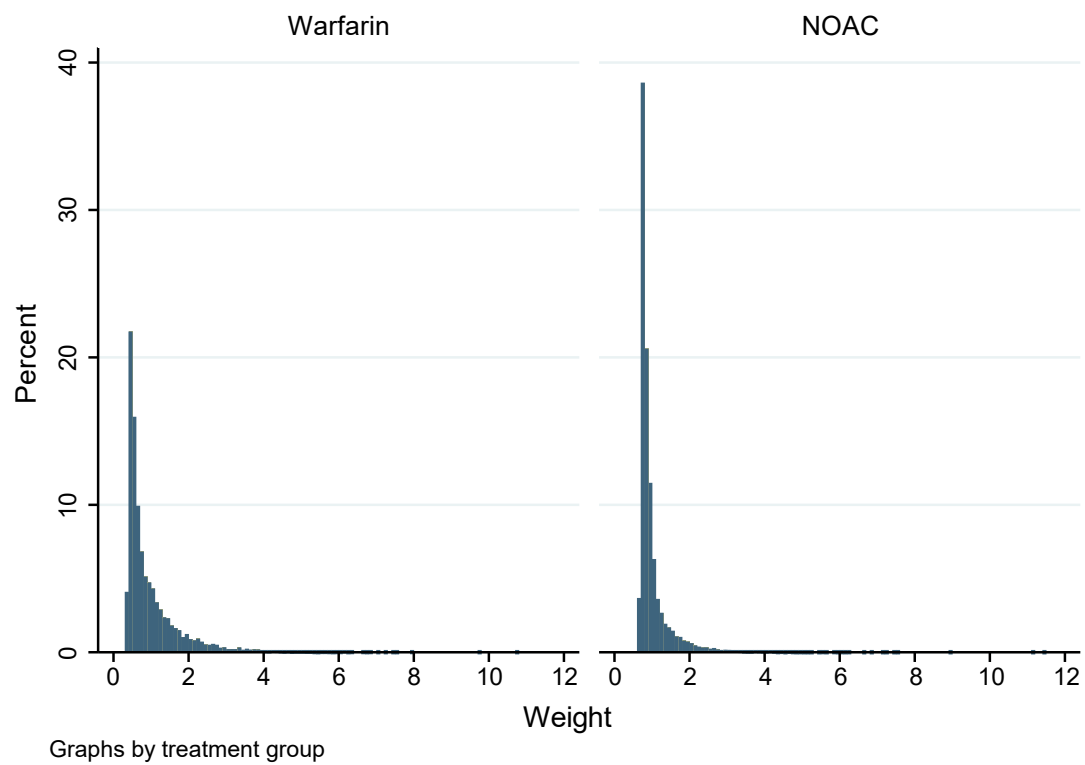


Figure 11. Distribution of weights obtained by stabilized IPTW in the NOAC and warfarin groups for the glycemic emergency analysis in Study 1

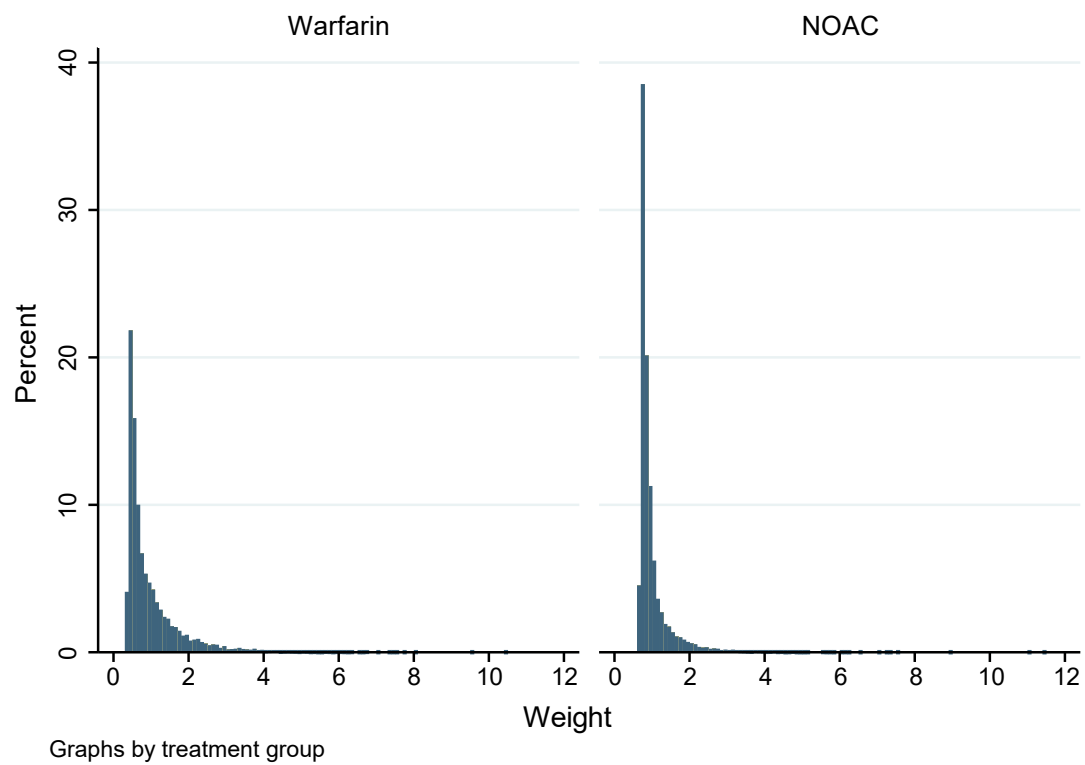


Figure 12. Distribution of weights obtained by stabilized IPTW in the NOAC and warfarin groups for the mortality analysis in Study 1

4.1.3 Risks of diabetes complications and mortality in patients taking NOACs versus warfarin

In the pseudo-population constructed by stabilized IPTW, NOAC users exhibited significantly lower risks of developing macrovascular complications (HR=0.84, 95% CI: 0.78-0.91, $p<0.001$), microvascular complications (HR=0.79, 95% CI: 0.73-0.85, $p<0.001$), glycemic emergencies (HR=0.91, 95% CI: 0.83-0.99, $p=0.043$), and mortality (HR=0.78, 95% CI: 0.75-0.82, $p<0.001$) compared to warfarin users (Table 10). We also observed lower cumulative incidences of macrovascular complications, microvascular complications, glycemic emergencies, and mortality among NOAC users compared to warfarin users (Figure 13A-D).

In the analyses for individual complications, significantly lower risks of coronary artery disease, stroke, dialysis, lower extremity amputation, and both cardiovascular and non-cardiovascular mortality were observed in NOAC users than in warfarin users (Table 11).

The analyses for individual NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) revealed a consistent trend of decreased complication and mortality risks for NOAC users compared to warfarin users (Table 12).

In the analyses stratified by age, sex, and hospital level, a consistent trend of reduced risks of diabetes complications and mortality among NOAC users was noted in each age, sex, and hospital level subgroup. However, all the analyses in the subgroup of age < 65 years did not reach statistical significance (Table 13).

Table 10. Risk of diabetes complications and mortality in atrial fibrillation patients with diabetes taking NOACs and those taking warfarin

Outcome	N*	Event no.	PY	IR [†]	HR [‡] (95% CI)	p-value
Macrovascular complication						
NOAC	6914	1,964	16,271	120.7	0.84 (0.78-0.91)	<0.001
Warfarin	3325	1,087	7,565	143.8	1.00 (ref.)	
Microvascular complication						
NOAC	16835	1,660	46,006	36.1	0.79 (0.73-0.85)	<0.001
Warfarin	8506	1,031	22,987	44.8	1.00 (ref.)	
Glycemic emergency						
NOAC	19358	1,292	55,026	23.5	0.91 (0.83-0.99)	0.043
Warfarin	9934	736	28,011	26.3	1.00 (ref.)	
Mortality						
NOAC	19909	5,098	58,328	87.4	0.78 (0.75-0.82)	<0.001
Warfarin	10300	3,415	30,023	113.7	1.00 (ref.)	

In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.

*A pseudo-population constructed by stabilized IPTW was used for analyses

[†]Incidence rate, per 1000 person-years.

[‡]The HR is calculated by a Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; N, number; NOAC, non-vitamin K antagonist oral anticoagulant; PY, person-year; ref., reference.

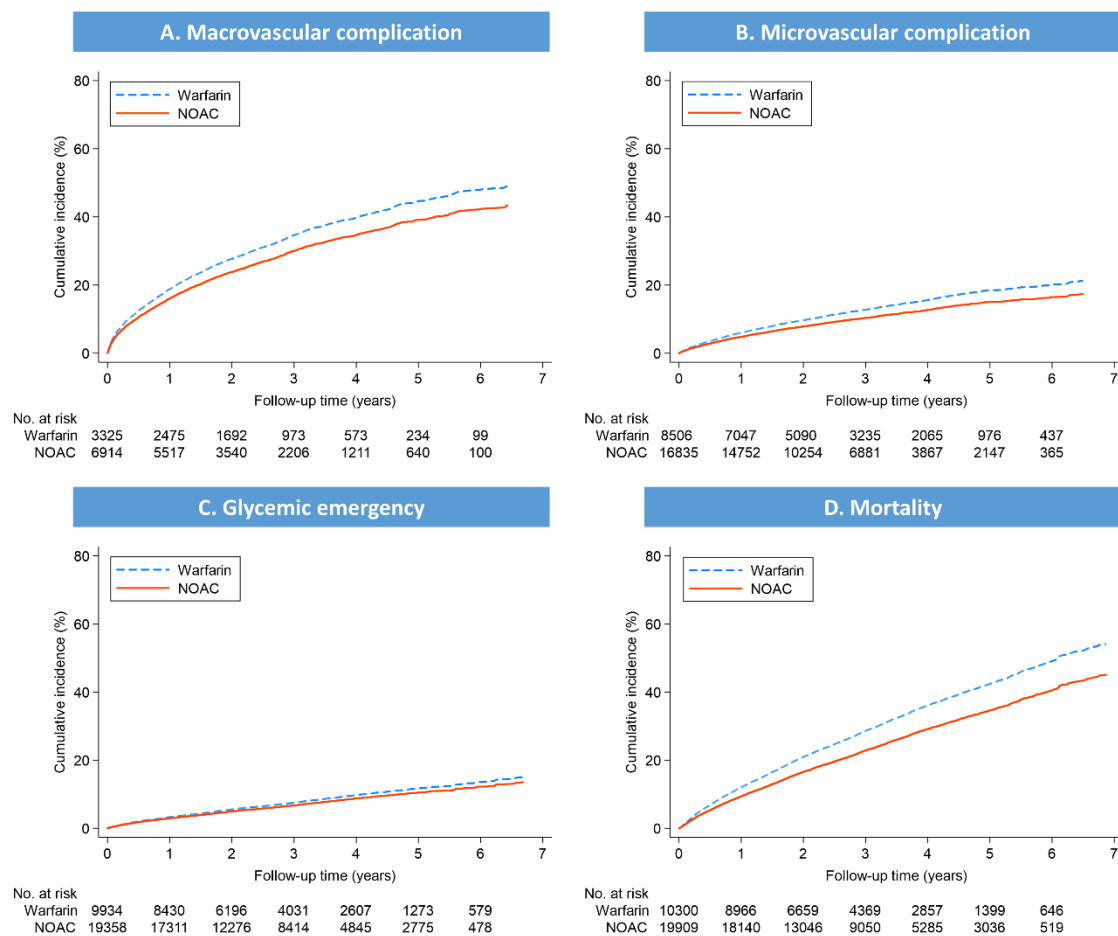


Figure 13. The cumulative incidence curves of (A) macrovascular complication, (B) microvascular complication, (C) glycemic emergency, and (D) mortality for NOAC and warfarin users after stabilized IPTW.

Abbreviations: NOAC, non-vitamin K antagonist oral anticoagulant; IPTW, inverse probability of treatment weighting

Table 11. Risk of individual diabetes complications in atrial fibrillation patients with diabetes taking NOACs and those taking warfarin

Outcome	N	Event no.	PY	IR [†]	HR [‡] (95% CI)	p-value
Coronary artery disease						
NOAC	11532	2,107	29,260	72.0	0.90 (0.84-0.97)	0.008
Warfarin	5638	1,118	14,048	79.6	1.00 (ref.)	
Stroke						
NOAC	12928	1,713	34,739	49.3	0.80 (0.74-0.87)	<0.001
Warfarin	6614	1,062	17,389	61.0	1.00 (ref.)	
Peripheral vascular disease						
NOAC	18835	634	54,030	11.7	0.90 (0.78-1.03)	0.128
Warfarin	9599	353	27,285	12.9	1.00 (ref.)	
Retinopathy						
NOAC	18392	609	51,919	11.7	1.04 (0.91-1.21)	0.56
Warfarin	9372	288	26,330	10.9	1.00 (ref.)	
Neuropathy						
NOAC	18157	745	51,575	14.5	0.93 (0.82-1.05)	0.24
Warfarin	9366	405	26,407	15.3	1.00 (ref.)	
Dialysis						
NOAC	19852	687	57,700	11.9	0.52 (0.46-0.58)	<0.001
Warfarin	10193	640	29,253	21.9	1.00 (ref.)	
Lower extremity amputation						
NOAC	19861	131	58,048	2.3	0.76 (0.58-0.99)	0.043
Warfarin	10263	88	29,807	2.9	1.00 (ref.)	



Diabetic ketoacidosis						
NOAC	19842	81	57,993	1.4	0.90 (0.62-1.33)	0.60
Warfarin	10246	43	29,810	1.4	1.00 (ref.)	
Hyperosmolar hyperglycemic state						
NOAC	19787	360	57,561	6.2	0.95 (0.79-1.13)	0.54
Warfarin	10218	200	29,603	6.8	1.00 (ref.)	
Hypoglycemia						
NOAC	19523	976	55,927	17.5	0.91 (0.82-1.02)	0.104
Warfarin	10049	554	28,523	19.4	1.00 (ref.)	
Cardiovascular mortality						
NOAC	19909	1,818	58,328	31.2	0.71 (0.66-0.76)	<0.001
Warfarin	10300	1,346	30,023	44.8	1.00 (ref.)	
Non-cardiovascular mortality						
NOAC	19909	3,279	58,328	56.2	0.83 (0.78-0.88)	<0.001
Warfarin	10300	2,069	30,023	68.9	1.00 (ref.)	

In each outcome analysis, patients who already experienced the corresponding outcome event before the index date were excluded.

[†]Incidence rate, per 1000 person-years.

[‡]The HR is calculated by a Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; N, number; NOAC, non-vitamin K antagonist oral anticoagulant; ref., reference



Table 12. Risk of diabetes complications and mortality associated with each NOAC versus warfarin

Comparison and outcome	HR [†] (95% CI)	p-value
Dabigatran vs. warfarin		
Macrovascular complication	0.81 (0.74-0.89)	<0.001
Microvascular complication	0.81 (0.74-0.89)	<0.001
Glycemic emergency	0.96 (0.86-1.08)	0.53
Mortality	0.78 (0.73-0.83)	<0.001
Rivaroxaban vs. warfarin		
Macrovascular complication	0.90 (0.82-0.99)	0.029
Microvascular complication	0.83 (0.75-0.91)	<0.001
Glycemic emergency	0.95 (0.85-1.06)	0.37
Mortality	0.83 (0.78-0.88)	<0.001
Apixaban vs. warfarin		
Macrovascular complication	0.81 (0.68-0.96)	0.013
Microvascular complication	0.84 (0.70-1.00)	0.045
Glycemic emergency	0.83 (0.66-1.04)	0.107
Mortality	0.85 (0.76-0.94)	0.003
Edoxaban vs. warfarin		
Macrovascular complication	0.74 (0.51-1.08)	0.119
Microvascular complication	0.56 (0.33-0.96)	0.036
Glycemic emergency	0.68 (0.36-1.32)	0.26
Mortality	0.86 (0.65-1.15)	0.32

In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.

[†]The HR is calculated by Cox proportional hazard models with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant.

Table 13. Risks of diabetes complications and mortality in atrial fibrillation patients with diabetes taking NOACs versus warfarin, stratified by age, sex, and hospital levels

Outcome and stratification	HR [†] (95% CI)	p-value
Age < 65 years		
Macrovascular complication	0.93 (0.79-1.11)	0.43
Microvascular complication	0.86 (0.72-1.03)	0.101
Glycemic emergency	1.11 (0.85-1.47)	0.44
Mortality	0.89 (0.76-1.03)	0.124
Age ≥ 65 years		
Macrovascular complication	0.82 (0.75-0.89)	<0.001
Microvascular complication	0.75 (0.69-0.83)	<0.001
Glycemic emergency	0.91 (0.82-1.01)	0.066
Mortality	0.82 (0.78-0.86)	<0.001
Male		
Macrovascular complication	0.85 (0.77-0.95)	0.003
Microvascular complication	0.81 (0.73-0.91)	<0.001
Glycemic emergency	0.93 (0.81-1.06)	0.27
Mortality	0.80 (0.75-0.86)	<0.001
Female		
Macrovascular complication	0.82 (0.73-0.92)	0.001
Microvascular complication	0.76 (0.67-0.86)	<0.001
Glycemic emergency	0.88 (0.77-1.00)	0.056
Mortality	0.77 (0.72-0.82)	<0.001
Medical center		
Macrovascular complication	0.83 (0.73-0.95)	0.006
Microvascular complication	0.77 (0.67-0.88)	<0.001
Glycemic emergency	0.91 (0.77-1.07)	0.24
Mortality	0.74 (0.68-0.80)	<0.001
Regional hospital		
Macrovascular complication	0.84 (0.75-0.94)	0.003
Microvascular complication	0.80 (0.71-0.90)	<0.001
Glycemic emergency	0.89 (0.78-1.02)	0.105
Mortality	0.83 (0.78-0.89)	<0.001

District hospital or clinic

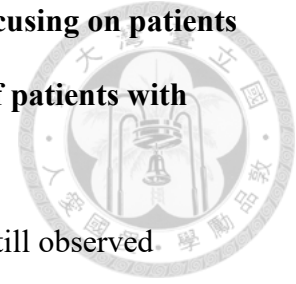
Macrovascular complication	0.89 (0.75-1.06)	0.176
Microvascular complication	0.87 (0.71-1.06)	0.153
Glycemic emergency	0.92 (0.73-1.17)	0.52
Mortality	0.72 (0.64-0.81)	<0.001



† The HR is calculated by a cause-specific Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant

4.1.4 Results of sensitivity analyses: on-treatment design, focusing on patients with high medication possession ratio, and exclusion of patients with chronic kidney disease



In the sensitivity analysis applying on-treatment design, we still observed significantly lower risks of macrovascular complications (HR=0.83, 95% CI: 0.75-0.92, $p<0.001$), microvascular complications (HR=0.68, 95% CI: 0.61-0.75, $p<0.001$), glycemic emergency (HR=0.81, 95% CI: 0.71-0.93, $p=0.003$), and mortality (HR=0.63, 95% CI: 0.59-0.68, $p<0.001$) for NOAC users compared with warfarin users. Furthermore, a significant association was observed between NOAC and lower complication hazards for many individual outcomes, including coronary artery disease, stroke, peripheral vascular disease, dialysis, lower extremity amputation, hypoglycemia, cardiovascular mortality, and non-cardiovascular mortality (Table 14).

In the sensitivity analysis limited to patients with a high medication possession ratio ($\geq 80\%$) for the index oral anticoagulant, larger effect sizes with more significant results than our primary analyses were observed: macrovascular complications (HR=0.66, 95% CI: 0.59-0.73, $p<0.001$); microvascular complications (HR=0.56, 95% CI: 0.50-0.63, $p<0.001$); glycemic emergency (HR=0.62, 95% CI: 0.54-0.71, $p<0.001$); mortality (HR=0.51, 95% CI: 0.47-0.55, $p<0.001$). The significant association between NOAC and lower complication risks was also observed for many individual outcomes (Table 14).

The sensitivity analysis excluding patients with chronic kidney diseases at baseline revealed similar findings to that of our primary analyses: macrovascular complications (HR=0.83, 95% CI: 0.77-0.90, $p<0.001$); microvascular complications (HR=0.89, 95% CI: 0.81-0.97, $p=0.011$); glycemic emergency (HR=0.91, 95% CI: 0.82-1.01, $p=0.063$); mortality (HR=0.78, 95% CI: 0.74-0.82, $p<0.001$) (Table 15).

Table 14. Risks of diabetes complications and mortality associated with NOAC versus warfarin in sensitivity analyses that applied an on-treatment design and that was limited to patients with a medication possession ratio $\geq 80\%$ during follow-up

Outcome	Analyses using on-treatment design (analog of per-protocol)		Analyses limited to patients with MPR $\geq 80\%$	
	HR [†] (95% CI)	p-value	HR [†] (95% CI)	p-value
Macrovascular complication	0.83 (0.75-0.92)	<0.001	0.66 (0.59-0.73)	<0.001
Coronary artery disease	0.87 (0.79-0.96)	0.006	0.62 (0.56-0.69)	<0.001
Stroke	0.73 (0.65-0.81)	<0.001	0.56 (0.50-0.63)	<0.001
Peripheral vascular disease	0.82 (0.68-0.99)	0.035	0.61 (0.50-0.74)	<0.001
Microvascular complication	0.68 (0.61-0.75)	<0.001	0.56 (0.50-0.63)	<0.001
Retinopathy	0.88 (0.73-1.05)	0.163	0.62 (0.51-0.75)	<0.001
Neuropathy	0.90 (0.76-1.07)	0.235	0.66 (0.55-0.79)	<0.001
Dialysis	0.31 (0.27-0.37)	<0.001	0.33 (0.28-0.39)	<0.001
Lower extremity amputation	0.56 (0.38-0.82)	0.003	0.48 (0.31-0.73)	0.001
Glycemic emergency	0.81 (0.71-0.93)	0.003	0.62 (0.54-0.71)	<0.001
Diabetic ketoacidosis	0.76 (0.45-1.27)	0.294	0.66 (0.37-1.18)	0.158
Hyperosmolar hyperglycemic state	0.89 (0.68-1.17)	0.402	0.69 (0.52-0.93)	0.013
Hypoglycemia	0.82 (0.71-0.96)	0.014	0.62 (0.53-0.73)	<0.001
Mortality	0.63 (0.59-0.68)	<0.001	0.51 (0.47-0.55)	<0.001
Cardiovascular mortality	0.59 (0.52-0.66)	<0.001	0.48 (0.43-0.55)	<0.001
Non-cardiovascular mortality	0.67 (0.61-0.73)	<0.001	0.54 (0.49-0.60)	<0.001

*A pseudo-population constructed by stabilized IPTW for analyses

[†]The HR is calculated by a Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MPR, medication possession ratio; NOAC, non-vitamin K antagonist oral anticoagulant



Table 15. Risks of diabetes complications and mortality associated with NOAC versus warfarin in the sensitivity analysis excluding patients with chronic kidney diseases at baseline

Outcome	N*	Event no.	PY	IR [†]	HR [‡] (95% CI)	p-value
Macrovascular complication						
NOAC	6,124	1,717	14,658	117.2	0.83 (0.77-0.90)	<0.001
Warfarin	2,862	931	6,623	140.6	1.00 (ref.)	
Microvascular complication						
NOAC	14,718	1,387	41,044	33.8	0.89 (0.81-0.97)	0.011
Warfarin	7,317	761	20,391	37.3	1.00 (ref.)	
Glycemic emergency						
NOAC	16,856	1,073	48,884	21.9	0.91 (0.82-1.01)	0.063
Warfarin	8,448	601	24,414	24.6	1.00 (ref.)	
Mortality						
NOAC	17,276	4,218	51,647	81.7	0.78 (0.74-0.82)	<0.001
Warfarin	8,719	2,777	25,997	106.8	1.00 (ref.)	

In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.

*The pseudo-population after stabilized IPTW with weight truncation

[†]Incidence rate, per 1000 person-years.

[‡]The HR is calculated by a Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; N, number; NOAC, non-vitamin K antagonist oral anticoagulant; PY, person-year; ref., reference.

4.1.5 Results of sensitivity analyses applying stabilized IPTW with weight truncation

In the analysis with weight truncation (reducing any weight greater than 5 down to this threshold), we still observed similar findings that NOACs were significantly associated with lower risks of macrovascular complications (HR=0.85, 95% CI: 0.79-0.92, $p<0.001$), microvascular complications (HR=0.79, 95% CI: 0.73-0.85, $p<0.001$), glycemic emergencies (HR=0.91, 95% CI: 0.83-0.99, $p=0.042$), and mortality (HR=0.79, 95% CI: 0.75-0.82, $p<0.001$) compared to warfarin (Table 16).

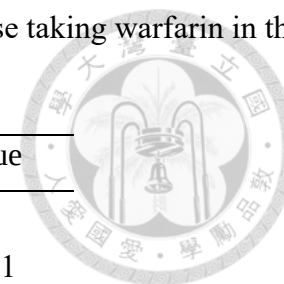


Table 16. Risk of diabetes complications and mortality in atrial fibrillation patients with diabetes taking NOACs and those taking warfarin in the sensitivity analyses applying stabilized IPTW with weight truncation

Outcome	N*	Event no.	PY	IR [†]	HR [‡] (95% CI)	p-value
Macrovascular complication						
NOAC	6,900	1,961	16,210	121.0	0.85 (0.79-0.92)	<0.001
Warfarin	3,296	1,073	7,528	142.5	1.00 (ref.)	
Microvascular complication						
NOAC	16,800	1,656	45,868	36.1	0.79 (0.73-0.85)	<0.001
Warfarin	8,465	1,028	22,925	44.8	1.00 (ref.)	
Glycemic emergency						
NOAC	19,316	1,287	54,846	23.5	0.91 (0.83-0.99)	0.042
Warfarin	9,875	733	27,916	26.3	1.00 (ref.)	
Mortality						
NOAC	19,868	5,090	58,130	87.6	0.79 (0.75-0.82)	<0.001
Warfarin	10,244	3,386	29,932	113.1	1.00 (ref.)	

In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.

*The pseudo-population after stabilized IPTW with weight truncation

[†]Incidence rate, per 1000 person-years.

[‡]The HR is calculated by a Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; N, number; NOAC, non-vitamin K antagonist oral anticoagulant; PY, person-year; ref., reference.

4.1.6 Results of sensitivity analyses applying propensity score matching

In the analyses with propensity score matching, a similar pattern of lower risks for macrovascular complications (HR=0.89, 95% CI: 0.81-0.98, $p=0.022$), microvascular complications (HR=0.83, 95% CI: 0.75-0.92, $p<0.001$), and mortality (HR=0.81, 95% CI: 0.76-0.86, $p<0.001$) was observed among patients using NOACs; the analysis for glycemic emergencies (HR=0.97, 95% CI: 0.86-1.09, $p=0.60$) did not yield statistically significant results (Table 17).

The baseline characteristics of the propensity score-matched population for the analyses of macrovascular complications, microvascular complications, glycemic emergencies, and mortality are presented in Table 18, Table 19, Table 20, and Table 21, respectively.

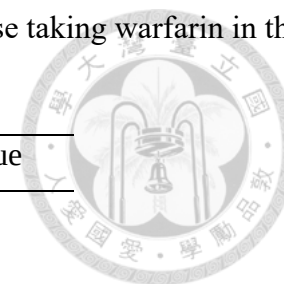


Table 17. Risk of diabetes complications and mortality in atrial fibrillation patients with diabetes taking NOACs and those taking warfarin in the analyses applying propensity score matching

Outcome	N*	Event no.	PY	IR [†]	HR [‡] (95% CI)	p-value
Macrovascular complication						
NOAC	2594	830	6,630	125.2	0.89 (0.81-0.98)	0.022
Warfarin	2594	891	6,404	139.1	1.00 (ref.)	
Microvascular complication						
NOAC	6403	711	19,329	36.8	0.83 (0.75-0.92)	<0.001
Warfarin	6403	836	19,105	43.8	1.00 (ref.)	
Glycemic emergency						
NOAC	7426	537	23,290	23.1	0.97 (0.86-1.09)	0.603
Warfarin	7426	554	23,178	23.9	1.00 (ref.)	
Mortality						
NOAC	7677	2,104	24,885	84.5	0.81 (0.76-0.86)	<0.001
Warfarin	7677	2,594	24,758	104.8	1.00 (ref.)	

In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.

*The population after propensity score matching was used for analyses

[†]Incidence rate, per 1000 person-years.

[‡]The HR is calculated by a Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; N, number; NOAC, non-vitamin K antagonist oral anticoagulant; PY, person-year; ref., reference.

Table 18. Baseline characteristics of NOAC and warfarin users in the propensity score-matched population for the analysis of macrovascular complications

	NOAC (N = 2594)		Warfarin (N = 2594)		SMD [†]
	N	%	N	%	
Age (years) [‡]	70.9 ± 10.1		71.0 ± 11.1		0.008
Sex					
Male	1,435	55.3	1,430	55.1	0.004
Female	1,159	44.7	1,164	44.9	0.004
Income level (NTD)					
Financially dependent	651	25.1	666	25.7	0.013
15840–29999	1,225	47.2	1,211	46.7	0.011
30000–44999	418	16.1	419	16.2	0.001
≥ 45000	300	11.6	298	11.5	0.002
Charlson comorbidity index ^{‡§}	2.2 ± 1.7		2.2 ± 1.7		0.015
CHA2DS2-VASc score ^{‡#}	3.3 ± 1.3		3.3 ± 1.4		0.008
Comorbidities					
Hypertension	1,872	72.2	1,845	71.1	0.023
Coronary artery disease	0	0.0	0	0.0	0.000
Congestive heart failure	630	24.3	627	24.2	0.003
COPD	293	11.3	297	11.4	0.005
Chronic kidney disease	334	12.9	344	13.3	0.011
Liver cirrhosis	165	6.4	171	6.6	0.009
Hyperlipidemia	935	36.0	890	34.3	0.036
Stroke	0	0.0	0	0.0	0.000
Rheumatoid arthritis	25	1.0	26	1.0	0.004
Gout	291	11.2	273	10.5	0.022
Dementia	79	3.0	76	2.9	0.007
Malignancy	218	8.4	233	9.0	0.021
Medication use					
Statins	838	32.3	812	31.3	0.022
ACEI or ARB	1,552	59.8	1,531	59.0	0.016
β blockers	1,109	42.8	1,102	42.5	0.005
Calcium channel blockers	1,148	44.3	1,125	43.4	0.018

	NOAC (N = 2594)		Warfarin (N = 2594)		SMD [†]
	N	%	N	%	
Diuretics	765	29.5	784	30.2	0.016
NSAID	856	33.0	863	33.3	0.006
Corticosteroids	218	8.4	222	8.6	0.006
Antipsychotics	78	3.0	75	2.9	0.007
Proton pump inhibitors	193	7.4	183	7.1	0.015
Baseline diabetes medications					
Metformin	1,275	49.2	1,274	49.1	0.001
Sulfonylurea	961	37.0	953	36.7	0.006
Meglitinide	167	6.4	163	6.3	0.006
AGI	229	8.8	233	9.0	0.005
TZD	146	5.6	148	5.7	0.003
DPP-4i	665	25.6	647	24.9	0.016
SGLT-2i	8	0.3	10	0.4	0.013
GLP-1	2	0.1	3	0.1	0.012
Insulin	268	10.3	270	10.4	0.003
Numbers of diabetes medications					
Without medications	826	31.8	778	30.0	0.040
1 type	600	23.1	677	26.1	0.069
2 types	592	22.8	595	22.9	0.003
≥ 3 types	576	22.2	544	21.0	0.030
Index year					
2012–2013	666	25.7	666	25.7	0.000
2014–2015	1,118	43.1	1,118	43.1	0.000
2016–2017	810	31.2	810	31.2	0.000
Hospital level of OAC initiation					
Medical center	904	34.8	921	35.5	0.014
Regional hospital	1,140	43.9	1,130	43.6	0.008
District hospital or clinic	550	21.2	543	20.9	0.007
Physician specialty					
Cardiologist	2,030	78.3	2,021	77.9	0.008

	NOAC (N = 2594)		Warfarin (N = 2594)		SMD [†]
	N	%	N	%	
Neurologist	55	2.1	49	1.9	0.017
Others	509	19.6	524	20.2	0.014

Data are presented as percentages unless otherwise noted.

All the covariates listed in the table were used to calculate the propensity score for IPTW.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Table 19. Baseline characteristics of NOAC and warfarin users in the propensity score-matched population for the analysis of microvascular complications

	NOAC (N = 6403)		Warfarin (N = 6403)		SMD [†]
	N	%	N	%	
Age (years) [‡]	72.9 ± 10.1		72.8 ± 11.0		0.018
Sex					
Male	3,518	54.9	3,518	54.9	0.000
Female	2,885	45.1	2,885	45.1	0.000
Income level (NTD)					
Financially dependent	1,780	27.8	1,792	28.0	0.004
15840–29999	3,063	47.8	3,006	46.9	0.018
30000–44999	890	13.9	907	14.2	0.008
≥ 45000	670	10.5	698	10.9	0.014
Charlson comorbidity index ^{‡§}	2.6 ± 1.8		2.6 ± 1.8		0.017
CHA2DS2-VASc score ^{‡#}	4.2 ± 1.7		4.2 ± 1.8		0.010
Comorbidities					
Hypertension	4,905	76.6	4,888	76.3	0.006
Coronary artery disease	2,231	34.8	2,214	34.6	0.000
Congestive heart failure	1,823	28.5	1,806	28.2	0.006
COPD	911	14.2	885	13.8	0.012
Chronic kidney disease	903	14.1	878	13.7	0.011
Liver cirrhosis	388	6.1	401	6.3	0.008
Hyperlipidemia	2,221	34.7	2,217	34.6	0.001
Stroke	1,778	27.8	1,784	27.9	0.000
Rheumatoid arthritis	53	0.8	46	0.7	0.012
Gout	678	10.6	688	10.7	0.005
Dementia	378	5.9	358	5.6	0.013
Malignancy	533	8.3	502	7.8	0.018
Medication use					
Statins	2,181	34.1	2,145	33.5	0.012
ACEI or ARB	3,908	61.0	3,914	61.1	0.002
β blockers	2,996	46.8	3,002	46.9	0.002
Calcium channel blockers	3,009	47.0	3,002	46.9	0.002

	NOAC (N = 6403)		Warfarin (N = 6403)		SMD [†]
	N	%	N	%	
Diuretics	2,142	33.5	2,156	33.7	0.005
NSAID	2,179	34.0	2,141	33.4	0.013
Corticosteroids	570	8.9	561	8.8	0.005
Antipsychotics	314	4.9	295	4.6	0.014
Proton pump inhibitors	476	7.4	509	7.9	0.019
Baseline diabetes medications					
Metformin	2,859	44.7	2,867	44.8	0.003
Sulfonylurea	2,128	33.2	2,125	33.2	0.001
Meglitinide	424	6.6	428	6.7	0.003
AGI	541	8.4	527	8.2	0.008
TZD	282	4.4	270	4.2	0.009
DPP-4i	1,516	23.7	1,541	24.1	0.009
SGLT-2i	22	0.3	17	0.3	0.014
GLP-1	5	0.1	5	0.1	0.000
Insulin	684	10.7	648	10.1	0.018
Numbers of diabetes medications					
Without medications	2,294	35.8	2,123	33.2	0.056
1 type	1,491	23.3	1,698	26.5	0.075
2 types	1,333	20.8	1,399	21.8	0.025
≥ 3 types	1,285	20.1	1,183	18.5	0.040
Index year					
2012–2013	1,788	27.9	1,788	27.9	0.000
2014–2015	2,923	45.7	2,923	45.7	0.000
2016–2017	1,692	26.4	1,692	26.4	0.000
Hospital level of OAC initiation					
Medical center	2,174	34.0	2,204	34.4	0.010
Regional hospital	2,911	45.5	2,892	45.2	0.006
District hospital or clinic	1,318	20.6	1,307	20.4	0.004
Physician specialty					
Cardiologist	4,246	66.3	4,265	66.6	0.006

	NOAC (N = 6403)		Warfarin (N = 6403)		SMD [†]
	N	%	N	%	
Neurologist	797	12.4	780	12.2	0.008
Others	1,360	21.2	1,358	21.2	0.001

Data are presented as percentages unless otherwise noted.

All the covariates listed in the table were used to calculate the propensity score for IPTW.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Table 20. Baseline characteristics of NOAC and warfarin users in the propensity score-matched population for the analysis of glycemic emergency

	NOAC (N = 7426)		Warfarin (N = 7426)		SMD [†]
	N	%	N	%	
Age (years) [‡]	72.7 ± 10.0		72.7 ± 10.8		0.005
Sex					
Male	4,091	55.1	4,102	55.2	0.003
Female	3,335	44.9	3,324	44.8	0.003
Income level (NTD)					
Financially dependent	2,083	28.1	2,099	28.3	0.005
15840–29999	3,463	46.6	3,470	46.7	0.002
30000–44999	1,091	14.7	1,076	14.5	0.006
≥ 45000	789	10.6	781	10.5	0.004
Charlson comorbidity index ^{‡§}	2.8 ± 1.9		2.8 ± 1.9		0.019
CHA2DS2-VASc score ^{‡#}	4.2 ± 1.6		4.2 ± 1.8		0.020
Comorbidities					
Hypertension	5,730	77.2	5,700	76.8	0.010
Coronary artery disease	2,659	35.8	2,609	35.1	0.000
Congestive heart failure	2,108	28.4	2,056	27.7	0.016
COPD	1,052	14.2	1,044	14.1	0.003
Chronic kidney disease	1,135	15.3	1,112	15.0	0.009
Liver cirrhosis	453	6.1	479	6.5	0.014
Hyperlipidemia	2,724	36.7	2,689	36.2	0.010
Stroke	2,199	29.6	2,133	28.7	0.000
Rheumatoid arthritis	59	0.8	59	0.8	0.000
Gout	812	10.9	812	10.9	0.000
Dementia	414	5.6	421	5.7	0.004
Malignancy	578	7.8	588	7.9	0.005
Medication use					
Statins	2,607	35.1	2,567	34.6	0.011
ACEI or ARB	4,683	63.1	4,625	62.3	0.016
β blockers	3,481	46.9	3,499	47.1	0.005
Calcium channel blockers	3,551	47.8	3,534	47.6	0.005

	NOAC (N = 7426)		Warfarin (N = 7426)		SMD [†]
	N	%	N	%	
Diuretics	2,546	34.3	2,499	33.7	0.013
NSAID	2,573	34.6	2,547	34.3	0.007
Corticosteroids	679	9.1	668	9.0	0.005
Antipsychotics	367	4.9	355	4.8	0.008
Proton pump inhibitors	613	8.3	617	8.3	0.002
Baseline diabetes medications					
Metformin	3,465	46.7	3,444	46.4	0.006
Sulfonylurea	2,668	35.9	2,647	35.6	0.006
Meglitinide	513	6.9	537	7.2	0.013
AGI	661	8.9	645	8.7	0.008
TZD	352	4.7	353	4.8	0.001
DPP-4i	1,899	25.6	1,931	26.0	0.010
SGLT-2i	27	0.4	24	0.3	0.007
GLP-1	6	0.1	5	0.1	0.005
Insulin	886	11.9	897	12.1	0.005
Numbers of diabetes medications					
Without medications	2,391	32.2	2,256	30.4	0.039
1 type	1,789	24.1	1,929	26.0	0.044
2 types	1,612	21.7	1,692	22.8	0.026
≥ 3 types	1,634	22.0	1,549	20.9	0.028
Index year					
2012–2013	2,100	28.3	2,100	28.3	0.000
2014–2015	3,389	45.6	3,389	45.6	0.000
2016–2017	1,937	26.1	1,937	26.1	0.000
Hospital level of OAC initiation					
Medical center	2,639	35.5	2,620	35.3	0.005
Regional hospital	3,340	45.0	3,337	44.9	0.001
District hospital or clinic	1,447	19.5	1,469	19.8	0.007
Physician specialty					
Cardiologist	4,864	65.5	4,882	65.7	0.005

	NOAC (N = 7426)		Warfarin (N = 7426)		SMD [†]
	N	%	N	%	
Neurologist	1,005	13.5	972	13.1	0.013
Others	1,557	21.0	1,572	21.2	0.005

Data are presented as percentages unless otherwise noted.

All the covariates listed in the table were used to calculate the propensity score for IPTW.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Table 21. Baseline characteristics of overall NOAC and warfarin users in the propensity score-matched population for the analysis of mortality

	NOAC (N = 7677)		Warfarin (N = 7677)		SMD [†]
	N	%	N	%	
Age (years) [‡]	72.9 ± 10.0		72.8 ± 10.8		0.003
Sex					
Male	4,209	54.8	4,239	55.2	0.008
Female	3,468	45.2	3,438	44.8	0.008
Income level (NTD)					
Financially dependent	2,158	28.1	2,144	27.9	0.004
15840–29999	3,608	47.0	3,587	46.7	0.005
30000–44999	1,098	14.3	1,110	14.5	0.004
≥ 45000	813	10.6	836	10.9	0.010
Charlson comorbidity index ^{‡§}	2.9 ± 1.9		2.8 ± 1.9		0.015
CHA2DS2-VASc score ^{‡#}	4.3 ± 1.6		4.2 ± 1.8		0.011
Comorbidities					
Hypertension	5,918	77.1	5,928	77.2	0.003
Coronary artery disease	2,692	35.1	2,745	35.8	0.000
Congestive heart failure	2,194	28.6	2,165	28.2	0.008
COPD	1,123	14.6	1,084	14.1	0.014
Chronic kidney disease	1,204	15.7	1,157	15.1	0.017
Liver cirrhosis	501	6.5	492	6.4	0.005
Hyperlipidemia	2,784	36.3	2,816	36.7	0.009
Stroke	2,274	29.6	2,231	29.1	0.000
Rheumatoid arthritis	61	0.8	60	0.8	0.001
Gout	836	10.9	832	10.8	0.002
Dementia	449	5.8	439	5.7	0.006
Malignancy	618	8.1	600	7.8	0.009
Medication use					
Statins	2,721	35.4	2,701	35.2	0.005
ACEI or ARB	4,837	63.0	4,782	62.3	0.015
β blockers	3,640	47.4	3,607	47.0	0.009
Calcium channel blockers	3,662	47.7	3,648	47.5	0.004

	NOAC (N = 7677)		Warfarin (N = 7677)		SMD [†]
	N	%	N	%	
Diuretics	2,697	35.1	2,662	34.7	0.010
NSAID	2,616	34.1	2,640	34.4	0.007
Corticosteroids	725	9.4	702	9.1	0.010
Antipsychotics	402	5.2	382	5.0	0.012
Proton pump inhibitors	644	8.4	646	8.4	0.001
Baseline diabetes medications					
Metformin	3,547	46.2	3,582	46.7	0.009
Sulfonylurea	2,761	36.0	2,755	35.9	0.002
Meglitinide	561	7.3	548	7.1	0.007
AGI	690	9.0	702	9.1	0.005
TZD	356	4.6	354	4.6	0.001
DPP-4i	2,033	26.5	2,013	26.2	0.006
SGLT-2i	26	0.3	25	0.3	0.002
GLP-1	6	0.1	5	0.1	0.005
Insulin	1,014	13.2	986	12.8	0.011
Numbers of diabetes medications					
Without medications	2,423	31.6	2,274	29.6	0.042
1 type	1,841	24.0	1,992	25.9	0.045
2 types	1,703	22.2	1,797	23.4	0.029
≥ 3 types	1,710	22.3	1,614	21.0	0.030
Index year					
2012–2013	2,166	28.2	2,166	28.2	0.000
2014–2015	3,503	45.6	3,503	45.6	0.000
2016–2017	2,008	26.2	2,008	26.2	0.000
Hospital level of OAC initiation					
Medical center	2,711	35.3	2,722	35.5	0.003
Regional hospital	3,493	45.5	3,459	45.1	0.009
District hospital or clinic	1,473	19.2	1,496	19.5	0.008
Physician specialty					
Cardiologist	5,038	65.6	5,044	65.7	0.002

	NOAC (N = 7677)		Warfarin (N = 7677)		SMD [†]
	N	%	N	%	
Neurologist	1,026	13.4	985	12.8	0.016
Others	1,613	21.0	1,648	21.5	0.011

Data are presented as percentages unless otherwise noted.

All the covariates listed in the table were used to calculate the propensity score for IPTW.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

4.1.7 Results of sensitivity analyses using multivariable regression models to adjust covariates without propensity score methods

In the analyses using multivariable regression models to adjust covariates without propensity score methods, we also observed similar trends that NOACs were associated with lower risks of macrovascular complications (HR=0.85, 95% CI: 0.78-0.92, $p<0.001$), microvascular complications (HR=0.80, 95% CI: 0.73-0.87, $p<0.001$), glycemic emergencies (HR=0.91, 95% CI: 0.82-1.01, $p=0.086$), and mortality (HR=0.80, 95% CI: 0.76-0.84, $p<0.001$) compared to warfarin (Table 22).

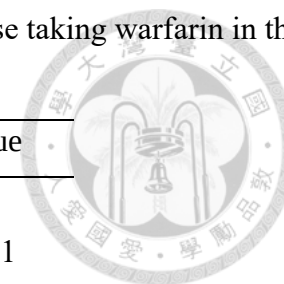


Table 22. Risk of diabetes complications and mortality in atrial fibrillation patients with diabetes taking NOACs and those taking warfarin in the analyses using multivariable regression models to adjust covariates without propensity score methods

Outcome	N*	Event no.	PY	IR [†]	HR [‡] (95% CI)	p-value
Macrovascular complication						
NOAC	6,916	1,854	14,790	125.4	0.85 (0.78-0.92)	<0.001
Warfarin	3,335	1,210	8,884	136.2	1.00 (ref.)	
Microvascular complication						
NOAC	16,783	1,450	41,038	35.3	0.80 (0.73-0.87)	<0.001
Warfarin	8,586	1,260	27,764	45.4	1.00 (ref.)	
Glycemic emergency						
NOAC	19,293	1,148	48,715	23.6	0.91 (0.82-1.01)	0.086
Warfarin	10,006	828	34,144	24.3	1.00 (ref.)	
Mortality						
NOAC	19,847	4,730	51,475	91.9	0.80 (0.76-0.84)	<0.001
Warfarin	10,372	3,730	36,592	101.9	1.00 (ref.)	

In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.

*The original population without applying any propensity score methods

[†]Incidence rate, per 1000 person-years.

[‡]The HR is calculated by a Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; N, number; NOAC, non-vitamin K antagonist oral anticoagulant; PY, person-year; ref., reference.

4.1.8 E-values and negative control outcomes

In the as-started analysis utilizing stabilized IPTW, the E-values for macrovascular complications, microvascular complications, glycemic emergencies, and mortality were respectively calculated as 1.51, 1.63, 1.43, and 1.66. Figure 14 illustrates the joint relationship between the two sensitivity parameters (exposure-confounder relationship and confounder-outcome relationship) that could potentially negate the estimated effect of NOAC versus warfarin on lowering complication risks (panel A for the analysis of macrovascular complications, panel B for microvascular complications, panel C for glycemic emergencies, and panel D for mortality).

The E-values derived from the on-treatment analysis were generally higher, with values of 1.53, 1.94, 1.77, and 2.1 corresponding to each of the four primary outcomes. Figure 15 illustrates the joint relationship between the two sensitivity parameters that could potentially negate the estimated effect (panel A for macrovascular complications, panel B for microvascular complications, panel C for glycemic emergencies, and panel D for mortality).

In the analyses of negative control outcomes (e.g., cancer, chronic obstructive pulmonary disease, and suicide death), as we expected, none of the outcomes showed a significant association with NOAC treatment (Table 23).

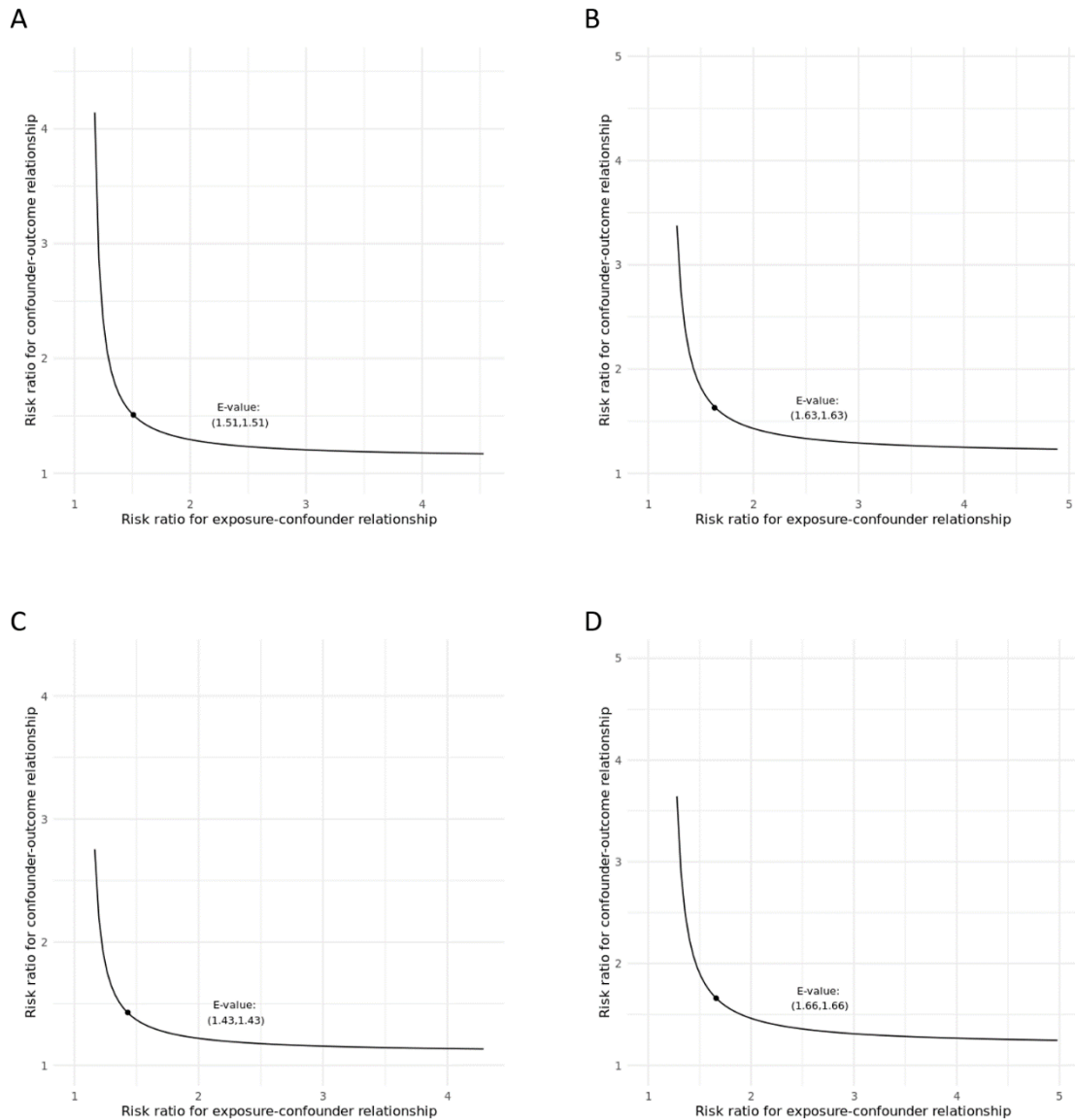


Figure 14. The joint relationship between the two sensitivity parameters (exposure-confounder relationship and confounder-outcome relationship) that could potentially negate the estimated effect of NOAC versus warfarin on lowering complication risks in the as-started analysis (the main analysis).

Panel A for the analysis of macrovascular complications; panel B for microvascular complications; panel C for glycemic emergencies; and panel D for mortality.

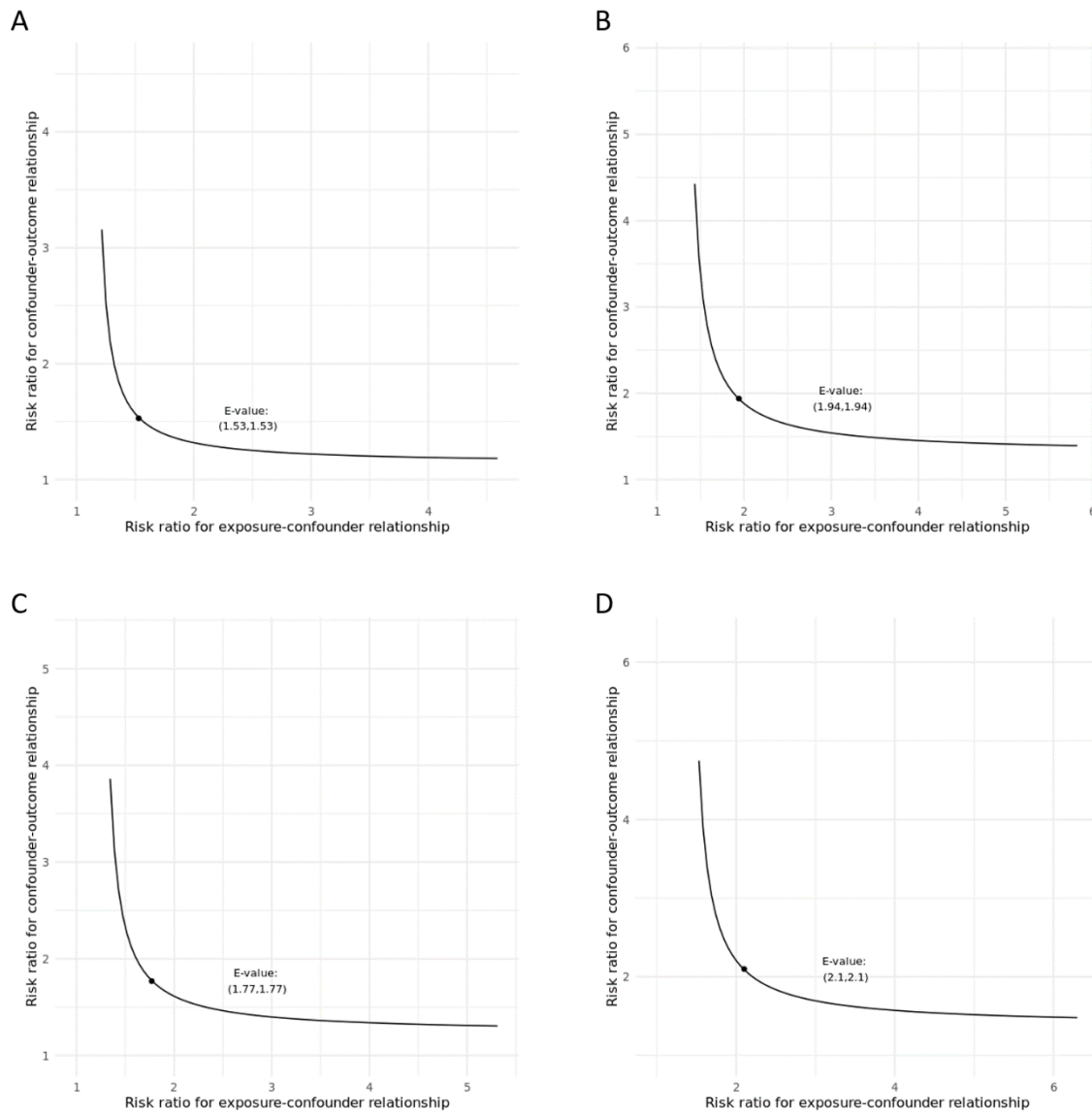


Figure 15. The joint relationship between the two sensitivity parameters (exposure-confounder relationship and confounder-outcome relationship) that could potentially negate the estimated effect of NOAC versus warfarin on lowering complication risks in the on-treatment analysis (sensitivity analysis).

Panel A for the analysis of macrovascular complications; panel B for microvascular complications; panel C for glycemic emergencies; and panel D for mortality.

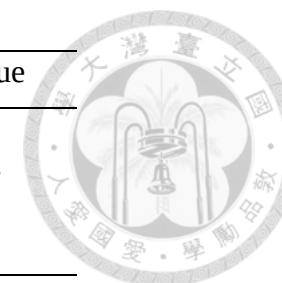


Table 23. Analyses for negative control outcomes

Outcome	N*	Event no.	PY	IR [†]	HR [‡] (95% CI)	p-value
Cancer						
NOAC	18,014	1,563	51,101	30.6	0.96 (0.88-1.04)	0.297
Warfarin	9,396	843	26,580	31.7	1.00 (ref.)	
Chronic obstructive pulmonary disease						
NOAC	15,856	3,692	40,342	91.5	0.98 (0.92-1.04)	0.431
Warfarin	8,183	1,936	20,633	93.8	1.00 (ref.)	
Suicide death						
NOAC	19,909	48	58,328	0.8	1.35 (0.76-2.41)	0.302
Warfarin	10,300	17	30,023	0.6	1.00 (ref.)	

In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.

*A pseudo-population constructed by stabilized IPTW for analyses

[†]Incidence rate, per 1000 person-years.

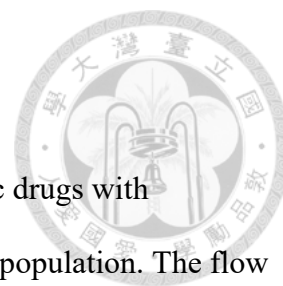
[‡]The HR is calculated by a Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; IPTW, inverse probability of treatment weighting; N, number; NOAC, non-vitamin K antagonist oral anticoagulant; PY, person-year; ref., reference.

4.2 Results of Study 2

4.2.1 Patient characteristics

A total of 56,774 patients with AF and DM taking antidiabetic drugs with concurrent use of NOACs or warfarin were included in the study population. The flow diagram of patient selection is shown in Figure 16. Patients' characteristics at baseline (according to their first observed follow-up periods) are shown in Table 24. The mean age was 73.5 years, and females accounted for 44.6% of the study population. We identified 800,691 and 286,384 periods attributable to concurrent use of antidiabetic agents with NOACs and warfarin, respectively. After stabilized IPTW, all characteristics were appropriately balanced between the NOAC and warfarin groups, with a standardized mean difference of <0.1 for all variables (Table 25).



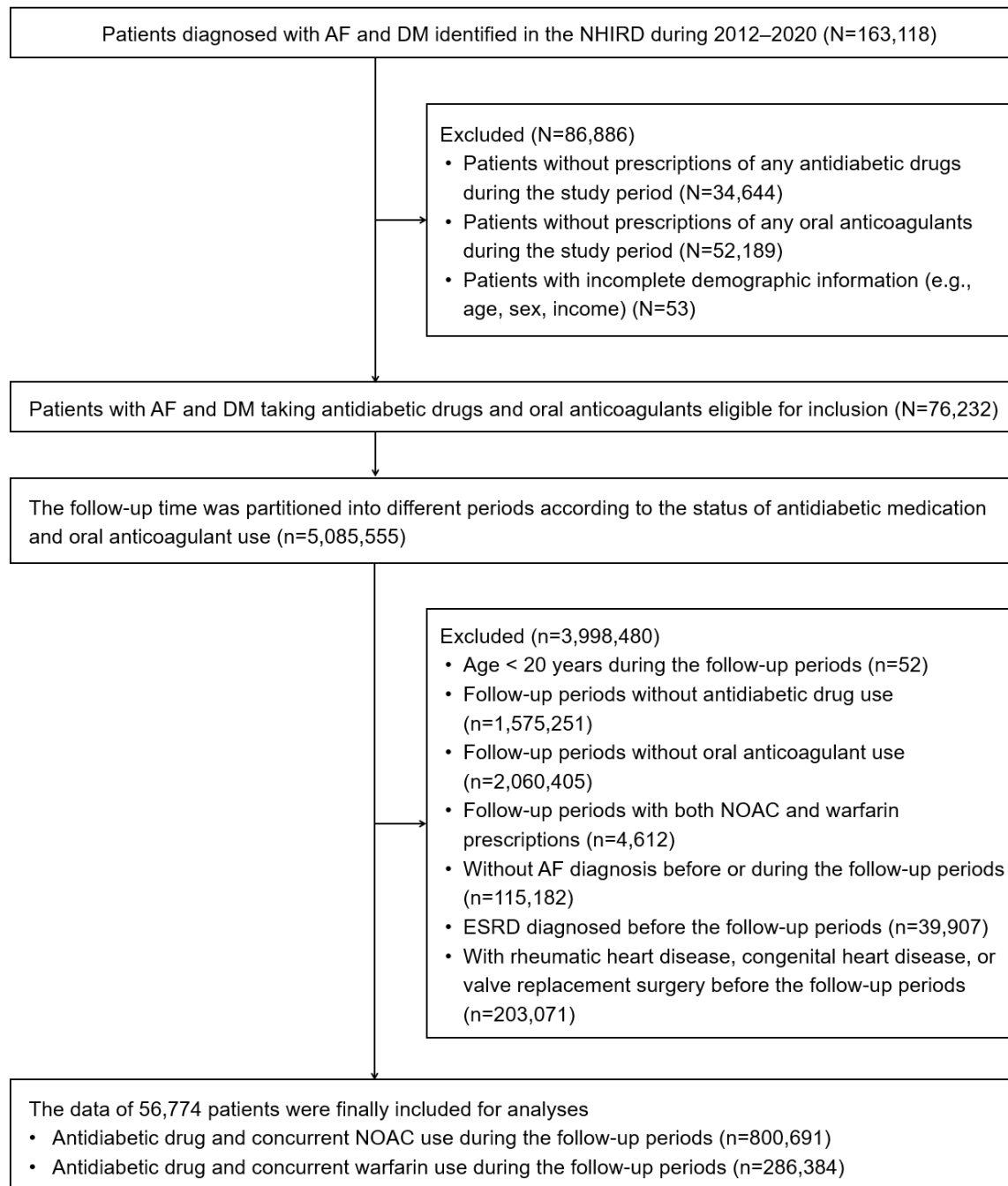


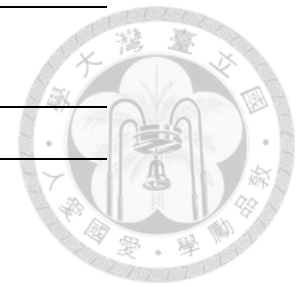
Figure 16. Study flow diagram of patient selection in Study 2.

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; ESRD, end-stage renal disease; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulant

Table 24. Characteristics and comorbidities at baseline among patients with atrial fibrillation and diabetes taking oral anticoagulants and antidiabetic drugs

	Overall population (N = 56,774)	
	N	%
Age (years) [†]	73.5 ± 10.2	
Sex		
Male	31,482	55.5
Female	25,292	44.6
Income level (NTD)		
Financially dependent	15,912	28.0
15,840–29,999	26,222	46.2
30,000–44,999	7,519	13.2
≥45,000	7,121	12.5
Charlson Comorbidity Index ^{†,‡}	3.1±2.1	
CHA2DS2-VASc score ^{†,§}	4.2±1.7	
Comorbidities		
Hypertension	43,546	76.7
Coronary artery disease	19,490	34.3
Congestive heart failure	15,381	27.1
COPD	7,738	13.6
Asthma	4,025	7.1
Chronic kidney disease	8,438	14.9
Cirrhosis	2,123	3.7
Hyperlipidemia	22,329	39.3
Stroke	17,381	30.6
Rheumatoid arthritis	441	0.8
Dementia	3,755	6.6
Depression	2,036	3.6
Malignancy	4,749	8.4
Baseline medication use		
Statins	25,558	45.0
ACEI/ARB	38,277	67.4
β-blocker	29,583	52.1
CCB	25,738	45.3
Diuretics	20,159	35.5
NSAID	17,024	30.0

	Overall population (N = 56,774)	
	N	%
Corticosteroids	3,694	6.5
Antipsychotics	2,999	5.3
PPI	5,184	9.1
Current diabetes medications		
Metformin	39,033	68.8
Sulfonylurea	21,210	37.4
Meglitinide	4,047	7.1
AGI	5,300	9.3
TZD	2,972	5.2
DPP-4i	20,713	36.5
SGLT-2i	2,538	4.5
GLP-1 RA	183	0.3
Insulin	7,720	13.6
No. of current diabetes medication types		
1	26,407	46.5
2	17,359	30.6
≥3	13,008	22.9
Duration of diabetes		
< 2 years	12,427	21.9
≥ 2 years	44,347	78.1
Duration of AF		
< 2 years	37,691	66.4
≥ 2 years	19,083	33.6
History of serious hypoglycemia	819	1.4
Index year		
2012–2014	15,727	27.7
2015–2017	19,547	34.4
2018–2020	21,500	37.9
Medical utilization in the previous year		
No. of outpatient visits [†]	29.8 ± 19.0	
No. of ER visits [†]	1.3 ± 2.0	
No. of hospitalizations [†]	1.0 ± 1.4	



Data are presented as percentages unless otherwise noted.

† Presented as mean $\pm$ standard deviation.

‡ Calculated without including scores for age.

§ Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category (CHA₂DS₂-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; AF, atrial fibrillation; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; ER, emergency room; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PPI, proton pump inhibitors; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

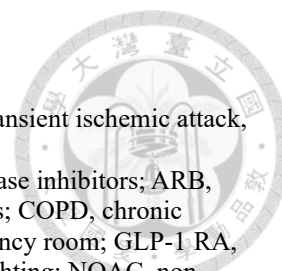


Table 25. Baseline characteristics according to each period with concurrent use of specific oral anticoagulants and antidiabetic drugs that were used as an analytic unit*

	Before IPTW			After IPTW [†]		
	NOAC (N=800,691)	Warfarin (N=286,384)	SMD [‡]	NOAC (N=801,404)	Warfarin (N=279,368)	SMD [‡]
Age (years) [§]	74.9±9.5	72.3±10.5	0.260	74.3±9.7	74.0±10.3	0.030
Sex						
Male	56.4	56.8	0.008	56.7	56.9	0.004
Female	43.6	43.2	0.008	43.3	43.1	0.004
Income level (NTD)						
Financially						
dependent	28.7	29.2	0.011	28.9	29.2	0.007
15,840–29,999	45.2	43.5	0.034	44.6	44.5	0.002
30,000–44,999	12.3	14.5	0.065	13.0	13.0	0.000
≥45,000	13.7	12.8	0.027	13.5	13.3	0.006
Charlson						
Comorbidity Index ^{§¶}	3.3±2.1	3.3±2.1	0.000	3.3±2.1	3.3±2.1	0.000
CHA2DS2-VASc						
score ^{§#}	4.3±1.6	4.2±1.7	0.061	4.3±1.6	4.3±1.7	0.000
Comorbidities						
Hypertension	73.6	72.5	0.025	73.4	73.5	0.002
Coronary artery						
disease	33.5	33.2	0.006	33.4	33.2	0.004
Congestive heart						
failure	27.9	30.0	0.046	28.3	28.3	0.000
COPD	13.7	13.0	0.021	13.5	13.5	0.000
Asthma	6.6	6.4	0.008	6.6	6.6	0.000
Chronic kidney						
disease	17.4	18.4	0.026	17.7	18.1	0.010
Cirrhosis	2.4	4.5	0.115	3.0	3.1	0.006
Hyperlipidemia	38.6	36.2	0.050	38.1	38.5	0.008
Stroke	31.5	32.0	0.011	31.7	31.0	0.015
Rheumatoid						
arthritis	0.7	0.6	0.012	0.7	0.6	0.012
Dementia	8.1	5.9	0.086	7.5	7.2	0.011
Depression	3.8	3.6	0.011	3.8	3.8	0.000
Malignancy	9.1	7.7	0.050	8.7	8.5	0.007
Baseline						
medications						
Statins	54.5	47.7	0.136	52.7	52.3	0.008

	Before IPTW			After IPTW [†]		
	NOAC (N=800,691)	Warfarin (N=286,384)	SMD [‡]	NOAC (N=801,404)	Warfarin (N=279,368)	SMD [‡]
ACEI/ARB	70.5	69.7	0.017	70.3	70.3	0.000
β-blocker	61.5	58.9	0.053	60.8	60.5	0.006
CCB	43.8	47.5	0.074	44.8	44.6	0.004
Diuretics	41.0	48.3	0.147	42.8	42.9	0.002
NSAID	27.6	26.1	0.034	27.2	27.2	0.000
Corticosteroids	6.4	5.9	0.021	6.2	6.2	0.000
Antipsychotics	7.2	6.0	0.048	6.9	6.6	0.012
PPI	11.3	9.5	0.059	10.9	11.0	0.003
Current diabetes medications						
Metformin	69.4	61.7	0.163	67.1	66.4	0.015
Sulfonylurea	37.1	44.9	0.159	39.2	39.6	0.008
Meglitinide	7.3	9.9	0.093	8.1	8.2	0.004
AGI	10.5	12.7	0.069	11.0	11.3	0.010
TZD	6.1	5.7	0.017	6.1	6.0	0.004
DPP-4i	46.7	38.2	0.173	44.6	44.7	0.002
SGLT-2i	8.7	2.2	0.289	7.0	6.4	0.024
GLP-1 RA	0.9	0.4	0.062	0.8	0.7	0.012
Insulin	16.0	17.6	0.043	16.6	16.8	0.005
No. of current diabetes medication types						
1	36.5	40.5	0.082	37.4	37.6	0.004
2	33.3	33.1	0.004	33.3	33.3	0.000
≥3	30.2	26.5	0.082	29.3	29.1	0.004
Duration of diabetes				6.1±2.8	6.0±2.9	0.035
< 2 years	8.9	13.5	0.146	10.3	8.8	0.051
≥ 2 years	91.1	86.5	0.146	89.7	91.2	0.051
Duration of AF						
< 2 years	34.3	34.7	0.008	34.8	32.3	0.053
≥ 2 years	65.7	65.3	0.008	65.2	67.7	0.053
History of serious hypoglycemia	1.6	1.9	0.023	1.7	1.7	0.000
Index year						
2012–2014	7.1	44.5	0.945	17.0	17.4	0.011
2015–2017	33.1	36.0	0.061	33.8	34.8	0.021
2018–2020	59.9	19.5	0.907	49.2	47.8	0.028

	Before IPTW			After IPTW [†]		
	NOAC (N=800,691)	Warfarin (N=286,384)	SMD [‡]	NOAC (N=801,404)	Warfarin (N=279,368)	SMD [‡]
Medical utilization in the previous year						
No. of outpatient visits [§]	32.0±19.0	32.5±19.2	0.026	32.1±19.2	32.1±18.6	0.000
No. of ER visits [§]	1.2±2.0	1.2±2.1	0.000	1.2±2.0	1.1±2.1	0.049
No. of hospitalizations [§]	0.8±1.4	0.8±1.3	0.000	0.8±1.3	0.8±1.3	0.000

Data are presented as percentages unless otherwise noted.

* Each period with concurrent use of the same combination of oral anticoagulants and antidiabetic drugs in each patient was used as the unit of analysis.

[†] All covariates listed in the table were used to calculate the propensity score for IPTW.

[‡] A standardized mean difference of <0.1 indicates a negligible difference.

[§] Presented as mean±standard deviation.

[¶] Calculated without including scores for age.

[#] Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; ER, emergency room; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PPI, proton pump inhibitors; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

4.2.2 Distribution of propensity scores and the weights calculated by stabilized IPTW

After applying stabilized IPTW with weight truncation, the distribution of propensity scores demonstrated good overlap between the NOAC and warfarin groups. The distributions of these scores, both before and after the application of stabilized IPTW, are presented in Figure 17.

Before weight truncation, the calculated weights in the NOAC group had a mean of 1.00, a median of 0.85, an IQR of 0.18, a maximum of 12.5, and a minimum of 0.74. In the warfarin group, the corresponding figures were a mean of 0.99, a median of 0.61, an IQR of 0.80, a maximum of 20.51, and a minimum of 0.28. Following weight truncation, the maximum weight was reduced to 5, while the other measures (such as mean, median, IQR, and minimum) remained unchanged. Figures 18 and 19 present the distributions of weights obtained by stabilized IPTW without and with weight truncation, respectively: Figure 18 illustrates the distribution without weight truncation, and Figure 19 shows the distribution with weight truncation.

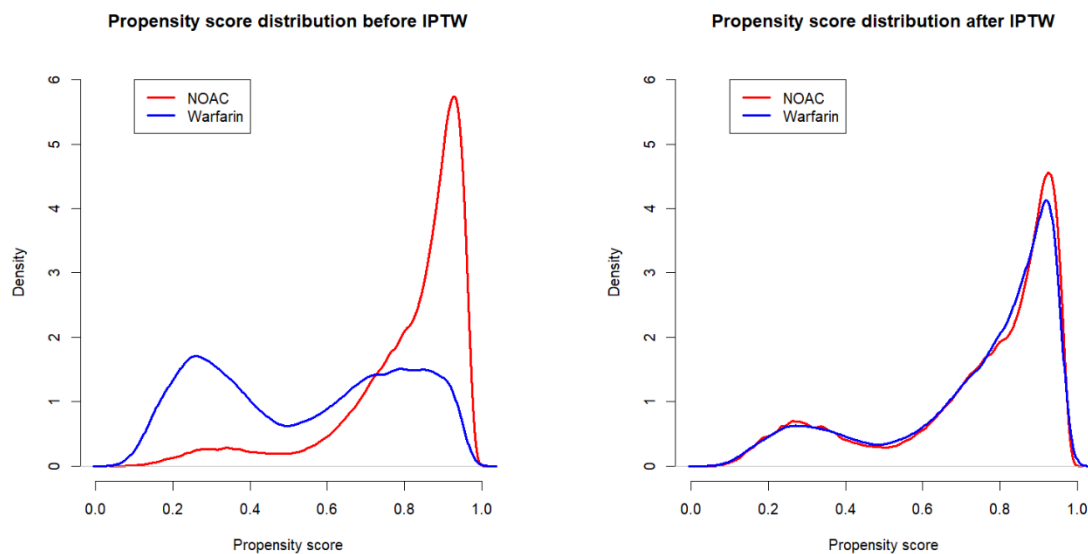


Figure 17. Distribution of propensity scores in the NOAC and warfarin groups before and after applying stabilized IPTW for the analysis of serious hypoglycemia risk in Study 2

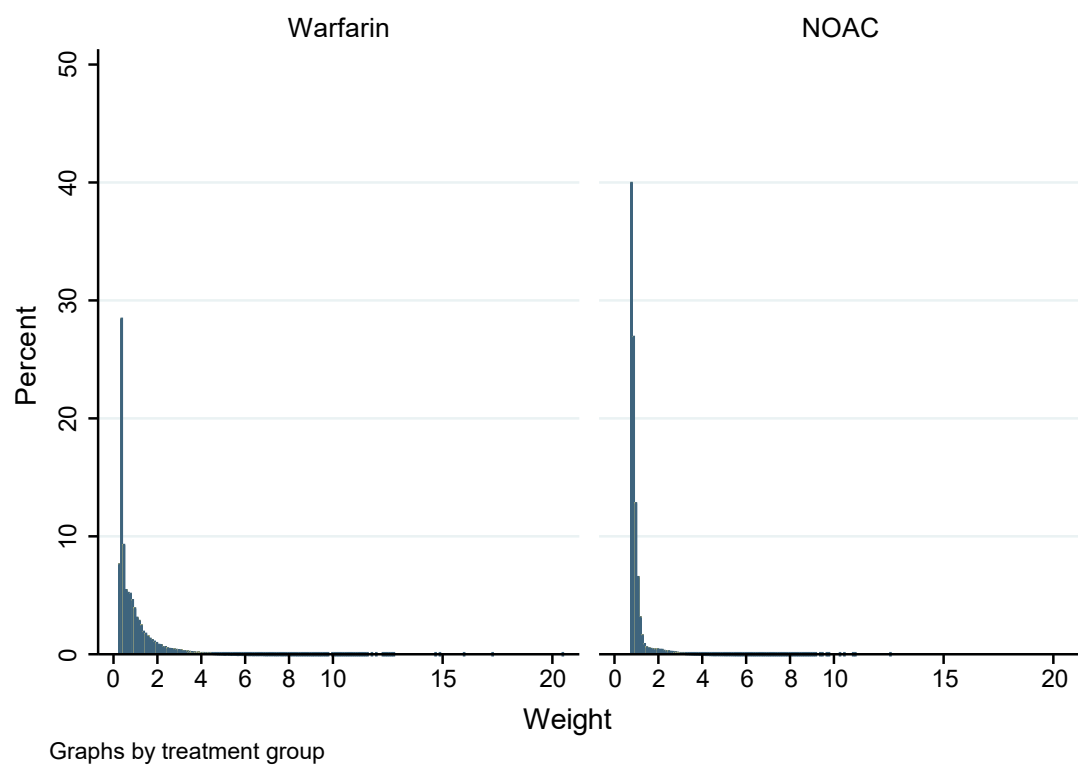


Figure 18. Distribution of weights obtained by stabilized IPTW without weight truncation in the NOAC and warfarin groups in Study 2

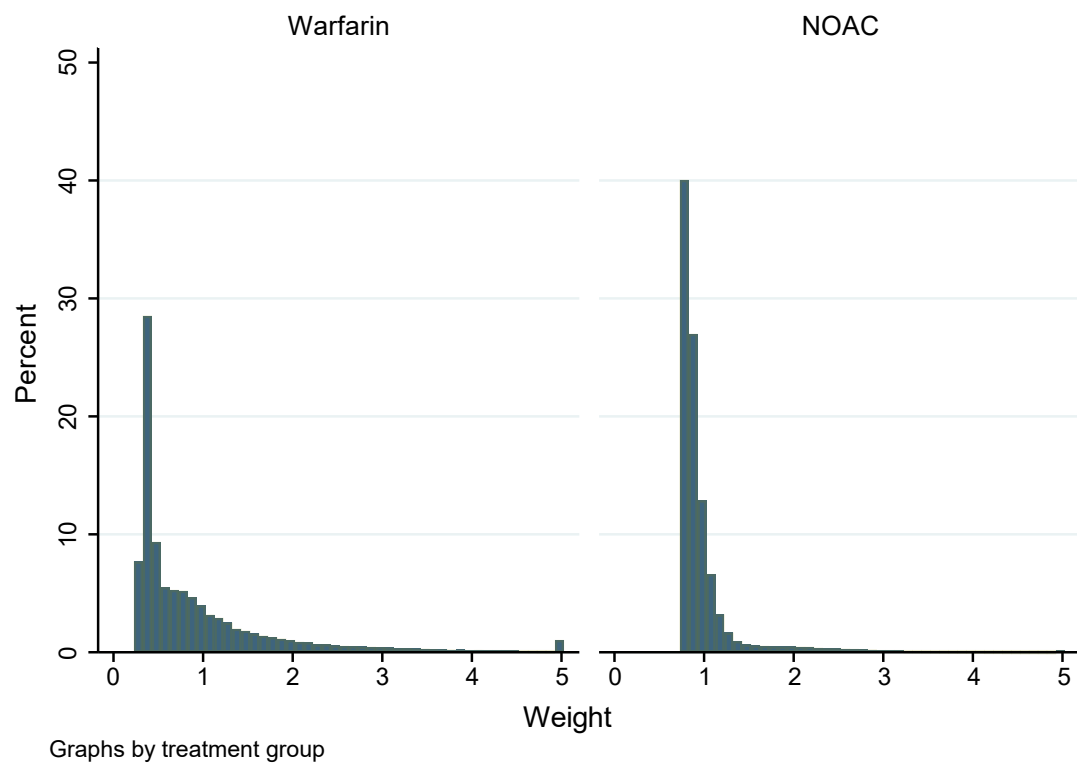


Figure 19. Distribution of weights obtained by stabilized IPTW with weight truncation in the NOAC and warfarin groups in Study 2

4.2.3 Risk of serious hypoglycemia in patients taking antidiabetic drugs with concurrent use of NOACs versus warfarin

Overall, concurrent use of NOACs with antidiabetic drugs had a significantly lower risk of serious hypoglycemia than that of warfarin with antidiabetic drugs (IRR=0.73, 95% CI: 0.63–0.85, $p<0.001$) (Figure 20). The detailed results (e.g., the follow-up time, event numbers, and incidence rates) are provided in Table 26.

Stratified analyses demonstrated that for both male and female subgroups, the concurrent use of NOACs correlated with a reduced risk of severe hypoglycemia in comparison to warfarin use. This significantly decreased risk associated with NOAC use was evident particularly in older patients aged 65 years and above, and in those prescribed two or more antidiabetic medications (Figure 20 and Table 26).

In the subgroup analyses for each specific NOAC, a significantly reduced risk of severe hypoglycemia was observed in users of dabigatran (IRR=0.76, 95% CI: 0.63–0.91, $p=0.002$), rivaroxaban (IRR=0.72, 95% CI: 0.61–0.86, $p<0.001$), and apixaban (IRR=0.71, 95% CI: 0.57–0.89, $p=0.003$). While the results for edoxaban did not achieve statistical significance, a comparable trend in lowering hypoglycemia risk was noted among its users (IRR=0.77, 95% CI: 0.57–1.03, $p=0.078$) (Figure 21 and Table 27).

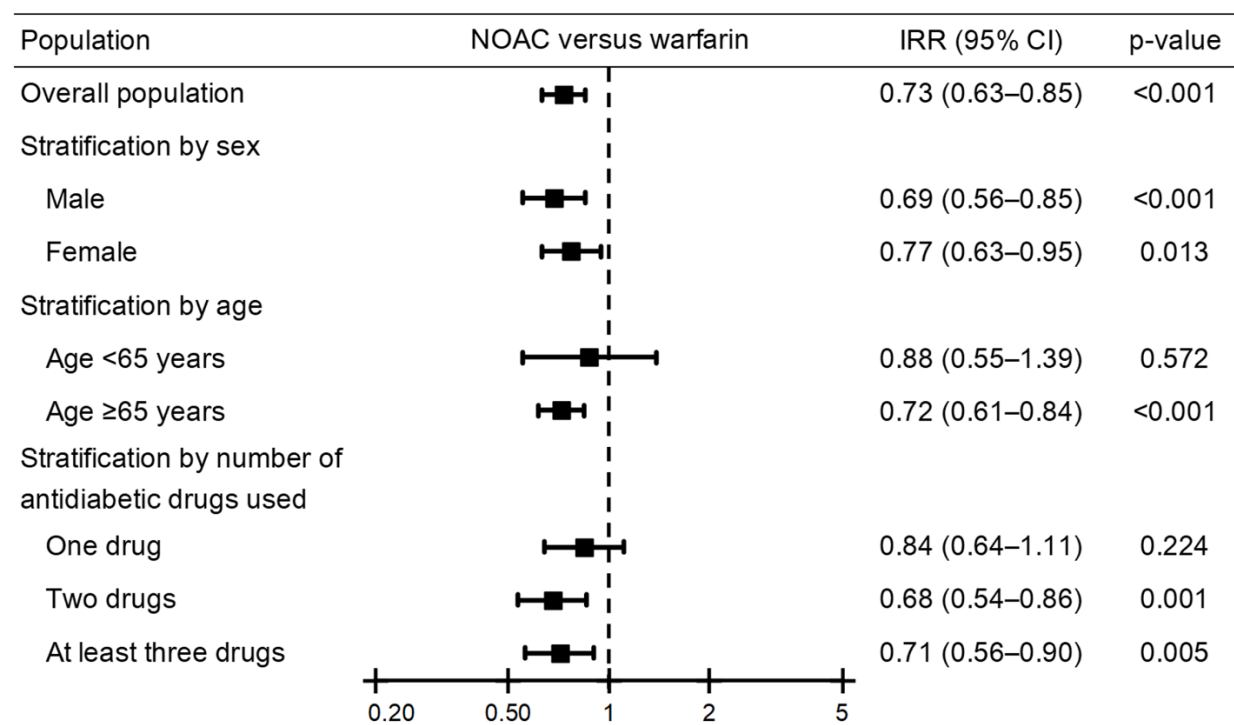


Figure 20. Risk of serious hypoglycemia in patients taking antidiabetic drugs with concurrent use of NOACs versus warfarin in the overall and stratified analyses

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; NOAC, non-vitamin K antagonist oral anticoagulant

Table 26. The event number, incidence rate and incidence rate ratio of serious hypoglycemia in patients taking antidiabetic drugs with concurrent use of NOAC versus warfarin

Population		Person-day	Event number	Incidence rate*	IRR [†] (95% CI)	p-value
Overall population	NOAC	26,807,039	1,276	4.8	0.73 (0.63–0.85)	<0.001
	Warfarin	8,707,347	565	6.5	1.00 (Reference)	
Stratification by sex	Male					
	NOAC	15,343,655	550	3.6	0.69 (0.56–0.85)	<0.001
	Warfarin	5,019,131	264	5.3	1.00 (Reference)	
	Female					
	NOAC	11,462,888	732	6.4	0.77 (0.63–0.95)	0.013
	Warfarin	3,676,946	300	8.2	1.00 (Reference)	
Stratification by age	Age <65 years					
	NOAC	3,404,949	72	2.1	0.88 (0.55–1.39)	0.572
	Warfarin	2,164,743	56	2.6	1.00 (Reference)	
	Age ≥65 years					
	NOAC	23,332,873	1,233	5.3	0.72 (0.61–0.84)	<0.001
	Warfarin	6,595,230	480	7.3	1.00 (Reference)	
Stratification by number of antidiabetic drugs used	One drug					
	NOAC	9,977,459	292	2.9	0.84 (0.64–1.11)	0.224
	Warfarin	3,609,741	126	3.5	1.00 (Reference)	
	Two drugs					
	NOAC	9,062,289	439	4.8	0.68 (0.54–0.86)	0.001
	Warfarin	2,884,916	204	7.1	1.00 (Reference)	

At least three drugs					
NOAC	7,749,286	557	7.2	0.71 (0.56–0.90)	0.005
Warfarin	2,220,737	224	10.1	1.00 (Reference)	

* Per 100,000 person-days

† The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NOAC, non-vitamin K antagonist oral anticoagulant

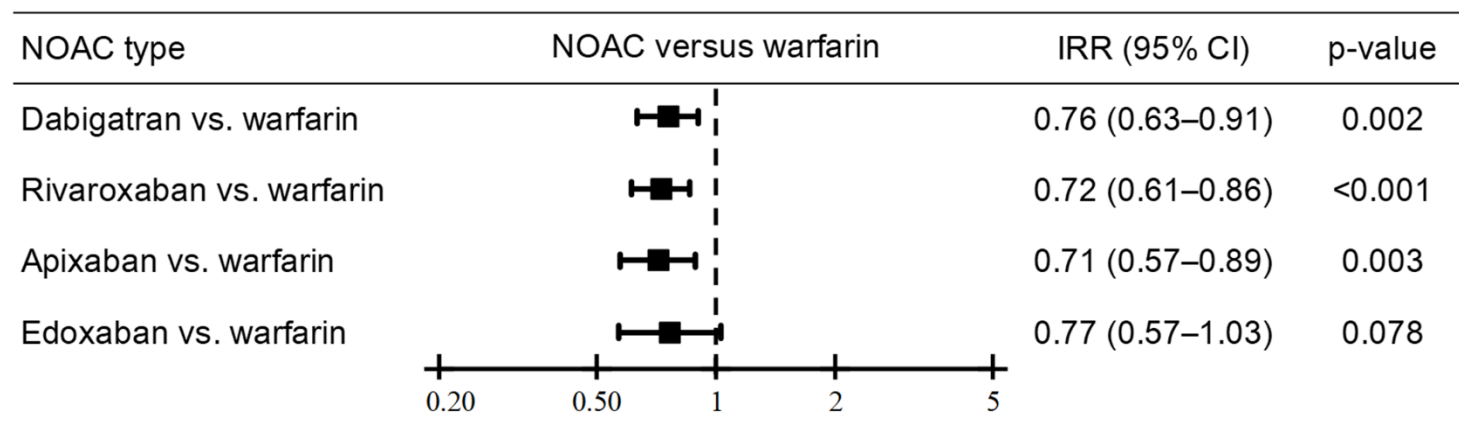


Figure 21. Risk of serious hypoglycemia in patients taking antidiabetic drugs with concurrent use of each NOAC versus warfarin

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; NOAC, non-vitamin K antagonist oral anticoagulant



Table 27. The event number, incidence rate and incidence rate ratio of serious hypoglycemia in patients taking antidiabetic medications with concurrent use of each NOAC versus warfarin

Medication	Person-day	Event number	Incidence rate*	IRR [†] (95% CI)	<i>p</i> -value
Dabigatran	7,654,348	356	4.7	0.76 (0.63–0.91)	0.002
Warfarin	8,785,662	547	6.2	1.00 (Reference)	
Rivaroxaban	10,461,826	502	4.8	0.72 (0.61–0.86)	<0.001
Warfarin	7,862,802	520	6.6	1.00 (Reference)	
Apixaban	4,390,716	226	5.1	0.71 (0.57–0.89)	0.003
Warfarin	6,334,269	451	7.1	1.00 (Reference)	
Edoxaban	3,298,918	167	5.1	0.77 (0.57–1.03)	0.078
Warfarin	3,713,313	243	6.5	1.00 (Reference)	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NOAC, non-vitamin K antagonist oral anticoagulant

4.2.4 Risk of serious hypoglycemia according to each antidiabetic drug with concurrent use of NOACs versus warfarin

In the subgroup analyses according to different concurrent antidiabetic drugs, the significantly lower risk of serious hypoglycemia associated with concurrent NOAC use was found in patients taking metformin (IRR=0.73, 95% CI: 0.59–0.89, $p=0.002$), DPP-4i (IRR=0.73, 95% CI: 0.59–0.92, $p=0.007$), or sulfonylurea (IRR=0.68, 95% CI: 0.56–0.81, $p<0.001$). The difference in serious hypoglycemia risks between NOAC and warfarin was not statistically significant in patients taking other antidiabetic drugs (Figure 22 and Table 28).

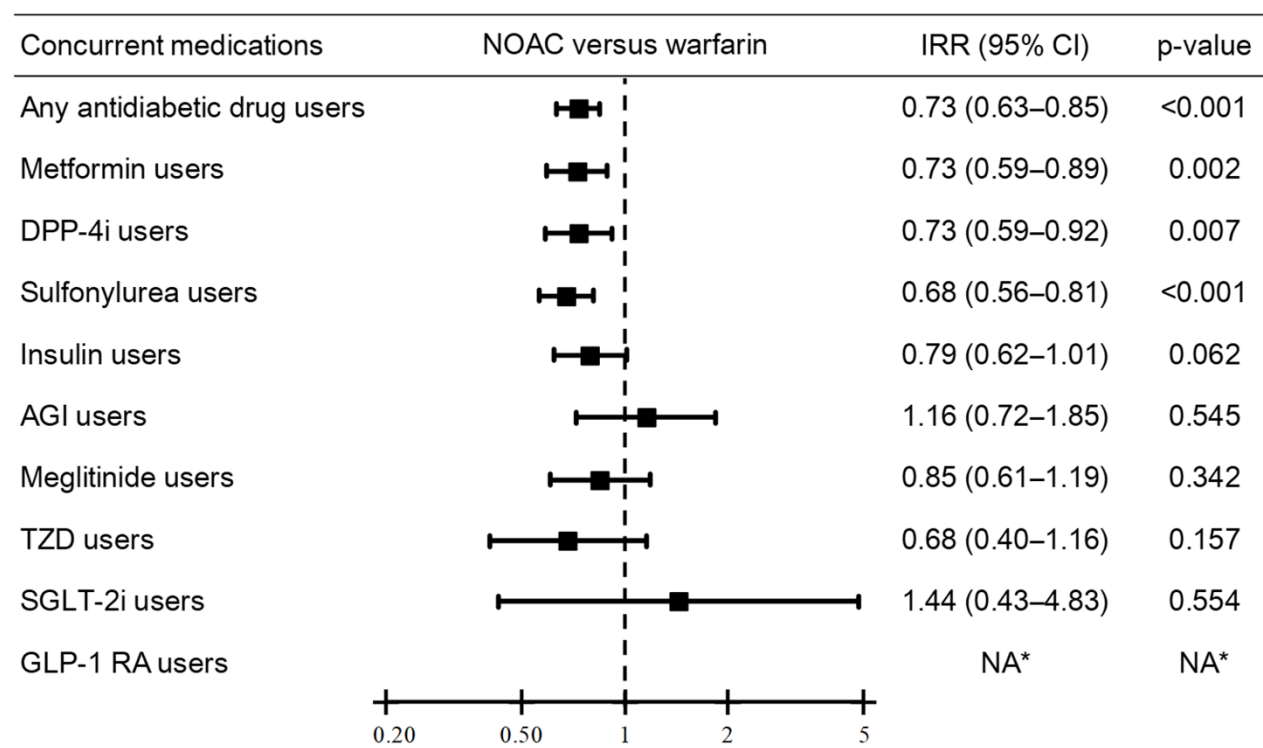


Figure 22. Risk of serious hypoglycemia in patients taking various antidiabetic drugs with concurrent use of NOACs versus warfarin

*Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione

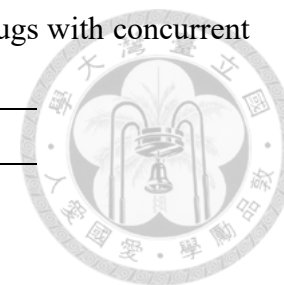


Table 28. The event number, incidence rate and incidence rate ratio of serious hypoglycemia according to antidiabetic drugs with concurrent use of NOAC versus warfarin

Concurrent medications	Person-day	Event number	Incidence rate [*]	IRR [†] (95% CI)	<i>p</i> -value
Any antidiabetic drugs					
NOAC	26,807,039	1,276	4.8	0.73 (0.63–0.85)	<0.001
Warfarin	8,707,347	565	6.5	1.00 (Reference)	
Metformin					
NOAC	19,352,161	748	3.9	0.73 (0.59–0.89)	0.002
Warfarin	5,578,463	295	5.3	1.00 (Reference)	
DPP-4i					
NOAC	12,706,701	614	4.8	0.73 (0.59–0.92)	0.007
Warfarin	3,388,180	224	6.6	1.00 (Reference)	
Sulfonylurea					
NOAC	9,796,663	724	7.4	0.68 (0.56–0.81)	<0.001
Warfarin	3,890,754	420	10.8	1.00 (Reference)	
Insulin					
NOAC	3,267,086	386	11.8	0.79 (0.62–1.01)	0.062
Warfarin	1,202,730	179	14.9	1.00 (Reference)	
AGI					
NOAC	2,612,129	152	5.8	1.16 (0.72–1.85)	0.545
Warfarin	1,022,866	54	5.2	1.00 (Reference)	
Meglitinide					
NOAC	1,683,623	175	10.4	0.85 (0.61–1.19)	0.342

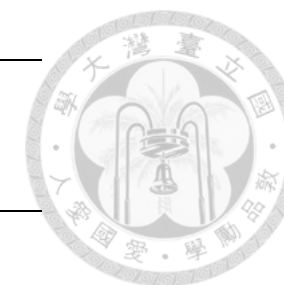
Warfarin	743,696	97	13.1	1.00 (Reference)	
TZD					
NOAC	1,551,623	87	5.6	0.68 (0.40–1.16)	0.157
Warfarin	459,988	38	8.2	1.00 (Reference)	
SGLT-2i					
NOAC	2,493,693	64	2.5	1.44 (0.43–4.83)	0.554
Warfarin	209,069	4	1.8	1.00 (Reference)	
GLP-1 RA					
NOAC	199,827	0	0.0	NA [‡]	NA [‡]
Warfarin	25,391	4	15.0	NA [‡]	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

[‡] Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione



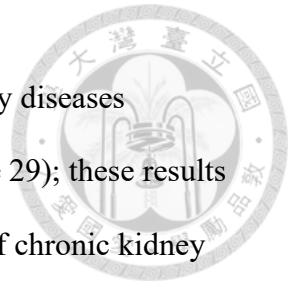
4.2.5 Results of sensitivity analyses

The sensitivity analysis excluding patients with chronic kidney diseases demonstrated findings consistent with the primary analysis (Table 29); these results suggest that our study's findings were not confounded by status of chronic kidney diseases.

The sensitivity analysis applying stabilized IPTW without weight truncation also demonstrated consistent results (Table 30), suggesting that the issues of extreme weights or weight truncation did not influence the study findings.

The two sensitivity analyses, one focusing on severe hypoglycemia cases diagnosed in the emergency department and the other on cases during hospitalization, both yielded results consistent with our primary analyses. These results are presented in Table 31 and Table 32, respectively.

The sensitivity analysis that excluded periods of less than 14 days also demonstrated findings in line with our primary analyses. The sensitivity analysis that excluded periods within 30 days after a change in oral anticoagulant types, for individuals who switched their medication, revealed comparable results. The outcomes of these two analyses are detailed in Table 33 and Table 34, respectively.



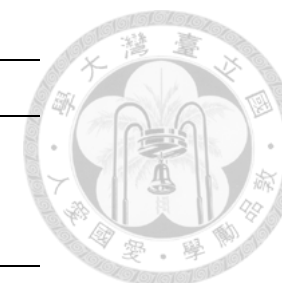


Table 29. Results of the sensitivity analysis excluding patients with chronic kidney diseases

Concurrent medications	Person-day	Event number	Incidence rate [*]	IRR [†] (95% CI)	<i>p</i> -value
Any antidiabetic drugs					
NOAC	22,779,959	926	4.1	0.74 (0.62–0.89)	0.001
Warfarin	7,297,861	393	5.4	1.00 (Reference)	
Metformin					
NOAC	17,291,791	631	3.6	0.73 (0.59–0.91)	0.005
Warfarin	5,165,393	256	5.0	1.00 (Reference)	
DPP-4i					
NOAC	10,452,877	448	4.3	0.81 (0.60–1.10)	0.178
Warfarin	2,643,846	138	5.2	1.00 (Reference)	
Sulfonylurea					
NOAC	8,431,811	544	6.4	0.68 (0.55–0.84)	<0.001
Warfarin	3,413,475	320	9.4	1.00 (Reference)	
Insulin					
NOAC	2,450,051	254	10.4	0.85 (0.61–1.16)	0.300
Warfarin	831,179	101	12.2	1.00 (Reference)	
AGI					
NOAC	2,155,815	107	5.0	1.07 (0.57–2.02)	0.831
Warfarin	827,833	40	4.8	1.00 (Reference)	
Meglitinide					
NOAC	1,238,608	122	9.8	1.08 (0.64–1.82)	0.782
Warfarin	501,228	46	9.2	1.00 (Reference)	

TZD					
NOAC	1,293,060	64	4.9	0.71 (0.39–1.29)	0.258
Warfarin	385,223	27	7.0	1.00 (Reference)	
SGLT-2i					
NOAC	2,182,051	43	2.0	0.98 (0.30–3.25)	0.976
Warfarin	188,921	4	2.0	1.00 (Reference)	
GLP-1 RA					
NOAC	145,426	0	0.0	NA [‡]	NA [‡]
Warfarin	16,047	4	25.2	NA [‡]	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

[‡] Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione



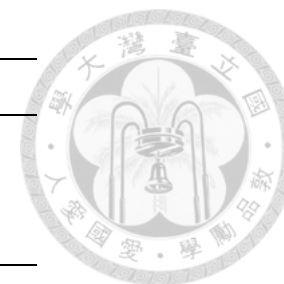


Table 30. Results of the sensitivity analysis applying stabilized IPTW without weight truncation

Concurrent medications	Person-day	Event number	Incidence rate [*]	IRR [†] (95% CI)	<i>p</i> -value
Any antidiabetic drugs					
NOAC	26,843,640	1,282	4.8	0.74 (0.64–0.86)	<0.001
Warfarin	8,813,735	568	6.4	1.00 (Reference)	
Metformin					
NOAC	19,371,744	748	3.9	0.73 (0.60–0.90)	0.003
Warfarin	5,667,403	297	5.2	1.00 (Reference)	
DPP-4i					
NOAC	12,713,081	615	4.8	0.74 (0.59–0.92)	0.008
Warfarin	3,417,810	225	6.6	1.00 (Reference)	
Sulfonylurea					
NOAC	9,817,548	727	7.4	0.68 (0.56–0.82)	<0.001
Warfarin	3,943,697	425	10.8	1.00 (Reference)	
Insulin					
NOAC	3,274,864	386	11.8	0.81 (0.63–1.03)	0.084
Warfarin	1,224,495	179	14.6	1.00 (Reference)	
AGI					
NOAC	2,617,753	152	5.8	1.18 (0.73–1.88)	0.501
Warfarin	1,041,730	54	5.1	1.00 (Reference)	
Meglitinide					
NOAC	1,687,593	175	10.4	0.85 (0.60–1.20)	0.365
Warfarin	760,837	99	13.0	1.00 (Reference)	

TZD					
NOAC	1,561,511	87	5.5	0.71 (0.42–1.21)	0.212
Warfarin	483,067	38	7.8	1.00 (Reference)	
SGLT-2i					
NOAC	2,493,693	64	2.5	1.56 (0.47–5.25)	0.469
Warfarin	226,320	4	1.7	1.00 (Reference)	
GLP-1 RA					
NOAC	199,827	0	0.0	NA [‡]	NA [‡]
Warfarin	36,827	4	10.3	NA [‡]	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

[‡] Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione

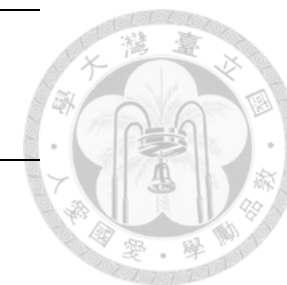
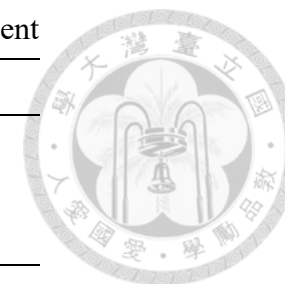


Table 31. Results of the sensitivity analysis focusing on severe hypoglycemia cases diagnosed in the emergency department

Concurrent medications	Person-day	Event number	Incidence rate [*]	IRR [†] (95% CI)	<i>p</i> -value
Any antidiabetic drugs					
NOAC	26,807,039	1,244	4.6	0.72 (0.62–0.84)	<0.001
Warfarin	8,707,347	557	6.4	1.00 (Reference)	
Metformin					
NOAC	19,352,161	731	3.8	0.72 (0.59–0.89)	0.002
Warfarin	5,578,463	290	5.2	1.00 (Reference)	
DPP-4i					
NOAC	12,706,701	599	4.7	0.73 (0.58–0.91)	0.005
Warfarin	3,388,180	221	6.5	1.00 (Reference)	
Sulfonylurea					
NOAC	9,796,663	708	7.2	0.67 (0.55–0.81)	<0.001
Warfarin	3,890,754	416	10.7	1.00 (Reference)	
Insulin					
NOAC	3,267,086	377	11.5	0.79 (0.62–1.01)	0.057
Warfarin	1,202,730	176	14.6	1.00 (Reference)	
AGI					
NOAC	2,612,129	150	5.7	1.14 (0.71–1.82)	0.588
Warfarin	1,022,866	54	5.2	1.00 (Reference)	
Meglitinide					
NOAC	1,683,623	171	10.1	0.83 (0.59–1.16)	0.267
Warfarin	743,696	95	12.8	1.00 (Reference)	



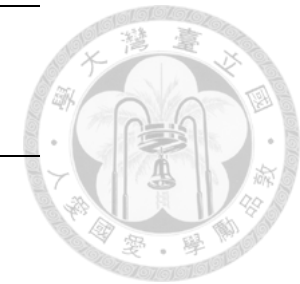
TZD					
NOAC	1,551,623	84	5.4	0.66 (0.39–1.12)	0.126
Warfarin	459,988	38	8.2	1.00 (Reference)	
SGLT-2i					
NOAC	2,493,693	61	2.5	1.40 (0.42–4.69)	0.590
Warfarin	209,069	4	1.8	1.00 (Reference)	
GLP-1 RA					
NOAC	199,827	0	0.0	NA [‡]	NA [‡]
Warfarin	25,391	4	15.0	NA [‡]	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

[‡] Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione



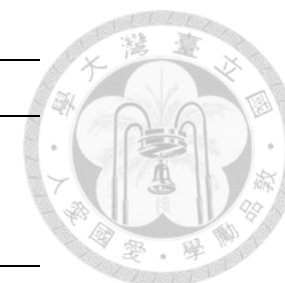


Table 32. Results of the sensitivity analysis focusing on severe hypoglycemia cases diagnosed during hospitalization

Concurrent medications	Person-day	Event number	Incidence rate [*]	IRR [†] (95% CI)	<i>p</i> -value
Any antidiabetic drugs					
NOAC	26,807,039	255	1.0	0.71 (0.51–0.98)	0.038
Warfarin	8,707,347	118	1.4	1.00 (Reference)	
Metformin					
NOAC	19,352,161	154	0.8	0.66 (0.43–1.01)	0.053
Warfarin	5,578,463	67	1.2	1.00 (Reference)	
DPP-4i					
NOAC	12,706,701	121	1.0	0.51 (0.33–0.78)	0.002
Warfarin	3,388,180	64	1.9	1.00 (Reference)	
Sulfonylurea					
NOAC	9,796,663	162	1.7	0.65 (0.44–0.96)	0.032
Warfarin	3,890,754	98	2.5	1.00 (Reference)	
Insulin					
NOAC	3,267,086	56	1.7	0.84 (0.45–1.54)	0.566
Warfarin	1,202,730	25	2.1	1.00 (Reference)	
AGI					
NOAC	2,612,129	25	1.0	1.75 (0.43–7.05)	0.434
Warfarin	1,022,866	6	0.6	1.00 (Reference)	
Meglitinide					
NOAC	1,683,623	34	2.0	0.69 (0.32–1.47)	0.336
Warfarin	743,696	22	3.0	1.00 (Reference)	

TZD					
NOAC	1,551,623	19	1.3	0.39 (0.13–1.11)	0.077
Warfarin	459,988	15	3.3	1.00 (Reference)	
SGLT-2i					
NOAC	2,493,693	13	0.5	0.68 (0.09–5.17)	0.705
Warfarin	209,069	2	0.8	1.00 (Reference)	
GLP-1 RA					
NOAC	199,827	0	0.0	NA [‡]	NA [‡]
Warfarin	25,391	0	0.0	NA [‡]	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

[‡] Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione





Table 33. Results of the sensitivity analysis that excluded periods of less than 14 days

Concurrent medications	Person-day	Event number	Incidence rate [*]	IRR [†] (95% CI)	<i>p</i> -value
Any antidiabetic drugs					
NOAC	25,673,465	1,042	4.1	0.72 (0.61–0.84)	<0.001
Warfarin	8,300,469	464	5.6	1.00 (Reference)	
Metformin					
NOAC	18,599,023	622	3.3	0.73 (0.59–0.91)	0.005
Warfarin	5,338,212	242	4.5	1.00 (Reference)	
DPP-4i					
NOAC	12,183,982	508	4.2	0.72 (0.57–0.92)	0.009
Warfarin	3,230,785	186	5.7	1.00 (Reference)	
Sulfonylurea					
NOAC	9,360,547	604	6.5	0.69 (0.57–0.85)	<0.001
Warfarin	3,704,609	340	9.2	1.00 (Reference)	
Insulin					
NOAC	3,038,995	286	9.4	0.79 (0.59–1.05)	0.104
Warfarin	1,112,383	134	12.0	1.00 (Reference)	
AGI					
NOAC	2,477,973	123	5.0	1.14 (0.65–1.99)	0.648
Warfarin	966,834	39	4.0	1.00 (Reference)	
Meglitinide					
NOAC	1,585,608	141	8.9	0.80 (0.56–1.15)	0.231
Warfarin	696,287	81	11.6	1.00 (Reference)	

TZD					
NOAC	1,473,036	76	5.2	0.69 (0.40–1.18)	0.175
Warfarin	436,608	32	7.4	1.00 (Reference)	
SGLT-2i					
NOAC	2,408,233	55	2.3	1.43 (0.42–4.87)	0.570
Warfarin	200,420	3	1.6	1.00 (Reference)	
GLP-1 RA					
NOAC	186,924	0	0.0	NA [‡]	NA [‡]
Warfarin	23,579	4	16.1	NA [‡]	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

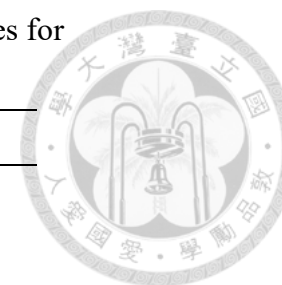
[‡] Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione



Table 34. Results of the sensitivity analysis that excluded periods within 30 days after a change in oral anticoagulant types for individuals who switched their medication

Concurrent medications	Person-day	Event number	Incidence rate [*]	IRR [†] (95% CI)	<i>p</i> -value
Any antidiabetic drugs					
NOAC	26,293,614	1,246	4.7	0.73 (0.63–0.84)	<0.001
Warfarin	8,657,480	561	6.5	1.00 (Reference)	
Metformin					
NOAC	18,976,596	736	3.9	0.73 (0.59–0.89)	0.002
Warfarin	5,549,870	294	5.3	1.00 (Reference)	
DPP-4i					
NOAC	12,501,423	606	4.8	0.74 (0.59–0.92)	0.008
Warfarin	3,365,709	222	6.6	1.00 (Reference)	
Sulfonylurea					
NOAC	9,556,490	711	7.4	0.69 (0.57–0.83)	<0.001
Warfarin	3,872,580	411	10.6	1.00 (Reference)	
Insulin					
NOAC	3,208,211	378	11.8	0.80 (0.63–1.02)	0.077
Warfarin	1,191,857	176	14.7	1.00 (Reference)	
AGI					
NOAC	2,551,384	150	5.9	1.17 (0.73–1.87)	0.526
Warfarin	1,017,414	54	5.3	1.00 (Reference)	
Meglitinide					
NOAC	1,650,333	171	10.3	0.84 (0.6–1.17)	0.302



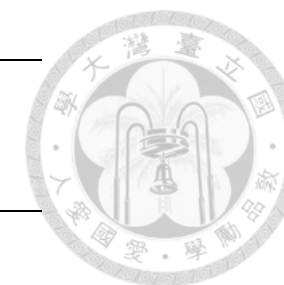
Warfarin	736,440	97	13.2	1.00 (Reference)	
TZD					
NOAC	1,524,179	87	5.7	0.69 (0.41–1.17)	0.172
Warfarin	457,069	38	8.3	1.00 (Reference)	
SGLT-2i					
NOAC	2,483,570	64	2.6	2.24 (0.51–9.84)	0.287
Warfarin	207,509	2	1.2	1.00 (Reference)	
GLP-1 RA					
NOAC	198,644	0	0.0	NA [‡]	NA [‡]
Warfarin	25,241	4	15.1	NA [‡]	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

[‡] Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione



4.2.6 E-values and negative control outcomes

In the overall analysis for concurrent use of NOAC versus warfarin and any antidiabetic drugs, the E-value was 2.08. In the specific subgroup analyses of individual antidiabetic drugs, where a significantly lower risk of hypoglycemia was observed with NOAC use, the E-values were respectively 2.08 for metformin, 2.08 for DPP-4i, and 2.30 for sulfonylureas. The plots illustrating the joint relationship between the two sensitivity parameters (exposure-confounder relationship and confounder-outcome relationship) that could potentially negate the estimated effect are presented in Figure 23 (panel A for the overall analysis and the subgroup analyses of metformin and DPP-4 inhibitors; panel B for the subgroup analysis for sulfonylureas).

Regarding the analysis of negative control outcomes (occurrence of conjunctivitis, influenza, urinary tract infection, and suicide death), as we expected, none of the outcomes demonstrated a significant association with the use of NOACs compared with warfarin (Table 35).

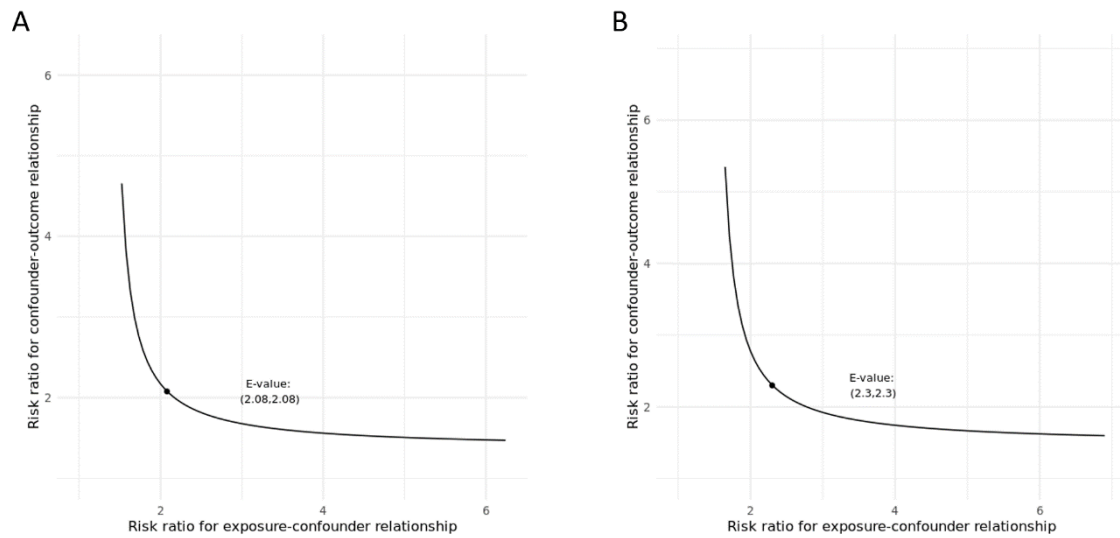


Figure 23. The joint relationship between the two sensitivity parameters (exposure-confounder relationship and confounder-outcome relationship) that could potentially negate the estimated effect of NOAC versus warfarin on lowering risk of severe hypoglycemia. Panel A for the overall analysis and the subgroup analyses of metformin and DPP-4 inhibitors; panel B for the subgroup analysis for sulfonylureas.

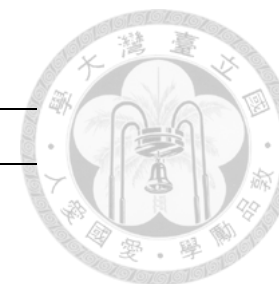


Table 35. The event number, incidence rate and incidence rate ratio of each negative control outcome in patients taking antidiabetic drugs with concurrent use of NOACs versus warfarin

Outcome	Person-day	Event number	Incidence rate*	IRR [†] (95% CI)	<i>p</i> -value
Conjunctivitis					
NOAC	26,807,039	67,402	251.4	1.03 (0.97–1.10)	0.281
Warfarin	8,707,347	19,809	227.5	1.00 (Reference)	
Influenza					
NOAC	26,807,039	5,021	18.7	0.91 (0.78–1.07)	0.277
Warfarin	8,707,347	1,651	19.0	1.00 (Reference)	
Urinary tract infection					
NOAC	26,807,039	47,016	175.4	1.03 (0.94–1.13)	0.489
Warfarin	8,707,347	15,931	183.0	1.00 (Reference)	
Suicide death					
NOAC	26,807,039	22	0.1	0.95 (0.28–3.24)	0.937
Warfarin	8,707,347	7	0.1	1.00 (Reference)	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

[‡] Not applicable because of the limited sample size.

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference

Chapter 5. Discussion



5.1 Discussion of Study 1

5.1.1 Summary of findings

In this nationwide retrospective cohort study, we observed that patients with AF and DM who were treated with NOACs demonstrated a reduced risk of diabetes-associated complications, including macrovascular and microvascular complications as well as glycemic emergencies, compared to those on warfarin. The mortality risk was also lower in those taking NOACs than those taking warfarin. Further analyses of individual NOACs, namely dabigatran, rivaroxaban, apixaban, and edoxaban, consistently indicated lower risks of complications and mortality in NOAC users versus those on warfarin. Additionally, various sensitivity analyses, such as those focusing on on-treatment evaluation and those restricted to patients with a high medication possession ratio, as well as the analyses of negative control outcomes, also supported our findings.

5.1.2 Comparison with previous studies

Our study demonstrated a significantly lower risk of macrovascular complications in NOAC users than warfarin users, aligning with previous studies that have shown a reduced risk of stroke/systemic embolism and major adverse cardiovascular events in patients with AF and DM taking NOACs.^{29,54,55} Notably, the effect of NOACs on lowering stroke risk in our analysis aligns closely with findings from a meta-analysis pooling data from four phase 3 randomized controlled trials (our study: HR = 0.80, 95% CI: 0.74-0.87; the meta-analysis: HR = 0.80, 95% CI: 0.69-0.93).²⁹ This accordance supports the notion that our study results obtained by target trial emulation

may closely mirror the findings of actual randomized controlled trials.

To date, only a few real-world studies have investigated renal outcomes in patients with AF and DM using different oral anticoagulants.^{60,61} Those previous studies have shown a significant reduction in the risk of declining estimated glomerular filtration rate and end-stage renal diseases among diabetic AF patients on NOACs compared to those on warfarin.^{60,61} Similarly, our study also discovered that NOACs were significantly associated with a lower risk of requiring dialysis compared with warfarin. Our findings further reinforce the notion that, for patients with AF and DM in the Asian population, the use of NOACs compared to warfarin may lead to better renal outcomes. Additionally, a retrospective claims analysis using US Truven MarketScan data suggested that rivaroxaban is associated with a lower risk of major limb amputation compared to warfarin;⁵⁴ their finding is compatible with our results focusing on the Asian population. Currently, there is no available evidence comparing the risk of retinopathy and neuropathy among diabetic AF patients on various oral anticoagulants. Our study fills this knowledge gap, revealing a significantly reduced risk of both retinopathy and neuropathy in patients with AF and DM who are consistent NOAC users, as indicated by a high medication possession ratio in the sensitivity analysis.

Previous research has indicated that warfarin might increase the risk of severe hypoglycemic events in patients on certain antidiabetic medications (such as sulfonylureas), likely due to drug-drug interactions.^{66,67} Building on these findings, our study suggests that NOACs may pose a lower risk of hypoglycemia compared to warfarin, as demonstrated in our on-treatment analysis. Specifically, in Study 2, we evaluated the effects of NOACs versus warfarin on severe hypoglycemia risk when used concurrently with each antidiabetic drug. These findings are further discussed in

section '5.2 Discussion of Study 2'. Regarding DKA and HHS, there is no existing research exploring the difference in risk of these conditions among diabetic patients with atrial fibrillation (AF) using NOACs versus warfarin. Interestingly, our sensitivity analyses, which included on-treatment analysis and those focusing on patients with a high medication possession ratio, suggested a trend towards a lower risk of DKA and HHS with NOAC use. Given the lack of other research findings on this issue, further studies are warranted to explore this topic and validate our findings.

We observed a lower all-cause mortality risk associated with NOAC use in diabetic patients with atrial fibrillation (AF), aligning with previous studies that evaluated the general and older AF population,^{63,64} as well as a United States study specifically assessing patients with AF and DM using Medicare data.⁵⁵ However, our study further discovered that both cardiovascular mortality and non-cardiovascular mortality risks were lower in the NOAC users in patients with AF and DM. This aspect had not been explored in previous research and indirectly supports the notion that the difference in effectiveness between NOACs and warfarin in diabetic AF patients may not solely be due to varying anticoagulant effects. Other plausible mechanisms, such as the impact on glycemic control or the anti-inflammatory effects of NOACs, are reasonable hypotheses worth considering. Notably, a prior retrospective study in Taiwan suggested a lower risk of all-cause mortality with dabigatran, but not with rivaroxaban, compared to warfarin among diabetic AF patients.⁵⁹ However, our study indicates a consistent trend of reduced mortality risk across all types of NOACs, differing from that previous Taiwanese study. This discrepancy may stem from the earlier study only including patients in Taiwan's diabetes pay-for-performance program and having a smaller sample size (only 322 dabigatran users and 320 rivaroxaban users), which might limit its

representativeness.⁵⁹ In contrast, our analysis encompassed the entire Taiwanese population, with a larger sample and longer follow-up period, thereby yielding potentially more reliable and generalizable results.

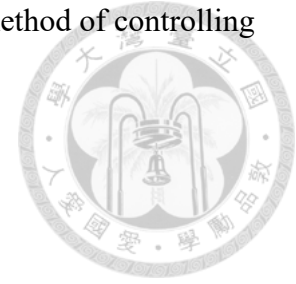


5.1.3 Sensitivity analyses

A portion of the participants initially on warfarin (46%) switched to NOACs during the study period. This switch might have led to an underestimation of the difference between NOAC and warfarin in our as-started analysis (analogous to intention-to-treat) due to potential exposure misclassification during the follow-up period. However, even with this conservative approach, NOAC users still exhibited a significantly lower risk of composite complication outcomes and mortality compared to those on warfarin. Importantly, our two sensitivity analyses (one involved on-treatment analysis, and the other was confined to patients with at least an 80% medication possession ratio of the index oral anticoagulant during follow-up) consistently revealed more significant results and larger effect sizes than the primary analyses. These findings support the robustness of the observed differences in risks of diabetes-related complications and mortality between NOAC and warfarin uses.

A previous study that compared the effects of dabigatran and warfarin on stroke risk highlighted that the presence of extreme weights in analysis with IPTW could significantly influence the results.⁹⁸ Consequently, we conducted several sensitivity analyses, including the use of stabilized IPTW with weight truncation and the use of propensity score matching. These analyses helped examine whether our study results were influenced by extreme values of weights and to determine if the use of different propensity score methods affected our findings. The results of these sensitivity analyses align with those of our main analyses, supporting that our study findings

were not affected by extreme weights when using IPTW as the method of controlling confounders in our analyses.



5.1.4 The choices of propensity score methods in our study

While propensity score methods can broadly be categorized into four types:⁸³ propensity score matching, IPTW using the propensity score, covariate adjustment using the propensity score, and stratification on the propensity score, our study did not employ the latter two methods (adjustment and stratification). This decision was based on previous literature which suggests that these two approaches might be more prone to bias.⁸⁴ Past studies have highlighted concerns about stratification, noting it suffers from biased inference due to residual confounding, which worsens with increasing sample size. Additionally, literature indicates that both stratification and covariate adjustment using the propensity score may lead to skewed estimations of odds ratios and hazard ratios, and that covariate adjustment is often more affected by residual confounding than matching or IPTW. Moreover, a significant drawback of covariate adjustment is its dependence on a regression model that relates the outcome to treatment status and other variables (the propensity score).⁸⁴ This approach assumes that the nature of the relationship between the propensity score and the outcome has been correctly modeled, a requirement not necessary when employing methods such as propensity score matching or IPTW.⁸¹ Hence, based on these literature recommendations, it is generally advised for researchers to prioritize either matching or weighting as the initial approach in employing propensity score methods.⁸⁴

5.1.5 Evaluation of potential unmeasured confounders

Although the use of propensity score methods in observational studies can help

control many measured confounders, they cannot entirely rule out the possibility of unknown or unmeasured confounders, even when using a target trial emulation framework. This limitation might compromise the causal interpretation of our study results. Therefore, we conducted further analysis on three negative control outcomes – conditions not anticipated to be causally linked to different oral anticoagulants, such as cancer, COPD, and suicide death. This negative control outcome analysis helped indirectly assess the potential presence of residual confounding or other design or analytical flaws that could result in spurious causal inferences. The results of these negative control outcome analyses were consistent with our expectations, showing no unexpected associations between the exposure (NOAC/warfarin use) and these outcomes. This consistency in the negative control outcome analysis indirectly reinforces our study findings, implying a potential causal relationship.

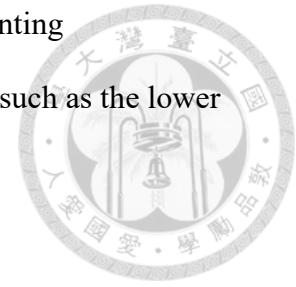
In our as-started analysis, the E-values for macrovascular complications, microvascular complications, glycemic emergencies, and mortality were 1.51, 1.63, 1.43, and 1.66, respectively. In the on-treatment analysis, the E-values were generally higher, with values of 1.53, 1.94, 1.77, and 2.1 corresponding to each of the four primary outcomes. Taking an E-value of 1.51 as an example, this indicates that any unmeasured confounder would need to have a risk ratio of 1.51 or greater with both the exposure (NOAC use) and the outcome (in this case, macrovascular complication) to negate the observed association between NOAC use and a lower risk of macrovascular complications. Although there is no definitive threshold for the significance of E-values, we consider it unlikely for an unmeasured confounder to simultaneously have a risk ratio greater than our calculated E-values with both the exposure and outcome. This consideration indirectly supported the robustness of our study findings.



5.1.6 Possible underlying mechanisms

Although the exact underlying mechanism remains unknown, several factors might explain our study findings. Previous studies have indicated the beneficial role of vitamin K in insulin sensitivity and glucose tolerance, which may be mediated by osteocalcin, a vitamin K-dependent protein requiring carboxylation by vitamin K to be activated.⁴²⁻⁴⁴ Furthermore, oxidative stress and inflammation play a crucial role in the pathogenesis and development of insulin resistance and diabetic complications. An interrelation between inflammation and metabolic abnormalities in diabetes causes endothelial injury and leads to vascular complications. Vitamin K suppresses oxidative stress and inflammatory responses via the inactivation of the nuclear factor kappa-B-related signaling pathway.^{42,44} Furthermore, previous animal studies suggested that vitamin K improved insulin resistance via its lipid-lowering efficacy.^{42,44} The aforementioned mechanisms suggest that antagonization of vitamin K by warfarin may lead to impaired insulin sensitivity and glucose tolerance and increase risk of developing diabetes complications; this provides plausible pharmacological explanations for our study findings. These hypotheses are additionally supported by two recent real-world cohort studies reporting that NOACs were associated with a lower risk of newly developed DM than warfarin in non-diabetic AF patients.^{48,49} In addition, preclinical studies have suggested the potential effects of direct thrombin or factor Xa inhibitors on anti-inflammatory activities and the stabilization of atherosclerotic plaques. These are also considered potential mechanisms for reducing complications related to diabetes in patients on NOACs.⁵⁰ Furthermore, the difference in anticoagulation mechanism between NOACs (direct thrombin inhibitors or factor Xa inhibitors) and warfarin (vitamin K antagonist),

which provides NOACs with equal or superior efficacy for preventing thromboembolism event, could also explain a part of our results, such as the lower risk of macrovascular complications with NOACs.



5.1.7 Clinical implications

In recent years, an increasing number of studies have suggested that NOACs may be more effective than warfarin in preventing strokes and have a lower risk of bleeding.^{38,39} Our research further indicates that in patients with diabetes, those treated with NOACs have a reduced risk of diabetes-related complications. Therefore, NOACs may be a better choice of anticoagulant. For clinicians managing patients with both AF and DM, this study provides crucial insights, underscoring the potential benefits of choosing NOACs over warfarin. This consideration is critical, especially given the substantial impact of diabetes complications on patient health, quality of life, and socioeconomic burden. The study's findings, which highlight reduced risks in both macrovascular and microvascular complications, as well as glycemic emergencies and mortality in patients treated with NOACs, are clinically important. These reductions could lead to better clinical outcomes, improving overall patient care and reducing healthcare costs.

However, due to the higher cost of NOACs compared to warfarin, this might still impact medication choices in patients or areas with limited medical resources, funding, or health insurance coverage. Given the significant health and societal burden of diabetes-related complications, choosing NOACs over warfarin to reduce the incidence of these complications could be beneficial overall, both in terms of patient health and economic and social financial burdens. Future studies that analyze this issue from a public health and cost-effectiveness perspective would be helpful for

clinical decision-making.

Furthermore, importantly, our study addresses a significant gap in research, particularly concerning Asian populations. Evidence regarding the effectiveness of NOACs compared to warfarin has been notably scarce for patients with AF and DM in these groups. Our results contribute valuable insights into the real-world effectiveness of NOACs versus warfarin in Asian cohorts. Understanding these effects is vital, considering potential genetic and lifestyle differences that may influence treatment outcomes in Asian patients compared to other populations. This research adds to the growing body of evidence favoring NOACs in certain patient populations, encouraging clinicians to reevaluate and potentially update their treatment protocols for patients with AF and DM.

5.1.8 Strengths and limitations

The key strengths of this study included its nationwide scope utilizing real-world data based on routine clinical practice, its novel insights into the relationship between different oral anticoagulants and a range of diabetes-related complications, and the solid validation of our findings through many sensitivity analyses. Nonetheless, there are some limitations to consider.

First, our study lacked detailed information on patients' lifestyle factors, substance use, body mass index, comprehensive laboratory results (such as blood glucose levels, lipid profiles, and renal function), and patient compliance. Although we employed propensity score methods to mitigate potential measured confounders, the presence of unknown or unmeasured confounders cannot be entirely ruled out. However, the results of our negative control outcome analyses did not indicate the presence of potential unaddressed confounders. Additionally, the E-values calculated were

considered acceptable, suggesting that our study results are likely reliable.

Second, due to the unavailability of INR data, our study could not assess or adjust for the potential impact of subtherapeutic INRs on stroke and mortality risk in warfarin users. However, the issue of a potentially lower optimal time in the therapeutic range for warfarin users is a well-known challenge in real-world settings.¹⁰⁴ Our study, aiming to assess the effectiveness of NOACs versus warfarin using real-world data, remains valuable despite this limitation. The lack of INR information does not detract from the significance of our findings. On the contrary, our results effectively reflect real-world conditions and the actual effectiveness of these treatments in routine clinical practice.

Third, for patients who changed their oral anticoagulant choice during the follow-up period, we were unable to ascertain the exact reasons for these changes. However, consistent results were obtained across our as-started analysis, on-treatment analysis, and analyses focusing on patients with high medication adherence, all indicating a lower risk of diabetes-related complications among NOAC users. Therefore, even though the specific reasons for changing treatments are unknown, the absence of this information is unlikely to impact the conclusions of our study.

Fourth, due to patient anonymity in the NHIRD, we identified study outcomes using diagnostic and procedure codes instead of directly verifying them through patients' medical records. There is a possibility that some patients with these conditions might not have sought medical care or their conditions were not correctly recorded in the healthcare claims system. Despite these limitations, we believe that the potential under-reporting of outcomes or misclassification errors would likely be non-differential between the NOAC and warfarin groups, leading to an underestimation of the true differences (bias toward the null).^{105,106} Consequently, the actual disparities in

diabetes-related complications between NOAC and warfarin users could be more pronounced than what we observed. Nevertheless, should future research efforts focus on validating the accuracy of various disease diagnosis codes within the NHIRD, the reliability of studies (such as ours) that utilize this database for analysis would be significantly enhanced.

Fifth, in our analysis targeting each specific outcome, individuals with any prior diagnosis of that outcome before the index date are initially excluded. This approach results in variations in the patient numbers included in different outcome analyses. Notably, the number of patients included for macrovascular complications analysis is relatively lower. This variation might be due to Taiwanese physicians potentially diagnosing certain conditions, such as coronary artery disease, more frequently, which leads to a higher exclusion rate of individuals before the index date. As previously stated, our database does not enable direct validation of the accuracy of these patient diagnoses, including their pre-index date medical history. Additionally, our methodology might overlook data from high-risk patients who experience recurrent events, such as recurrent myocardial infarction or stroke. Consequently, future research, potentially involving prospective cohort studies or clinical trials that offer more comprehensive data and validated medical histories, is crucial to address these challenges.

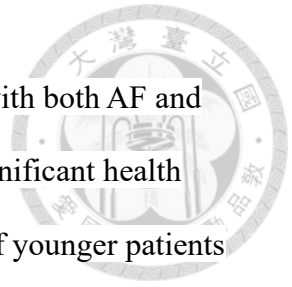
Sixth, because the database used in this study only includes data up to the year 2018, there is a limited number of patients who use newer diabetic medications, such as SGLT-2i and GLP-1 RA. Since these diabetes medications may also affect the risk of diabetes-related complications, they could potentially influence our comparative results between NOACs and warfarin. Consequently, future research is required, incorporating more recent data and including more diabetic patients treated with these

newer drugs, to validate our findings.

Additionally, because of our patient selection criteria (those with both AF and DM), the majority of our study population were older and had significant health issues, mirroring real-world scenarios. Of note, in the subgroup of younger patients (under 65 years), the sample size was relatively smaller, and we observed no statistically significant link between NOAC use and the study outcomes.

Consequently, it remains to be investigated whether the results seen in the older and more medically complex population are applicable to younger, healthier individuals. Further studies are needed to explore this issue.

Lastly, although our study utilized data from Taiwan's NHIRD, representing the entire Taiwanese population, further research is still needed to explore and confirm whether our findings can be extrapolated to different regions, countries, and ethnic groups.



5.2 Discussion of Study 2

5.2.1 Summary of findings

In this nationwide retrospective cohort study, we observed that patients with AF and DM on antidiabetic medication who concurrently used NOACs experienced a significantly lower risk of serious hypoglycemia compared to those concurrently using warfarin. A similar trend of reduced hypoglycemia risk was observed across each NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) when compared to warfarin. Subgroup analyses based on various antidiabetic drugs showed that the significantly lower risk of serious hypoglycemia associated with NOACs was evident in patients taking metformin, DPP-4 inhibitors, or sulfonylureas.

5.2.2 Comparison with previous studies

Previous observational studies have examined the risk of serious hypoglycemia in patients on antidiabetic medications, comparing those using warfarin with those not using warfarin. These studies indicated an elevated risk of serious hypoglycemia in patients taking sulfonylureas alongside warfarin.^{66,67} However, these comparisons were limited to warfarin users and non-users, lacking an active comparator. Such findings are susceptible to confounding by indication, as anticoagulant treatment and non-treatment groups may represent different populations or patient conditions (e.g., different disease severity, comorbidities, or patients' preferences). Further, in clinical practice, when oral anticoagulants are indicated for stroke prevention, they would be prescribed regardless of potential hypoglycemia risks. Thus, the critical clinical question is not about whether to use oral anticoagulants but about choosing a better oral anticoagulant with a lower risk of severe hypoglycemia. With the introduction of NOACs as alternatives to warfarin, it becomes essential to compare the risk of severe



hypoglycemia between NOACs and warfarin in this specific population. To date, however, there has been limited research addressing this comparison.

In our Study 1, which extensively evaluated various diabetes-related complications within a single study, we discovered that NOACs may potentially reduce the risk of hypoglycemia compared to warfarin in patients with AF and DM. This finding likely represents the first direct comparison of the impacts of NOACs and warfarin on hypoglycemia risk. However, Study 1 did not differentiate among the various concurrent antidiabetic drugs, an aspect that is crucial considering that the underlying mechanisms of hypoglycemia might be linked to potential drug-drug interactions between specific antidiabetic drugs and oral anticoagulants.⁶⁶ Furthermore, the design of Study 1 did not account for potential time-varying exposures and confounders, which is a critical factor considering that the use of medications, particularly antidiabetic drugs, can significantly change over several years of follow-up. The risk of hypoglycemia is closely related to the type and quantity of antidiabetic medications being used at any given time.

A recent observational study in the UK, specifically targeting patients on sulfonylureas, highlighted an increased risk of severe hypoglycemia in those concurrently using sulfonylureas and warfarin, compared to those using sulfonylureas alone (HR=1.25; 95% CI: 1.16–1.35).⁶² This finding is in line with the aforementioned earlier studies.^{66,67} However, the authors of that study noted the possibility of residual confounding, as their supplementary analyses showed no significant difference in severe hypoglycemia risk between warfarin and NOAC users (HR=1.01; 95% CI: 0.67–1.52).⁶² Furthermore, only a limited number of severe hypoglycemia events were observed in that study, making it challenging to draw definitive conclusions.

Another recent cohort study in the UK, also specifically targeting patients on

sulfonylureas, found that the concurrent use of warfarin with sulfonylureas, compared to using sulfonylureas alone, was associated with a significantly higher risk of hypoglycemia (HR=1.38; 95% CI: 1.10–1.76, $P = 0.010$).⁶⁸ However, this study did not specify or limit the severity of hypoglycemia or whether it required hospitalization or treatment with high-concentration glucose. Interestingly, the same study also compared the concurrent use of NOACs with sulfonylureas versus sulfonylureas alone and found no significant difference in hypoglycemia risk between the two. However, there was a trend toward a lower risk of hypoglycemia in NOAC users compared to non-users (HR 0.54; 95% CI: 0.27–1.10, $P = 0.091$). Despite these findings, the study was limited by the lack of an active comparator (NOAC vs warfarin) and insufficient sample size and event numbers for NOAC users (only 14 hypoglycemia events), and it did not include analyses for users of other antidiabetic drugs.⁶⁸

Our present study (Study 2) focused on patients with AF and DM, employing an active-comparator approach to assess the risk of serious hypoglycemia between different oral anticoagulants (NOACs versus warfarin) among patients on various antidiabetic drugs. We innovatively segmented each patient's follow-up time into separate periods based on their use of antidiabetic and oral anticoagulant medications, capturing data on exposures and covariates for each period to account for time-varying factors. Furthermore, our study conducted more extensive analyses, including various subgroup, stratified, and sensitivity analyses, which were more comprehensive than those in prior studies.^{62,66,67} As a result, our study bridges previously existing knowledge gaps and offers more reliable insights into this critical clinical matter.

5.2.3 Sensitivity analyses

We have conducted various sensitivity analyses, all of which supported our

research findings. One of the analyses, which excluded patients with any diagnosis of CKD, helped confirm that CKD likely does not cause confounding by indication. Another sensitivity analysis, applying stabilized IPTW without weight truncation, verified that truncating weights or not does not affect our study results. Similarly, the sensitivity analysis that separately analyzed emergency department diagnoses or inpatient diagnoses of hypoglycemia showed the same trend, indicating that these different outcome definitions do not influence our study findings.

Regarding the potential but unknown incubation period or lagged effect from the use of NOAC or warfarin on hypoglycemia risk, we analyzed data by excluding periods with a short duration (less than 14 days), as well as periods within 30 days after switching oral anticoagulants. Both analyses yielded similar results, indirectly supporting the possibility that a potential incubation period or lagged effect might not alter our research findings.

5.2.4 Unavailability of diabetes severity and the issue of potential unmeasured confounders

The severity of diabetes is closely related to the risk of hypoglycemia; however, our use of claims-based data limited our ability to directly assess each patient's diabetes severity during the observation period. Nevertheless, in the pseudo-population established through stabilized IPTW (Table 25), the types and quantities of diabetes medications used in the NOAC and warfarin groups were very similar. Additionally, current clinical guidelines do not consider a patient's glycemic control or diabetes severity when selecting oral anticoagulants. Therefore, there's likely no significant difference in diabetes severity between the NOAC and warfarin groups, and this factor probably doesn't influence our study's results. Notably, previous

literature has shown that the adapted Diabetes Complication Severity Index is effective in predicting hospitalization risk and healthcare costs for diabetes patients and may also act as a useful surrogate for diabetes severity in research using claims-based data.¹⁰⁷ Future research may benefit from incorporating this index to address and control for diabetes severity when evaluating diabetes-related study outcomes, such as hypoglycemia or other complication risks.

In addition, the results of all negative control outcome analyses aligned with our expectations, indirectly suggesting the absence of potential residual confounding or other design and analytical flaws that could lead to biased causal conclusions. Moreover, in the overall analysis involving patients taking any antidiabetic drugs and in the subgroup analyses for those taking metformin, DPP-4 inhibitors, and sulfonylureas, the E-values were 2.08, 2.08, 2.08, and 2.30, respectively. We believe it is unlikely for an unmeasured confounder to simultaneously have a risk ratio greater than these E-values in relation to both the exposure and the outcome. This supports the robustness of our study's conclusions.

5.2.5 Challenges in conducting randomized controlled trials and the sample size issue for this investigation

While randomized controlled trials remain the gold standard for establishing causality in research, conducting a randomized controlled trial for this study poses considerable challenges. One reason is that randomized controlled trials are not ideally suited for studying potential adverse events, such as hypoglycemia, as the primary outcome. This arises from ethical concerns over the potential harm to participants. Additionally, our investigation aimed to explore the concurrent use of NOACs versus warfarin with various antidiabetic medications. Despite using data

from the entire Taiwanese population, concerns about potential insufficient statistical power in the sub-analyses for various antidiabetic medications may still persist in this single study. Designing and executing a randomized controlled trial with adequate power to examine these potential intricate interactions across different medications is thus very difficult. The necessary sample size for a randomized controlled trial greatly increases when considering the different types of antidiabetic drugs used in combination with NOACs and warfarin. Therefore, it is unlikely that future randomized controlled trials will be designed and performed to explore this issue. Consequently, the best evidence for discussing this issue might still rely on observational studies.

On the other hand, before conducting this retrospective observational study using an existing database, we did not pre-calculate the required sample size for statistical power assurance. This is because of the fact that, unlike randomized controlled trials where ethical considerations require power calculations to minimize risks to participants, observational studies using existing databases are not subject to these same ethical constraints. Previous literature has clarified that the main objective in observational studies is to estimate and quantify the effect as accurately and unbiasedly as possible, not merely to 'detect' it.¹⁰⁸ Addressing imprecise effect estimates involves promoting multiple observational studies rather than avoiding them. Conducting multiple studies, even with potentially imprecise estimates, is more beneficial than conducting none. This approach may yield a range of estimates, which, despite potential individual imprecision, can be collectively refined through meta-analysis. Therefore, the decision to conduct an observational analysis, especially using an existing database, should not be deterred by the potential insufficient power or imprecision of the results. As the previous literature suggested, for important causal

questions, the best practice is to analyze the data, publish the results, encourage similar efforts by others, and then consolidate these findings through meta-analysis.¹⁰⁸ This approach, rather than leaving a question unaddressed, helps in progressively understanding the important issue. We therefore hope that more research on this topic will be conducted in the future, facilitating the accumulation of relevant evidence and enhancing our understanding of the important clinical issue.

5.2.6 Potential underlying mechanisms

While the exact underlying mechanisms of our findings are not fully understood, several hypotheses are suggested. Warfarin functions as a vitamin K antagonist, while NOACs do not have this property. There is growing evidence indicating that vitamin K may positively influence insulin sensitivity and diabetes management.⁴²⁻⁴⁴ Recent clinical research and our Study 1 also suggested that NOACs might provide superior glycemic control and reduce the risks of diabetes development and diabetes-related complications compared with warfarin.^{48,49} Since poorly controlled diabetes is a well-known risk factor for hypoglycemic events,^{15,16} the differing impact of these drugs on vitamin K could explain our study results. In addition, both warfarin and certain antidiabetic drugs (such as sulfonylureas) mainly undergo metabolism via the cytochrome P450 2C9 hepatic pathway.⁶⁵⁻⁶⁷ This shared metabolic pathway could lead to potential drug-drug interactions that might impair sulfonylurea metabolism, thereby increasing the risk of hypoglycemia. Our study observed the lowest incidence rate ratio (IRR) of serious hypoglycemia in the sulfonylurea subgroup, which supports the hypothesis that interactions between warfarin and sulfonylureas might precipitate hypoglycemia events. Nonetheless, the exact biological mechanisms underlying our findings are still unclear, highlighting the need for further research in this area.



5.2.7 Clinical implications

This study holds significant clinical relevance. Hypoglycemia, a dangerous but common side effect of diabetes treatment, can lead to neurological damage, cardiovascular events, and even mortality. Preventing these severe episodes is crucial for reducing both individual health impacts and the broader healthcare and economic burdens.^{109,110} Our research provides solid real-world evidence that NOACs are associated with a lower risk of severe hypoglycemia compared to warfarin in patients receiving antidiabetic medications. These findings should inform clinicians in selecting the most appropriate medications to prevent serious hypoglycemic events in patients with AF and DM who require both anticoagulant and antidiabetic treatments. In cases where patients are being treated with antidiabetic drugs, the use of NOACs instead of warfarin may be a strategic decision to minimize the risk of severe hypoglycemia.

5.2.8 Strengths and limitations

This study is reinforced by its comprehensive, nationwide scope, leveraging real-world data to provide insightful findings. By segmenting patients' follow-up time into distinct periods, and using each as a unit of analysis while meticulously collecting patient characteristics for every interval, the study design allows for a more nuanced control of potential time-sensitive factors. This approach help enhance the accuracy and depth of our findings. However, it is important to consider and address a few limitations of the study.

First, we employed Taiwan's NHIRD as our research data source. This database presented certain limitations, as the NHIRD does not offer detailed information on

aspects such as patient lifestyle habits, substance use, and laboratory test results. Furthermore, the database lacks comprehensive data regarding patients' adherence to medical treatments, the severity of their medical conditions, and socio-domestic factors. Although we implemented stabilized IPTW to manage numerous potential measured confounders, we cannot entirely rule out the possibility of residual imbalances between groups due to unmeasured confounders, which might have influenced our results. Nevertheless, the results from our negative control outcome analyses showed no clear signs of potential unaddressed confounding factors. Furthermore, the E-values derived from our main analyses were considered satisfactory, suggesting that the conclusions of our study are likely robust.

Second, our study specifically evaluated serious hypoglycemic events that require the administration of high-concentration intravenous glucose, either in the emergency department or during hospitalization. This definition ensures a high positive predictive value in identifying outcome events. Even if there is an underestimation of outcomes, this situation would likely be non-differential between the NOAC and warfarin groups, thereby biasing the results towards the null.^{105,106} Considering that our study has already shown statistically significant differences, the actual disparity in the risk of severe hypoglycemia between NOACs and warfarin might be greater than what we have observed. However, our study did not investigate cases of mild hypoglycemia. The reason for this is that many patients, particularly those with mild symptoms, might not seek medical assistance, leading to the exclusion of these mild events from our study. As a result, our findings cannot be extrapolated to patients experiencing mild hypoglycemia.

Third, during the study period covered by our database, the prescription rates of SGLT-2i and GLP-1 RA were relatively low. This situation is probably due to the late

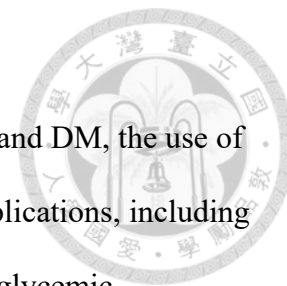
introduction and coverage of these medications by Taiwan's National Health Insurance, along with their comparatively high costs. Consequently, the small number of patients in the subgroup analyses for SGLT-2i and GLP-1 RA led to wide confidence intervals or an inability to estimate the study outcome accurately. Further research is essential to effectively address this issue and accumulate more evidence.

Fourth, due to the fact that some antidiabetic drugs are second-line treatments and may often be used in conjunction with other antidiabetic drugs, it is challenging to conduct stratified analyses specifically on patients who are exclusively using a single type of diabetes medication. Such patients are relatively rare, resulting in a limited number of patients for analysis, particularly among those using second-line diabetes medications. Therefore, in our subgroup analyses of various antidiabetic drugs, we did not exclude patients who were concurrently using other types of drugs. However, we have accounted for and adjusted the use of other diabetes medications within our propensity score methods. This approach reflects the complexity of real-world medication use patterns.

Fifth, due to the inherent limitations of observational studies, we cannot conclusively ascertain whether the modest treatment effect observed in our study is causal. Additional research is necessary to verify our findings.

Lastly, our findings are derived from data analysis specific to the Taiwanese population. Consequently, the applicability of our findings to different populations in other regions, countries, or of various ethnicities requires further research for clarification.

Chapter 6. Conclusion



In conclusion, Study 1 revealed that among patients with AF and DM, the use of NOACs was associated with lower risks of diabetes-related complications, including both macrovascular and microvascular complications, as well as glycemic emergencies, and also reduced mortality compared to warfarin use. Additionally, Study 2 indicated that patients on antidiabetic medications, when concurrently using NOACs, had a significantly lower risk of serious hypoglycemia than those concurrently using warfarin. Therefore, NOACs may represent a preferable therapeutic choice over warfarin in reducing these complications and mortality for patients with AF and DM requiring oral anticoagulant treatment.

Looking forward, our research paves the way for further exploration and supplementation in future studies. First, conducting similar studies across various countries and ethnic groups is crucial to establish the generalizability of our findings. Given the potential genetic and lifestyle variations among different populations, it is important to determine whether the benefits of NOACs observed in our Taiwanese cohort are consistent in other countries and among various population groups.

Secondly, additional research is needed to understand how NOACs and warfarin potentially influence glycemic control and the development of diabetes-related complications through various pathophysiological mechanisms and pharmacological pathways. These may include mechanisms both related to and independent of vitamin K's function.

Third, if feasible, conducting randomized controlled trials could further validate the causal relationships suggested by our findings from observational studies. However, considering the potential practical challenges of implementing randomized controlled trials on this subject, especially in relation to the issues explored in Study 2,

the anticipation of more well-designed observational studies on this topic is warranted. These studies should ideally include more detailed information on patients' lifestyle factors, disease severity, comprehensive laboratory examination results, drug compliance, and socioeconomic status, and should also require a robust research design. Regarding the subgroup analyses of various concurrent antidiabetic drugs in Study 2, our research was limited by the outdated data period and insufficient sample size to explore newer antidiabetic drug subgroups (e.g., SGLT-2i, GLP-1 RA). Future studies are still needed to thoroughly assess users of these newer antidiabetic drugs.

Fourth, future studies could benefit from investigating both the long-term health and economic impacts of using NOACs over warfarin, particularly regarding healthcare costs associated with managing diabetes-related complications. Such research would be valuable in guiding healthcare policies and decisions on anticoagulant prescriptions, especially in regions with limited medical resources or funding.

Finally, our study estimated the average treatment effect of NOAC versus warfarin in the whole Taiwanese population; however, the exact individualized treatment effect for each individual patient remains uncertain and unexplored. Future studies in personalized medicine, potentially taking into account detailed individual patient characteristics, genetic makeup, and specific health and environmental conditions, would be worth developing. Such studies may help optimize treatment choices and outcomes for each individual patient with AF and DM, thereby improving the prognosis for each patient.

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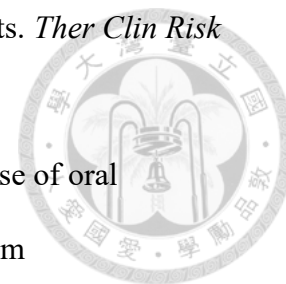
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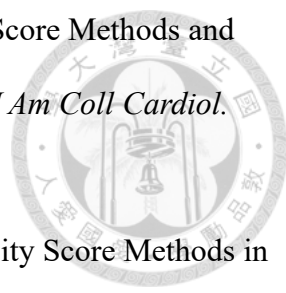
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Appendix

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II. Published Articles

- Study 1:** Diabetes-Related Complications and Mortality in Patients With Atrial Fibrillation Receiving Different Oral Anticoagulants A Nationwide Analysis. *Ann Intern Med.* 2022 Apr;175(4):490-498. doi: 10.7326/M21-3498.
- Study 2:** Risk of serious hypoglycaemia in patients with atrial fibrillation and diabetes concurrently taking antidiabetic drugs and oral anticoagulants: a nationwide cohort study. *Eur Heart J Cardiovasc Pharmacother.* 2023 Jul 29;9(5):427-434. doi: 10.1093/ehjcvp/pvad038.

I. Supplemental Tables

Table S1. The diagnostic codes used for identifying baseline comorbidities in Study 1

Disease	ICD-9-CM codes	ICD-10-CM codes
Hypertension	401-405	I10-I16
Coronary artery disease	410-414	I20-I25
Congestive heart failure	428	I50
COPD	490-492, 494, 496	J40-J44, J47
Chronic kidney disease	582, 583, 585, 586, 588	N03, N04, N05, N18, N19
Liver cirrhosis	571	K74
Hyperlipidemia	272.0-272.4	E78.0-E78.5
Stroke	430-438	I60-I69
Rheumatoid arthritis	714.0	M05, M06
Gout	274	M10
Dementia	290, 294.1, 331.0, 331.2	F01-F03, G30, G31.1
Malignancy	140-208, 209.0-209.3	C00-C80, C7A, C81~C96

COPD, chronic obstructive pulmonary disease

Table S2. The comorbidities and their corresponding diagnostic codes used for calculating the Charlson Comorbidity Index

Condition	Weights	ICD-9-CM codes	ICD-10-CM codes
Myocardial infarction	1	410.x, 412.x	I21.x, I22.x, I25.2
Congestive heart failure	1	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	1	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 47.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	1	362.34, 430.x–438.x	G45.x, G46.x, H34.0, I60.x–I69.x
Dementia	1	290.x, 294.1, 331.2	F00.x–F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	1	416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Rheumatic disease	1	446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	1	531.x–534.x	K25.x–K28.x
Mild liver disease	1	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complication	1	250.0–250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0

			E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complication	2	250.4–250.7	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
Hemiplegia or paraplegia	2	334.1, 342.x, 343.x, 344.0–344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Renal disease	2	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Any malignancy	2	140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
Moderate or severe liver disease	3	456.0–456.2, 572.2–572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumor	3	196.x–199.x	C77.x–C80.x
AIDS/HIV	6	042.x–044.x	B20.x–B22.x, B24.x

The Charlson Comorbidity Index was determined by summing the weighted scores in the table, with diagnostic codes defined according to the previous literature by Quan et al (Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005, 43(11):1130-1139.)

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus

Table S3. The factors and diagnostic codes used for calculating the CHA2DS2-VASc score

The sum of the scores corresponding to the following components constitutes the CHA2DS2-VASc Score.

Component	Score	ICD-9-CM codes	ICD-10-CM codes
Congestive heart failure	1	428	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29
Hypertension	1	401-405	I10-I15
Aged ≥ 75 years	2	NA	NA
Diabetes mellitus	1	250	E11
Stroke	2	433-438	I63-I69
Vascular disease (myocardial infarction, peripheral artery disease, or aortic plaque)	1	410, 412, 440, 440.2, 420.3, 440.4, 443.81, 443.89, 443.9	I21, I22, I25.2, I70, I70.2- I70.7, I70.92, I73.89, I73.9
Aged 65–74 years	1	NA	NA
Sex category (i.e. female gender)	1	NA	NA

NA, not applicable

Table S4. The Anatomical Therapeutic Chemical (ATC) codes used for identifying the prescriptions of medications in Study 1

Drug names	ATC codes
Antidiabetic drugs	
Metformin	A10BA, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25, A10BD26, A10BD27
Sulfonylurea	A10BB, A10BD02, A10BD04, A10BD06
Meglitinide	A10BX02, A10BX03, A10BX08, A10BD14
AGI	A10BF, A10BD17
TZD	A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12, A10BD26
DPP-4i	A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18, A10BD19, A10BD21, A10BD22, A10BD24, A10BD25, A10BD27
SGLT-2i	A10BK, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25, A10BD27
GLP-1	A10BJ, A10AE54
Insulin	A10A
Other drugs	
Statins	C10AA
ACEI/ARB	C09
b-blocker	C07
CCB	C08
Diuretics	C03
NSAID	M01A
Corticosteroids	H02AB
Antipsychotics	N05A
PPI	A02BC

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione

Table S5. The diagnostic codes used for identifying comorbidities in Study 2

Disease	ICD-9-CM codes	ICD-10-CM codes
Hypertension	401-405	I10-I16
Coronary artery disease	410-414	I20-I25
Congestive heart failure	428	I50
COPD	490-492, 494, 496	J40-J44, J47
Asthma	493	J45
Chronic kidney disease	582, 583, 585, 586, 588	N03, N04, N05, N18, N19
Liver cirrhosis	571	K74
Hyperlipidemia	272.0-272.4	E78.0-E78.5
Stroke	430-438	I60-I69
Rheumatoid arthritis	714.0	M05, M06
Dementia	290, 294.1, 331.0, 331.2	F01-F03, G30, G31.1
Depression	296.2, 296.3, 300.4, and 311	F32, F33, F34.1
Malignancy	140-208, 209.0-209.3	C00-C80, C7A, C81~C96

COPD, chronic obstructive pulmonary disease

Table S6. The Anatomical Therapeutic Chemical (ATC) codes used for identifying the prescriptions of medications in Study 2

Drug names	ATC codes
Antidiabetic drugs	
Metformin	A10BA, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25, A10BD26, A10BD27
Sulfonylurea	A10BB, A10BD02, A10BD04, A10BD06
Meglitinide	A10BX02, A10BX03, A10BX08, A10BD14
AGI	A10BF, A10BD17
TZD	A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12, A10BD26
DPP-4i	A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18, A10BD19, A10BD21, A10BD22, A10BD24, A10BD25, A10BD27
SGLT-2i	A10BK, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25, A10BD27
GLP-1	A10BJ, A10AE54
Insulin	A10A
Other drugs	
Statins	C10AA
ACEI/ARB	C09
b-blocker	C07
CCB	C08
Diuretics	C03
NSAID	M01A
Corticosteroids	H02AB
Antipsychotics	N05A
PPI	A02BC

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione

II. Published Articles



Study 1:

Huang HK, Liu PP, Lin SM, Hsu JY, Yeh JI, Lai EC, Peng CC, Munir KM, Loh CH, Tu YK.

Diabetes-related complications and mortality in patients with atrial fibrillation receiving different oral anticoagulants : A nationwide analysis. *Annals of Internal Medicine*.

2022;175:490-498

Study 2:

Huang HK, Liu PP, Lin SM, Yeh JI, Hsu JY, Peng CC, Munir KM, Loh CH, Tu YK. Risk of serious hypoglycaemia in patients with atrial fibrillation and diabetes concurrently taking antidiabetic drugs and oral anticoagulants: A nationwide cohort study. *European Heart Journal - Cardiovascular Pharmacotherapy*. 2023;9:427-434

Diabetes-Related Complications and Mortality in Patients With Atrial Fibrillation Receiving Different Oral Anticoagulants

A Nationwide Analysis

Huei-Kai Huang, MD; Peter Pin-Sung Liu, MS; Shu-Man Lin, MD; Jin-Yi Hsu, MD; Jih-I Yeh, MD, PhD; Edward Chia-Cheng Lai, PhD; Carol Chiung-Hui Peng, MD; Kashif M. Munir, MD; Ching-Hui Loh, MD, DrPH; and Yu-Kang Tu, DDS, MSc, PhD

Background: Evidence about the association between types of oral anticoagulants and hazards of diabetes complications is limited in patients with atrial fibrillation (AF) and diabetes mellitus (DM).

Objective: To compare the hazards of diabetes complications and mortality between patients with AF and DM receiving non-vitamin K antagonist oral anticoagulants (NOACs) and those receiving warfarin.

Design: A retrospective cohort study.

Setting: Nationwide data obtained from Taiwan's National Health Insurance Research Database.

Patients: Patients with AF and DM receiving NOACs or warfarin between 2012 and 2017 in Taiwan were enrolled. Treatment groups were determined by patients' first initiation of oral anticoagulants.

Measurements: Hazards of diabetes complications (macrovascular complications, microvascular complications, and glycemic emergency) and mortality in the NOAC and warfarin users were investigated with a target trial design. Cause-specific Cox proportional hazards models were used to estimate hazard ratios (HRs). Propensity score methods with stabilized inverse probability of treatment weighting

were applied to balance potential confounders between treatment groups.

Results: In total, 19 909 NOAC users and 10 300 warfarin users were included. Patients receiving NOACs had significantly lower hazards of developing macrovascular complications (HR, 0.84 [95% CI, 0.78 to 0.91]; $P < 0.001$), microvascular complications (HR, 0.79 [CI, 0.73 to 0.85]; $P < 0.001$), glycemic emergency (HR, 0.91 [CI, 0.83 to 0.99]; $P = 0.043$), and mortality (HR, 0.78 [CI, 0.75 to 0.82]; $P < 0.001$) than those receiving warfarin. Analyses with propensity score matching showed similar results. Several sensitivity analyses further supported the robustness of our findings.

Limitation: The claims-based data did not allow for detailed data on patients' lifestyles and laboratory examinations to be obtained.

Conclusion: Non-vitamin K antagonist oral anticoagulants were associated with lower hazards of diabetes complications and mortality than warfarin in patients with AF and DM.

Primary Funding Source: Hualien Tzu Chi Hospital.

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For author, article, and disclosure information, see end of text.
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Atrial fibrillation (AF), the most common and clinically significant cardiac arrhythmia, is an important public health problem in the aging population worldwide (1, 2). Patients with AF are more likely to have stroke in their lifetime; thus, many of them receive long-term oral anticoagulants for stroke prevention (3). Warfarin blocks the function of the vitamin K epoxide reductase complex in the liver and has been a cornerstone oral anticoagulant for preventing stroke in patients with AF for decades. Non-vitamin K antagonist oral anticoagulants (NOACs) have been approved as another choice of oral anticoagulants for stroke prevention and have shown equal or superior efficacy and safety compared with warfarin (4, 5).

Diabetes mellitus (DM) is one of the most common chronic medical conditions and is an important risk factor for AF. In patients with AF, the presence of diabetes, especially poor glycemic status, increases the stroke, thromboembolism,

and cardiovascular mortality risks (6-9); thus, glycemic control is critical to improving clinical prognoses in patients with AF and DM. Evidence suggests that vitamin K plays a role in improving insulin sensitivity and glucose tolerance by regulating vitamin K-dependent proteins, anti-inflammatory signaling, and lipid metabolism (10-12). However, warfarin interferes with vitamin K function, whereas NOACs act by mechanisms independent of vitamin K. Therefore, NOAC or warfarin use may yield different effects on glycemic control and diabetes-related complications.

Real-world population-based studies have suggested that NOACs are associated with a lower risk for incident diabetes than warfarin in patients with AF and without DM (13, 14). However, the influence of different oral anticoagulants on the risk for diabetes-related complications is not completely understood and is a critical issue in improving prognoses in patients with AF and DM requiring oral anticoagulant treatment. Therefore, we aimed to investigate the hazards of diabetes complications (including macrovascular complications, microvascular complications, and glycemic emergency) and mortality in patients with AF and DM receiving NOACs or warfarin.

See also:

Web-Only
Supplement

METHODS

Data Sources

This nationwide retrospective cohort study used data from Taiwan's National Health Insurance Research Database (NHIRD), which comprises health care data of approximately 23.6 million persons, almost Taiwan's entire population. The details of NHIRD have been reported elsewhere (15, 16), and a summary is provided in **Supplement Note 1** (available at [Annals.org](#)). A brief description of how data were obtained and curated from NHIRD can be found in **Supplement Note 2** (available at [Annals.org](#)). The Research Ethics Committee of Hualien Tzu Chi Hospital approved our study (REC No: IRB107-152-C), and informed consent was waived.

Study Population and Exposure

We pursued a target trial design to emulate a randomized controlled trial with observational data (**Supplement Table 1**, available at [Annals.org](#)) (17–19). We initially retrieved data on adult patients aged 20 years or older, with diagnoses of both AF and DM, who received oral anticoagulants between 2012 and 2017. The AF diagnosis was defined by International Classification of Diseases, Ninth Revision, Clinical Modification code 427.31 or International Classification of Diseases, 10th Revision, Clinical Modification codes I48.0, I48.1, I48.2, and I48.91, and the diabetes diagnosis by International Classification of Diseases, Ninth Revision, Clinical Modification code 250 or International Classification of Diseases, 10th Revision, Clinical Modification codes E08–E13, applied at least once in an inpatient service or twice in an outpatient service. Patients were divided into NOAC and warfarin groups on the basis of their first prescription of the oral anticoagulant type. “Time zero” (index date) was defined as the time of initiating oral anticoagulant treatment (the first day of receiving NOAC or warfarin); follow-up began on the index date. This as-started design (analog of intention to treat) emulated a target trial to strengthen causal inference from observational data (17).

We excluded patients initially diagnosed with AF or DM after the index date. Patients receiving any oral anticoagulants in 2011 were also excluded to increase the likelihood of capturing those with newly initiated oral anticoagulant treatment since 2012 (when NOACs were introduced in Taiwan). Patients with rheumatic heart disease, congenital heart disease, valve replacement surgery, or end-stage renal disease (ESRD) at baseline were excluded because they were more likely to receive warfarin than NOACs, giving rise to the possible bias of confounding by indication (20). Patients with ESRD were defined as those who had received a catastrophic illness certificate of ESRD. Patients with index dates in 2018 were excluded to ensure at least 1 year of follow-up.

Study Outcomes and Follow-up

Four primary outcomes were evaluated: macrovascular complications (composite outcome of coronary artery disease, stroke, and peripheral vascular disease), microvascular complications (composite outcome of retinopathy, neuropathy, receiving dialysis, and lower extremity amputations), glycemic emergency (composite outcome

of diabetic ketoacidosis, hyperosmolar hyperglycemic state, and hypoglycemia), and all-cause mortality. Secondary outcomes included individual components of the composite outcomes and the cardiovascular and noncardiovascular mortality. Outcome events were defined as diagnoses of the outcomes or corresponding procedures provided during the follow-up period; the diagnostic or procedure codes used are summarized in **Supplement Table 2** (available at [Annals.org](#)). We defined specific outcome events (coronary artery disease, stroke, peripheral vascular disease, diabetic retinopathy, and diabetic neuropathy) as conditions diagnosed on an inpatient basis or at least 3 times on an outpatient basis; the date of the first-time diagnosis was assigned as the event date. The outcome events for diabetic ketoacidosis, hyperosmolar hyperglycemic state, and hypoglycemia were identified by using any diagnosis made only in inpatient service or the emergency department. Information on death was obtained by cross-referencing with the National Register of Deaths. Patients with an outcome event before their index dates were excluded from the analyses for that corresponding outcome. Persons were followed from the index date until the occurrence of the corresponding outcome, death, or 31 December 2018 (the last date of our database), whichever came first. In each outcome analysis, patients were followed up until that outcome was observed; patients were not censored if other outcomes (rather than the corresponding outcome) occurred earlier.

Covariates and Confounders

Patients' baseline basic and clinical information were obtained from the database. Medical conditions diagnosed at least once in inpatient or twice in outpatient services within the year before the index date were considered preexisting comorbidities. We calculated the Charlson Comorbidity Index to quantify the overall comorbidity status (21). We calculated CHA₂DS₂-VASc score, which is commonly used to predict stroke and thromboembolic event risk in clinical practice (22, 23). Baseline medications, which were considered potential confounders, were retrieved; a drug prescribed for at least 30 days within the year before the index date was defined as a baseline medication. We identified each antidiabetic medication type used at baseline on the basis of the drugs prescribed within 1 month before the index date. The medical specialty of the physician prescribing oral anticoagulants, the hospital level where the administration of oral anticoagulants was initiated, index year, and monthly income were included as covariates. Monthly income was assessed on the basis of the income-related insurance premiums. The management for missing data and the specifications for the covariates are described in **Supplement Note 3** (available at [Annals.org](#)).

Subgroup and Stratified Analyses

On the basis of the first prescribed type of NOAC, we further subclassified NOAC users into 4 subgroups (dabigatran, rivaroxaban, apixaban, and edoxaban) and compared each NOAC subgroup with warfarin users to estimate the relative effect of each NOAC on diabetes

complications and mortality hazards. In addition, we did a stratified analysis according to age (<65 and ≥65 years), sex, and hospital level to investigate the moderating effects of these factors on the comparisons between NOACs and warfarin.

Propensity Score Methods

We used 2 propensity score methods, namely stabilized inverse probability of treatment weighting (IPTW) and propensity score matching, to reduce the systematic differences in baseline characteristics between NOAC and warfarin groups (24–26). The analyses with stabilized IPTW estimated the average treatment effect in the whole population (27); those with propensity score matching estimated the average treatment effect among the treated population (24). The details of and reasons why we used propensity score methods are described in **Supplement Notes 4** and **5** (available at [Annals.org](https://annals.org)).

Statistical Analyses

The difference in baseline characteristics was evaluated using standardized mean difference, with a value of less than 0.1 indicating negligible difference (**Supplement Note 6**, available at [Annals.org](https://annals.org)). We used cause-specific Cox proportional hazards models, with deaths treated as censoring events, to estimate cumulative incidences and cause-specific hazard ratios (HRs) for each outcome (except for all-cause mortality) in our main analyses (28). In the analysis of all-cause mortality, the cumulative incidences and HRs were estimated by Cox proportional hazards models. We also used Fine-Gray subdistribution hazards models, with death treated as a competing risk, to estimate cumulative incidences and subdistribution HRs (except for the analysis of all-cause mortality where no competing risk existed) (29). The differences of cumulative incidences with 95% CI between treatment groups were reported. When estimating the HRs, we included shared frailty into the models to account for potential cluster effect and variations among hospitals or clinics (30, 31); the shared frailty estimates the cluster random effect because persons within the same hospital or clinic are not independent. The proportional hazards assumptions were evaluated before analyses, and no violation was identified. A 2-tailed probability value less than 0.05 was considered statistically significant. Data management and statistical analyses were done using SAS, version 9.4 (SAS Institute); R, version 4.1.1 (R Foundation for Statistical Computing); and Stata, version 15 (StataCorp) (details are shown in the **Supplement** for statistical code, available at [Annals.org](https://annals.org)).

Sensitivity Analyses

We did various sensitivity analyses to assess the robustness of our study findings as follows. First, we applied an on-treatment design (analog of per protocol) as a sensitivity analysis, which could consider treatment adherence during follow-up (17). In the on-treatment design, censoring also occurred at the time when patients switched the oral anticoagulant or 90 days after discontinuing index oral anticoagulant treatment. Second, we did a sensitivity analysis limited to patients receiving the index oral anticoagulant (the initially prescribed oral anticoagulant) with a high

medication possession ratio (≥80%) during follow-up. The medication possession ratio was calculated for each patient by dividing the number of days a patient received oral anticoagulants by their follow-up in days (32).

We did additional sensitivity analyses that excluded patients with any chronic kidney disease diagnosis at baseline, that applied propensity score fine stratification with 50 strata (estimating the average treatment effect in the whole population), and that used multivariable regression models to obtain adjusted HRs without applying propensity score methods. We also calculated E-values to assess how strong an unmeasured confounder would have to be to disregard an observed treatment-outcome relationship (33). Furthermore, we used 3 negative control outcomes (occurrence of cancer, chronic obstructive pulmonary disease, and suicide), for which no causal effect is expected, to indirectly evaluate whether potential unmeasured confounders existed (34).

Role of the Funding Source

The funder had no role in study design, data collection, data analysis, data interpretation, writing of the report, decision to submit for publication, or approval of the manuscript for publication.

RESULTS

Patient Characteristics

Our original study population contained 30 219 patients after applying the inclusion and exclusion criteria (**Supplement Table 3**, available at [Annals.org](https://annals.org)). We further used 2 propensity score methods to generate the population for analyses. We constructed a pseudopopulation that contained 19 909 NOAC users and 10 300 warfarin users after stabilized IPTW. When the propensity score-matching method was used, 7677 patients each were included in the NOAC and the warfarin groups (**Table 1**). The patient selection flowchart is shown in the **Appendix Figure** (available at [Annals.org](https://annals.org)). The baseline characteristics of patients for analyses of macrovascular complications, microvascular complications, and glycemic emergency are presented in **Supplement Tables 4** to **6** (available at [Annals.org](https://annals.org)), respectively. All patients in our study population were included in the analysis for mortality, and their baseline characteristics are shown in **Table 1**. The overall mean follow-up duration was 2.9 years. The mean age was 73.8 years; female patients accounted for 45.8% of all patients. Of note, all baseline characteristics were appropriately balanced between the treatment groups after both propensity score methods were applied (**Table 1** and **Supplement Tables 4** to **6**). The level of the hospital, where the oral anticoagulant was initially prescribed, between NOAC and warfarin users was also balanced among each index year period (**Supplement Table 7**, available at [Annals.org](https://annals.org)).

Cumulative Incidences of Diabetes Complications and Mortality

We found lower cumulative incidences of macrovascular complication, microvascular complication, glycemic emergency, and mortality in NOAC users than warfarin users after stabilized IPTW (**Figure**). The differences of

Table 1. Baseline Characteristics of Overall NOAC and Warfarin Users in the Population After Inverse Probability of Treatment Weighting or Propensity Score Matching

Characteristic	Population After IPTW*			Population After Propensity Score Matching*		
	NOAC (n = 19 909)	Warfarin (n = 10 300)	SMD†	NOAC (n = 7677)	Warfarin (n = 7677)	SMD†
Mean age (SD), y	73.8 (10.0)	73.9 (10.8)	0.011	72.9 (10.0)	72.8 (10.8)	0.003
Sex, %						
Male	54.3	54.3	0.002	54.8	55.2	0.008
Female	45.7	45.7	0.002	45.2	44.8	0.008
Income level, %						
Financially dependent	28.7	28.8	0.002	28.1	27.9	0.004
15 840–29 999 NTD	46.8	47.2	0.008	47.0	46.7	0.005
30 000–44 999 NTD	13.5	13.3	0.007	14.3	14.5	0.004
≥45 000 NTD	11.0	10.7	0.009	10.6	10.9	0.010
Mean Charlson Comorbidity Index (SD)‡	2.9 (1.9)	2.9 (1.9)	0.004	2.9 (1.9)	2.8 (1.9)	0.015
Mean CHA₂DS₂-VASc score (SD)	4.4 (1.6)	4.4 (1.8)	0.009	4.3 (1.6)	4.2 (1.8)	0.011
Comorbidities, %						
Hypertension	77.8	77.9	0.003	77.1	77.2	0.003
Coronary artery disease	35.3	35.0	0.000	35.1	35.8	0.000
Congestive heart failure	27.8	28.4	0.015	28.6	28.2	0.008
Chronic obstructive pulmonary disease	14.2	14.5	0.008	14.6	14.1	0.014
Chronic kidney disease	14.2	14.2	0.001	15.7	15.1	0.017
Liver cirrhosis	5.5	5.7	0.006	6.5	6.4	0.005
Hyperlipidemia	36.9	36.7	0.004	36.3	36.7	0.009
Stroke	31.1	31.0	0.000	29.6	29.1	0.000
Rheumatoid arthritis	0.7	0.7	0.003	0.8	0.8	0.001
Gout	10.4	10.4	0.001	10.9	10.8	0.002
Dementia	6.4	6.1	0.012	5.8	5.7	0.006
Cancer	8.2	8.1	0.002	8.1	7.8	0.009
Medication use, %						
Statins	36.6	36.6	0.002	35.4	35.2	0.005
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	63.1	63.1	0.000	63.0	62.3	0.015
β-blockers	46.6	46.6	0.001	47.4	47.0	0.009
Calcium-channel blockers	46.9	47.3	0.009	47.7	47.5	0.004
Diuretics	32.8	33.2	0.009	35.1	34.7	0.010
Nonsteroidal anti-inflammatory drugs	34.4	34.7	0.008	34.1	34.4	0.007
Corticosteroids	9.0	9.2	0.007	9.4	9.1	0.010
Antipsychotics	5.2	5.3	0.005	5.2	5.0	0.012
Proton-pump inhibitors	8.1	7.8	0.008	8.4	8.4	0.001
Baseline diabetes medications, %						
Metformin	48.6	48.4	0.005	46.2	46.7	0.009
Sulfonylurea	34.8	35.1	0.006	36.0	35.9	0.002
Meglitinide	7.0	6.8	0.009	7.3	7.1	0.007
α-glucosidase inhibitors	8.9	8.9	0.001	9.0	9.1	0.005
Thiazolidinediones	4.7	4.9	0.010	4.6	4.6	0.001
Dipeptidyl peptidase-4 inhibitors	27.6	27.7	0.001	26.5	26.2	0.006
Sodium-glucose cotransporter-2 inhibitors	0.8	0.9	0.005	0.3	0.3	0.002
Glucagon-like peptide-1	0.1	0.1	0.005	0.1	0.1	0.005
Insulin	12.3	12.5	0.006	13.2	12.8	0.011
Number of diabetes medications, %						
Without medications	30.8	28.7	0.046	31.6	29.6	0.042
1 type	24.2	26.5	0.054	24.0	25.9	0.045
2 types	22.6	23.2	0.013	22.2	23.4	0.029
≥3 types	22.4	21.7	0.019	22.3	21.0	0.030
Index year, %						
2012–2013	22.7	22.7	0.000	28.2	28.2	0.000
2014–2015	35.5	36.0	0.011	45.6	45.6	0.000
2016–2017	41.8	41.2	0.011	26.2	26.2	0.000

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Table 1—Continued

Characteristic	Population After IPTW*			Population After Propensity Score Matching*		
	NOAC (n = 19 909)	Warfarin (n = 10 300)	SMD†	NOAC (n = 7677)	Warfarin (n = 7677)	SMD†
Hospital level of oral anticoagulant initiation, %						
Medical center	37.4	36.7	0.014	35.3	35.5	0.003
Regional hospital	44.8	45.7	0.017	45.5	45.1	0.009
District hospital or clinic	17.8	17.6	0.004	19.2	19.5	0.008
Physician specialty, %						
Cardiologist	65.4	65.4	0.001	65.6	65.7	0.002
Neurologist	15.3	14.9	0.011	13.4	12.8	0.016
Others	19.3	19.7	0.011	21.0	21.5	0.011

IPTW = inverse probability of treatment weighting; NOAC = non-vitamin K antagonist oral anticoagulant; NTD = New Taiwan dollar; SMD = standardized mean difference.

* All of the covariates listed in the table were used to calculate the propensity score for weighting or matching.

† A standardized mean difference of <0.1 indicates a negligible difference.

‡ Calculated without including scores for age.

cumulative incidence with CI between treatment groups at each year since treatment commencement are provided in **Supplement Table 8** (available at [Annals.org](#)); the curves for differences of cumulative incidence are shown in **Supplement Figure 1** (available at [Annals.org](#)). The analyses after propensity score matching showed similar results.

Hazards of Diabetes Complications and Mortality

In the analyses with stabilized IPTW, NOAC users showed significantly lower hazards of developing macrovascular complications (HR, 0.84 [95% CI, 0.78 to 0.91]; $P < 0.001$), microvascular complications (HR, 0.79 [CI, 0.73 to 0.85]; $P < 0.001$), glycemic emergency (HR, 0.91 [CI, 0.83 to 0.99]; $P = 0.043$), and mortality (HR, 0.78 [CI, 0.75 to 0.82]; $P < 0.001$) than warfarin users (**Table 2**). In the analyses with propensity score matching, similarly lower hazards of macrovascular complications, microvascular complications, and mortality were seen in patients receiving NOACs; the analysis for glycemic emergency was not statistically significant.

The analyses for individual NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) showed a similar trend of lower complication and mortality hazards in NOAC users than in warfarin users (**Supplement Table 9**, available at [Annals.org](#)).

In the analyses for individual complications, significantly lower hazards of coronary artery disease, stroke, dialysis, lower extremity amputation, and both cardiovascular and noncardiovascular mortality were seen in NOAC users than in warfarin users (**Appendix Table 1**, available at [Annals.org](#)).

Results of Analyses Stratified by Age, Sex, and Hospital Level

In the analyses with stabilized IPTW, generally, a similar trend for lower hazards of diabetes complications and mortality in NOAC users was seen in each age, sex, and hospital level subgroup. However, all of the analyses in the subgroup of age less than 65 years did not reach statistical significance (**Supplement Table 10**, available at [Annals.org](#)). Analyses with propensity score matching showed similar findings.

Results of Sensitivity Analyses

In the sensitivity analysis applying on-treatment design, we still saw significantly lower hazards of macrovascular complications (HR, 0.83 [CI, 0.75 to 0.92]; $P < 0.001$), microvascular complications (HR, 0.68 [CI, 0.61 to 0.75]; $P < 0.001$), glycemic emergency (HR, 0.81 [CI, 0.71 to 0.93]; $P = 0.003$), and mortality (HR, 0.63 [CI, 0.59 to 0.68]; $P < 0.001$) for NOAC users compared with warfarin users. Furthermore, a significant association was seen between NOAC and lower complication hazards for many individual outcomes (**Appendix Table 2**, available at [Annals.org](#)). In the sensitivity analysis limited to patients with a high medication possession ratio ($\geq 80\%$) for the index oral anticoagulant, a larger effect size with more significant results was seen in analyses for most composite and individual outcomes, including retinopathy and neuropathy (**Appendix Table 2**). The other sensitivity analyses (for example, excluding patients with chronic kidney diseases at baseline, applying propensity score fine stratification, and analyses with multivariable regression model) also showed similar findings to that of our primary analyses (**Supplement Tables 11 and 12**, available at [Annals.org](#)).

The E-values for point estimates in the as-started analysis with stabilized IPTW for macrovascular complications, microvascular complications, glycemic emergency, and mortality were 1.51, 1.63, 1.43, and 1.66, respectively. The E-values based on the on-treatment analysis were generally larger: 1.53, 1.94, 1.77, and 2.1, respectively, for the 4 primary outcomes.

Regarding the analyses for negative control outcomes (cancer, chronic obstructive pulmonary disease, and suicide), none of the outcomes showed significant association with NOAC treatment (**Supplement Table 13**, available at [Annals.org](#)).

Analyses by Fine-Gray Subdistribution Hazards Model

Generally, the subdistribution HRs showed a similar trend of lower hazards of diabetes complications in NOAC users than warfarin users (**Supplement Tables 14 and 15**, available at [Annals.org](#)). The cumulative incidence curves

estimated by Fine-Gray subdistribution hazards models also showed compatible findings (Supplement Figure 2, available at [Annals.org](#)).

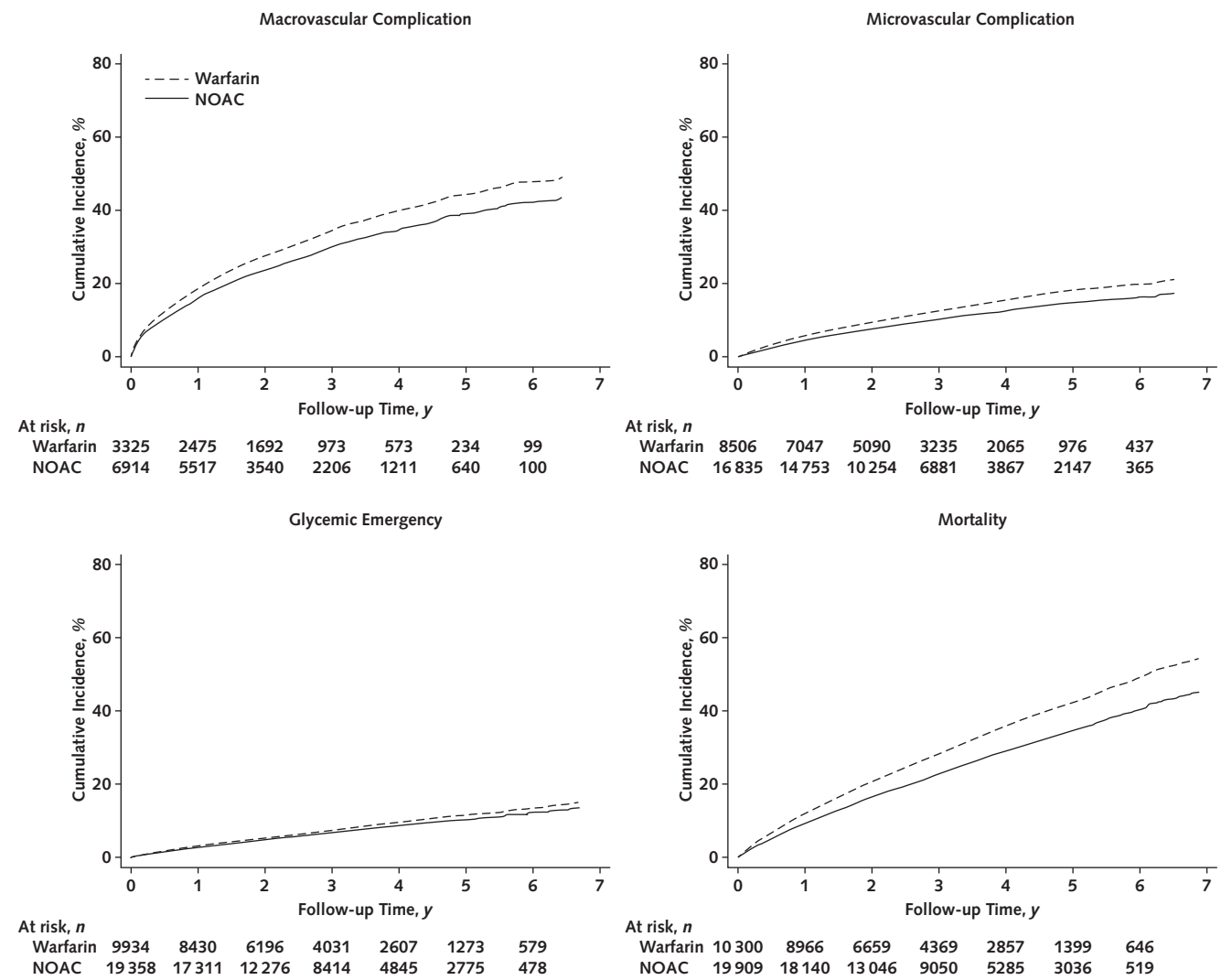
DISCUSSION

In this nationwide retrospective cohort study, patients with AF and DM and without ESRD receiving NOACs had lower hazards of developing diabetes complications and mortality than those receiving warfarin. The sensitivity analyses that applied on-treatment analysis or were limited to those with a high medication possession ratio also supported our study findings.

Our study could not determine the exact mechanisms of the better outcomes in NOAC users; however, several factors may explain our findings. Previous studies indicated that vitamin K could benefit insulin sensitivity

and glucose tolerance and suppress the oxidative stress and inflammatory responses by various mechanisms (10–12). Thus, antagonization of vitamin K by warfarin may lead to impaired insulin sensitivity and glucose tolerance and increase the risk for diabetes complications. These hypotheses are additionally supported by 2 recent real-world cohort studies reporting that NOACs were associated with a lower hazard of newly developed DM than warfarin in patients with AF who did not have DM (13, 14). In addition, some preclinical studies have suggested that there are potential effects of direct thrombin or factor Xa inhibitors on anti-inflammatory activities and atherosclerotic plaque stabilization (35). The difference in anticoagulation mechanism between NOAC and warfarin could also explain the lower hazard of macrovascular complications with NOAC.

Figure. The cumulative incidence curves of macrovascular complication, microvascular complication, and glycemic emergency, estimated by cause-specific Cox proportional hazards model, and the mortality curve, estimated by Cox proportional hazards model, for NOAC and warfarin users after stabilized inverse probability of treatment weighting.



NOAC = non-vitamin K antagonist oral anticoagulant.

Table 2. Hazards of Diabetes Complications and Mortality in Patients With Atrial Fibrillation and Diabetes Receiving NOACs and Those Receiving Warfarin

Outcome*	Population After IPTW†				Population After Propensity Score Matching			
	Patients, n	Incidence Rate‡	HR§ (95% CI)	P Value	Patients, n	Incidence Rate‡	HR§ (95% CI)	P Value
Macrovascular complication				<0.001				0.022
NOAC	6914	120.7	0.84 (0.78-0.91)		2594	125.2	0.89 (0.81-0.98)	
Warfarin	3325	143.8	1.00 (Reference)		2594	139.1	1.00 (Reference)	
Microvascular complication				<0.001				<0.001
NOAC	16 835	36.1	0.79 (0.73-0.85)		6403	36.8	0.83 (0.75-0.92)	
Warfarin	8506	44.8	1.00 (Reference)		6403	43.8	1.00 (Reference)	
Glycemic emergency				0.043				0.60
NOAC	19 358	23.5	0.91 (0.83-0.99)		7426	23.1	0.97 (0.86-1.09)	
Warfarin	9934	26.3	1.00 (Reference)		7426	23.9	1.00 (Reference)	
Mortality				<0.001				<0.001
NOAC	19 909	87.4	0.78 (0.75-0.82)		7677	84.5	0.81 (0.76-0.86)	
Warfarin	10 300	113.7	1.00 (Reference)		7677	104.8	1.00 (Reference)	

HR = hazard ratio; IPTW = inverse probability of treatment weighting; NOAC = non-vitamin K antagonist oral anticoagulant.
* In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.
† A pseudopopulation constructed by stabilized IPTW for analyses.
‡ Per 1000 person-years.
§ The HR is calculated by a cause-specific Cox proportional hazards model with shared frailty model considering cluster-specific random effects of the individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

There were a considerable number of warfarin users (46%) changing their oral anticoagulant to NOAC during the follow-up. Thus, our as-started analysis may have underestimated the difference between NOAC and warfarin use. Nevertheless, such a conservative approach still showed a significantly lower hazard for composite complication outcomes and mortality in NOAC users than in warfarin users. Of note, our sensitivity analyses that applied on-treatment analysis and were limited to patients with a medication possession ratio 80% or greater generally showed more significant results with a larger effect size than the main analyses did. In addition, the E-values were not small for our primary outcomes (at least 1.5), and none of the negative control outcomes showed significant association with NOAC treatment. These sensitivity analyses support the conclusion that the difference in hazards of diabetes-related complications and mortality between NOAC and warfarin is robust.

Our study showed a significantly lower hazard of macrovascular complications in NOAC users, in line with previous studies indicating a lower risk for stroke or systemic embolism in NOAC users (7). To date, only a few real-world studies have investigated renal outcomes with different oral anticoagulants, specifically in patients with AF and DM (36, 37). Previous studies showed a significant decrease in the risk for declining estimated glomerular filtration rate and ESRD in patients with AF and DM receiving NOACs than in those receiving warfarin (36, 37). Our study also found that NOAC was significantly associated with a lower dialysis hazard in both the main analysis and the sensitivity analysis, excluding patients with chronic kidney diseases at baseline. Furthermore, evidence comparing the risk for retinopathy and neuropathy among patients with DM receiving different oral anticoagulants is scarce. Our study addresses the current knowledge gap and shows a significantly lower hazard of

retinopathy and neuropathy in NOAC users with a high medication possession ratio. Previous evidence has suggested that warfarin may increase the risk for serious hypoglycemic events in patients receiving specific anti-diabetic drugs (for example, sulfonylureas) because of potential drug-drug interaction (38, 39). Our study suggests that NOAC use may lead to a lower hypoglycemia hazard than warfarin in the on-treatment analysis. However, future studies are needed to evaluate whether this benefit of NOAC varies between different concurrent antidiabetic medications. Finally, we saw an overall lower mortality hazard associated with NOAC in patients with AF and DM, which is consistent with previous studies evaluating the general and older AF population (40, 41).

The main strengths of this study were the large-scale nationwide analysis using real-world data, the novel findings that comprehensively showed the association between different oral anticoagulants and hazards of diabetic complications, and the study robustness that was supported by sensitivity analyses. However, some limitations exist. First, we could not obtain data on patients' lifestyle, substance use, body mass index, and detailed laboratory results (for example, blood glucose level, lipid profile, and renal function). Patients' adherence, medication dosing, and the adequacy of comorbidity management could not be accessed. Although propensity score methods were used to eliminate potential confounding effects, unknown or unmeasured patient- and provider-level confounders may still exist. Second, because the international normalized ratio data were unavailable, our study could not evaluate or adjust for the influence of potential subtherapeutic international normalized ratios on stroke and mortality hazard in warfarin users. For patients changing oral anticoagulant choice during follow-up, we could not determine the exact reasons for treatment change. Further studies are needed to address

these issues. Third, given the patient anonymity policy of NHIRD, we used diagnostic and procedure codes to identify study outcomes rather than directly access patients' medical records to verify diagnostic accuracy. Also, some patients with those outcome conditions may not have sought medical assistance or not have been recorded in the medical claim system. Nevertheless, we feel that the underreporting of outcome events or the misclassification errors are expected to occur nondifferentially in the NOAC and warfarin groups and thus biased the estimates toward the null (42, 43). Therefore, the exact differences between NOAC and warfarin use regarding diabetes complications may be greater than what we observed. Fourth, our study population mainly consisted of old and sick patients owing to our inclusion criteria, reflecting real-world scenarios. In the subgroup of younger patients (age <65 years), the sample size was relatively small, and a non-significant association between NOAC and study outcomes was found. Whether our findings in patients who are older and sick could be extrapolated to a younger, less sick population warrants further research. Fifth, our study used data from NHIRD in Taiwan, and more studies using databases of other regions or countries are required to validate our findings.

In conclusion, this nationwide cohort study showed that, compared with warfarin use, NOAC use was associated with lower hazards of diabetes-related complications and mortality among patients with AF and DM and without ESRD. Therefore, NOAC may be a better therapeutic choice than warfarin for decreasing these complications and mortality in patients with AF and DM requiring oral anticoagulant treatment. Future prospective studies and randomized controlled trials are necessary to determine the causal relations.

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Appendix Table 1. Hazards of Individual Diabetes Complications in Patients With Atrial Fibrillation and Diabetes Receiving NOACs and Those Receiving Warfarin

Outcome*	Population After IPTW†				Population After Propensity Score Matching			
	Patients, n	Incidence Rate‡	HR§ (95% CI)	P Value	Patients, n	Incidence Rate‡	HR§ (95% CI)	P Value
Coronary artery disease				0.008				0.056
NOAC	11 532	72.0	0.90 (0.84–0.97)		4251	69.3	0.91 (0.83–1.00)	
Warfarin	5638	79.6	1.00 (Reference)		4251	75.9	1.00 (Reference)	
Stroke				<0.001				<0.001
NOAC	12 928	49.3	0.80 (0.74–0.87)		5051	48.8	0.80 (0.72–0.89)	
Warfarin	6614	61.0	1.00 (Reference)		5051	59.9	1.00 (Reference)	
Peripheral vascular disease				0.128				0.194
NOAC	18 835	11.7	0.90 (0.78–1.03)		7187	11.8	0.89 (0.76–1.06)	
Warfarin	9599	12.9	1.00 (Reference)		7187	13.0	1.00 (Reference)	
Retinopathy				0.56				0.22
NOAC	18 392	11.7	1.04 (0.91–1.21)		7029	12.4	1.12 (0.94–1.33)	
Warfarin	9372	10.9	1.00 (Reference)		7029	10.9	1.00 (Reference)	
Neuropathy				0.24				0.72
NOAC	18 157	14.5	0.93 (0.82–1.05)		7005	15.1	0.97 (0.83–1.14)	
Warfarin	9366	15.3	1.00 (Reference)		7005	15.3	1.00 (Reference)	
Dialysis				<0.001				<0.001
NOAC	19 852	11.9	0.52 (0.46–0.58)		7614	12.4	0.57 (0.49–0.66)	
Warfarin	10 193	21.9	1.00 (Reference)		7614	20.9	1.00 (Reference)	
Lower-extremity amputation				0.043				0.019
NOAC	19 861	2.3	0.76 (0.58–0.99)		7656	2.1	0.66 (0.46–0.93)	
Warfarin	10 263	2.9	1.00 (Reference)		7656	3.2	1.00 (Reference)	
Diabetic ketoacidosis				0.60				0.34
NOAC	19 842	1.4	0.90 (0.62–1.33)		7645	1.5	0.80 (0.51–1.27)	
Warfarin	10 246	1.4	1.00 (Reference)		7645	1.8	1.00 (Reference)	
Hyperosmolar hyperglycemic state				0.54				0.87
NOAC	19 787	6.2	0.95 (0.79–1.13)		7623	5.7	0.98 (0.78–1.24)	
Warfarin	10 218	6.8	1.00 (Reference)		7623	5.8	1.00 (Reference)	
Hypoglycemia				0.104				0.22
NOAC	19 523	17.5	0.91 (0.82–1.02)		7498	17.0	0.92 (0.80–1.05)	
Warfarin	10 049	19.4	1.00 (Reference)		7498	18.7	1.00 (Reference)	
Cardiovascular death				<0.001				<0.001
NOAC	19 909	31.2	0.71 (0.66–0.76)		7677	30.1	0.72 (0.65–0.79)	
Warfarin	10 300	44.8	1.00 (Reference)		7677	42.2	1.00 (Reference)	
Noncardiovascular death				<0.001				<0.001
NOAC	19 909	56.2	0.83 (0.78–0.88)		7677	54.4	0.87 (0.80–0.93)	
Warfarin	10 300	68.9	1.00 (Reference)		7677	62.6	1.00 (Reference)	

HR = hazard ratio; IPTW = inverse probability of treatment weighting; NOAC = non-vitamin K antagonist oral anticoagulant.

* In each outcome analysis, patients who already experienced the corresponding outcome event before the index date were excluded.

† A pseudopopulation constructed by stabilized IPTW for analyses.

‡ Per 1000 person-years.

§ The HR is calculated by a cause-specific Cox proportional hazards model with shared frailty model considering cluster-specific random effects of the individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Appendix Table 2. Hazard of Diabetes Complications and Mortality Associated With NOAC Versus Warfarin in Sensitivity Analyses That Applied an On-Treatment Design and Was Limited to Patients With a Medication Possession Ratio $\geq 80\%$ During Follow-up

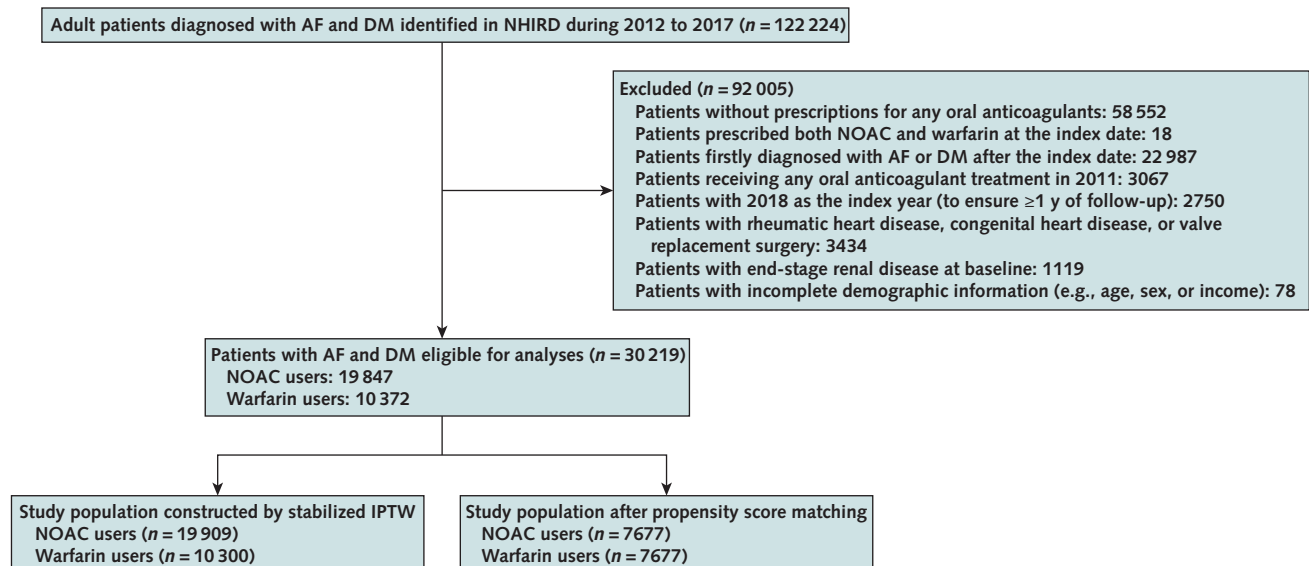
Outcome	Analyses Using On-Treatment Design (Analog of Per Protocol)				Analyses Limited to Patients With Medication Possession Ratio $\geq 80\%$			
	Population After IPTW*		Population After Propensity Score Matching		Population After IPTW*		Population After Propensity Score Matching	
	HR† (95% CI)	P Value	HR† (95% CI)	P Value	HR† (95% CI)	P Value	HR† (95% CI)	P Value
Macrovascular complication	0.83 (0.75–0.92)	<0.001	0.86 (0.76–0.98)	0.021	0.66 (0.59–0.73)	<0.001	0.63 (0.54–0.72)	<0.001
Coronary artery disease	0.87 (0.79–0.96)	0.006	0.90 (0.80–1.03)	0.114	0.62 (0.56–0.69)	<0.001	0.70 (0.61–0.80)	<0.001
Stroke	0.73 (0.65–0.81)	<0.001	0.71 (0.61–0.81)	<0.001	0.56 (0.50–0.63)	<0.001	0.56 (0.47–0.65)	<0.001
Peripheral vascular disease	0.82 (0.68–0.99)	0.035	0.84 (0.66–1.07)	0.158	0.61 (0.50–0.74)	<0.001	0.68 (0.53–0.87)	0.003
Microvascular complication	0.68 (0.61–0.75)	<0.001	0.70 (0.61–0.80)	<0.001	0.56 (0.50–0.63)	<0.001	0.55 (0.47–0.63)	<0.001
Retinopathy	0.88 (0.73–1.05)	0.163	0.96 (0.76–1.20)	0.69	0.62 (0.51–0.75)	<0.001	0.74 (0.59–0.94)	0.012
Neuropathy	0.90 (0.76–1.07)	0.24	0.97 (0.79–1.20)	0.79	0.66 (0.55–0.79)	<0.001	0.69 (0.56–0.87)	0.001
Dialysis	0.31 (0.27–0.37)	<0.001	0.29 (0.23–0.37)	<0.001	0.33 (0.28–0.39)	<0.001	0.30 (0.24–0.38)	<0.001
Lower-extremity amputation	0.56 (0.38–0.82)	0.003	0.53 (0.32–0.88)	0.014	0.48 (0.31–0.73)	0.001	0.73 (0.42–1.28)	0.27
Glycemic emergency	0.81 (0.71–0.93)	0.003	0.85 (0.72–1.01)	0.066	0.62 (0.54–0.71)	<0.001	0.70 (0.58–0.85)	<0.001
Diabetic ketoacidosis	0.76 (0.45–1.27)	0.29	0.79 (0.44–1.43)	0.43	0.66 (0.37–1.18)	0.158	0.69 (0.35–1.37)	0.29
Hyperosmolar hyperglycemic state	0.89 (0.68–1.17)	0.40	0.98 (0.69–1.39)	0.90	0.69 (0.52–0.93)	0.013	0.84 (0.57–1.24)	0.37
Hypoglycemia	0.82 (0.71–0.96)	0.014	0.74 (0.61–0.90)	0.002	0.62 (0.53–0.73)	<0.001	0.70 (0.57–0.86)	0.001
Mortality	0.63 (0.59–0.68)	<0.001	0.64 (0.58–0.70)	<0.001	0.51 (0.47–0.55)	<0.001	0.54 (0.48–0.59)	<0.001
Cardiovascular	0.59 (0.52–0.66)	<0.001	0.55 (0.47–0.64)	<0.001	0.48 (0.43–0.55)	<0.001	0.50 (0.42–0.59)	<0.001
Noncardiovascular	0.67 (0.61–0.73)	<0.001	0.71 (0.63–0.80)	<0.001	0.54 (0.49–0.60)	<0.001	0.58 (0.50–0.66)	<0.001

HR = hazard ratio; IPTW = inverse probability of treatment weighting; NOAC = non-vitamin K antagonist oral anticoagulant.

*A pseudopopulation constructed by stabilized IPTW for analyses.

† The HR is calculated by a cause-specific Cox proportional hazards model with shared frailty model considering cluster-specific random effects of the individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

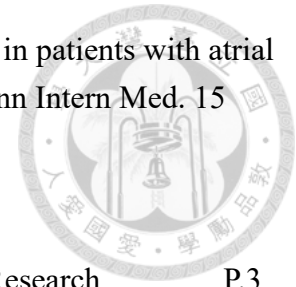
Appendix Figure. Study flow diagram of patient selection.



AF = atrial fibrillation; DM = diabetes mellitus; IPTW = inverse probability of treatment weighting; NHIRD = National Health Insurance Research Database; NOAC = non-vitamin K antagonist oral anticoagulant.

Supplementary Material*

Huang H, Liu PP, Lin S, et al. Diabetes-related complications and mortality in patients with atrial fibrillation receiving different oral anticoagulants. A nationwide analysis. *Ann Intern Med*. 15 February 2022. [Epub ahead of print]. doi:10.7326/M21-3498



A. Supplement Notes

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* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Supplement Note 1: A brief introduction about the National Health Insurance Research Database (NHIRD)

The National Health Insurance program is a mandatory single-payer program administered by the Taiwan government since 1995 and has covered >99% of Taiwan's population.⁽¹⁾ The NHIRD includes the healthcare data of approximately 23.6 million individuals, representing Taiwan's entire population. The NHIRD data include patient demographic information and medical claims for all inpatient, outpatient, and emergency care services. The diagnostic and procedure codes in NHIRD were derived using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes before 2016 and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes since 2016. The NHIRD is maintained by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan; for research purposes, anonymized data has been made available.

Supplement Note 2: How the data was obtained and curated from the nationwide databases

Our study was conducted using the NHIRD with cross-referencing with the National Register of Deaths in Taiwan. The information contained in NHIRD is stored in several different datasheets (such as registry for beneficiaries, ambulatory care claims, inpatient claims, prescriptions dispensed at pharmacies, registry for medical facilities, etc.). Researchers can obtain detailed patient-level information by linking these datasheets with individual personal identification numbers. To access the database, the researchers should submit formal applications to Taiwan's Ministry of Health and Welfare. To ensure the rationality of accessing the data, all applications are reviewed by peer experts before researchers can access any data. To strengthen the protection of health data, the Ministry of Health and Welfare established a Health and Welfare Data Center (HWDC), which is a data repository site centralizing many health-related databases (including NHIRD and the National Register of Deaths) for data management and analyses. The Health and Welfare Data Center manages those databases under tight supervision; all researchers/analysts are required to perform onsite analysis in the Health and Welfare Data Center through a remote connection to the Ministry of Health and Welfare servers. After performing analyses in the Health and Welfare Data Center, the results brought out from the center must be reviewed by data custodians to prevent any disclosure of patient identity; individual-level data are forbidden to be taken out. The details for how researchers can obtain access to the databases and how the databases are curated can be referred to in a previous review article entitled "Taiwan's National Health Insurance Research Database: past and future."⁽²⁾

Supplement Note 3: Dealing with missing data and the specification for the covariates

There are a few patients with missing data of age, sex, or income (n=78, accounting for 0.26% of our study population), and those patients have been excluded from our analyses (shown in the study flow diagram, **Appendix Figure**); no other missing data existed. The age, Charlson comorbidity index, and CHA2DS2-VASc score are specified as continuous variables; the other covariates (sex, income level, comorbidity, medication use, numbers of diabetes medications, index year, hospital level, and physician specialty) are specified as categorical variables.

Supplement Note 4: Propensity score methods in our main analyses

The propensity score was calculated to estimate the probability of receiving NOAC treatment for each patient by a logistic regression model including all covariates in Table 1. We applied two propensity score methods in our main analyses: stabilized inverse probability of treatment weighting (IPTW) and propensity score matching. The IPTW help us construct a pseudo-population with balanced patient baseline characteristics between treatment groups; the stabilization for weights avoided the inaccurate or unstable weights for subjects with a very low probability of receiving the treatment received and has been suggested in previous literature.(3, 4) The propensity score matching was conducted using the 1:1 nearest-neighbor matching algorithm without replacement; a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score was adopted. Previous studies have suggested that such a setting for matching could minimize the mean squared error of the estimated treatment effect and eliminate at least 98% of the bias in the crude estimator in several scenarios.(4, 5) To ensure that the index year was similar between the NOAC and warfarin groups, matching was conducted within the stratum of the index year. For each study outcome, stabilized IPTW or propensity score matching was performed to generate a comparison set before data analyses.

Supplement Note 5: Reasons for applying propensity score methods

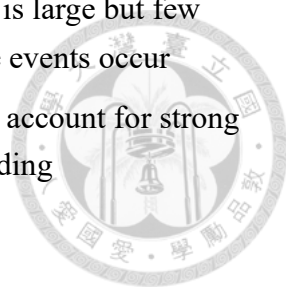
We chose propensity score methods (including stabilized IPTW and propensity score matching), rather than regression-based adjustments, to estimate treatment effects in our primary analyses for the following reasons. Propensity score methods allow one to separate the design of the study from the analysis of the study; this is more similar to the procedure in randomized controlled trials. Using propensity score methods (either matching, weighting, or stratification), the study sample could be constructed without any reference to the outcome.(4, 6) Furthermore, propensity score methods can increase flexibility when outcomes (binary or time-to-event in nature) are rare and treatment is

common. Previous literature has suggested that for every covariate entered into a regression model, at least 10 outcome events should be observed. Therefore, insufficient outcome events may preclude adequate regression-based adjustments for all baseline variables in our study, and an overfitting issue may exist (4).

Nevertheless, the application of propensity score matching in our study still has some limitations. The population after matching (nearest neighbor matching within calipers) may not represent the overall new-user population since many unmatched patients were excluded from further analyses; only patients with overlapped propensity scores (within calipers) in the NOAC and warfarin groups were included. This may affect the study's conclusions, which are based only on the selected subset of matched patients (7). However, the parallel analysis with IPTW may complement this drawback since the weighting method did not exclude patients from the analysis. Our matching method estimated the average treatment effect among the treated population (ATT), whereas the IPTW method estimated the average treatment effect in the whole population (ATE). (4, 8). Therefore, both types of target of inference could be estimated in our study.

The following table summarizes a comparison between the propensity score methods and traditional multivariable regression we applied for covariate adjustments.(9)

Analysis method	Justification of using the method	Limitation
IPTW using PS	<ul style="list-style-type: none"> - Retains original cohort population with different weights - Exchangeable weighted population with more balanced covariates for risk comparison - Provides an average treatment effect in the entire study population 	<ul style="list-style-type: none"> - Stabilized weights or weight trimming should be considered to avoid the extreme weights
PS matching	<ul style="list-style-type: none"> - More straightforward and easy to understand for the most readers - Exchangeable matched population with more balanced covariates for risk comparison - Provides an average treatment effect in a condition of all patients being treated with NOAC 	<ul style="list-style-type: none"> - Exclusion of unmatched patients from the analysis
PS fine stratification	<ul style="list-style-type: none"> - Retains original cohort population with different weights within the 	<ul style="list-style-type: none"> - Relatively hard to understand for readers

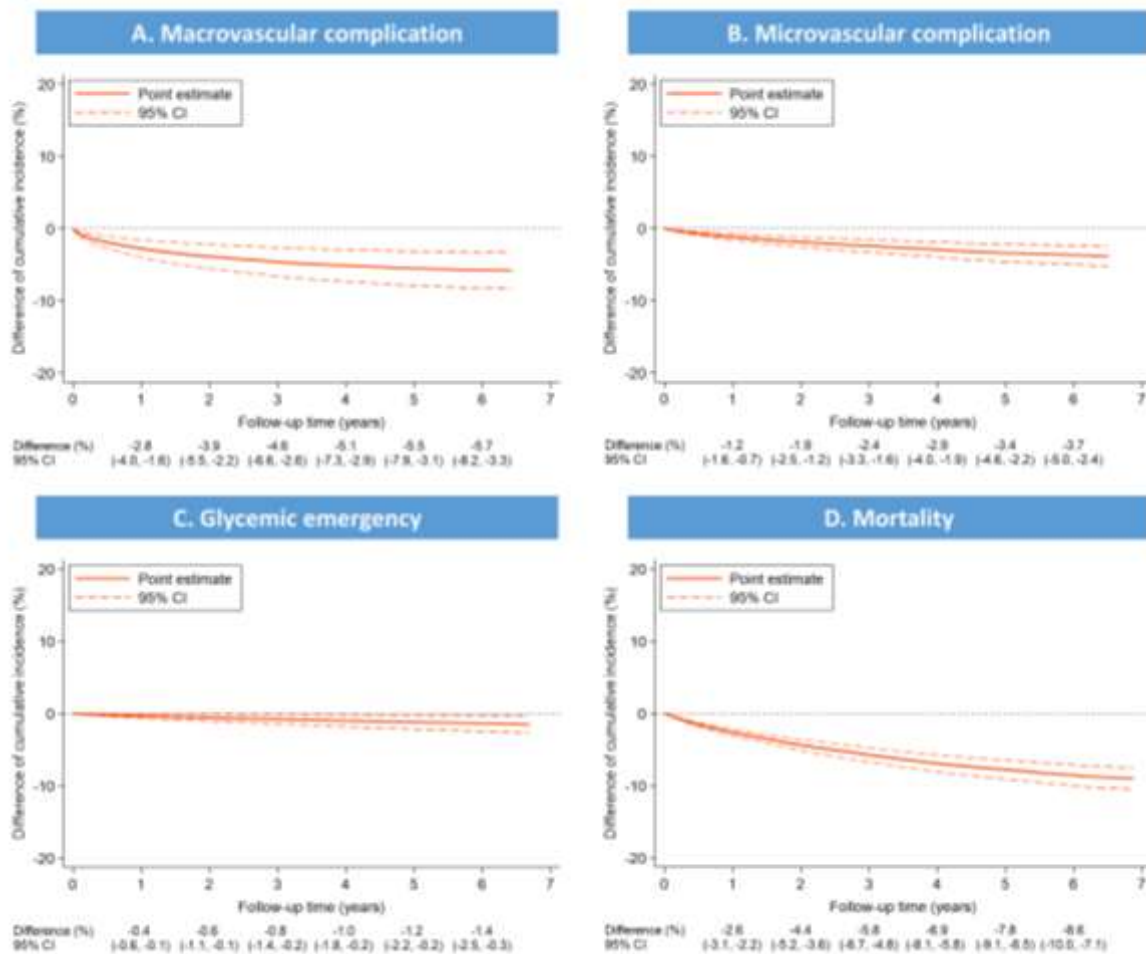


	same strata of propensity score	- Performs less well if the number of strata is large but few outcome events occur
	- Exchangeable weighted population with more balanced covariates for risk comparison	- May not account for strong confounding
	- Provides an average treatment effect in the entire study population	
Traditional multivariable regression	- Retains original cohort population	- May be not suitable when there are many covariates with small sample sizes or few outcome events
	- More commonly used and easy to perform	
	- Easy to understand by most readers	

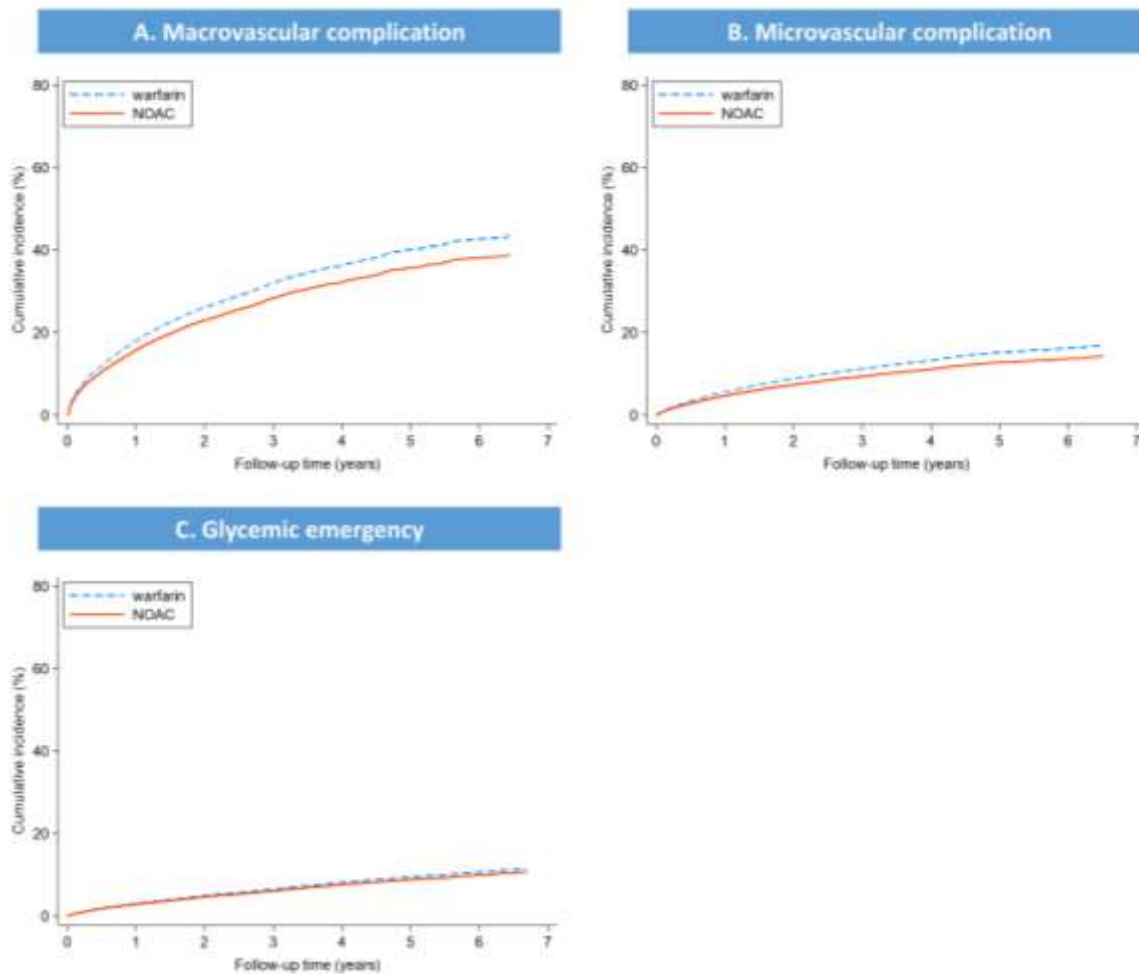
Abbreviations: IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; PS, propensity score

Supplement Note 6: Reasons for reporting standardized mean difference

We reported the standardized mean difference (SMD, rather than p values), which is widely used in propensity score matched/weighted samples to evaluate the balance in baseline covariates between treatment groups. Previous studies have suggested that the SMD is preferred to significance testing of covariates between experimental and control groups since it is not confounded by sample size or the statistical power of the test employed (7, 10, 11).



Supplement Figure 1. The differences of cumulative incidence with 95% CI between NOAC and warfarin groups for (A) macrovascular complication, (B) microvascular complication, and (C) glycemic emergency, estimated by cause-specific Cox proportional hazard model, and (D) mortality, estimated by Cox proportional hazard model, after stabilized inverse probability of treatment weighting.



Supplement Figure 2. The cumulative incidence curves of (A) macrovascular complication, (B) microvascular complication, and (C) glycemic emergency, estimated by Fine-Gray subdistribution hazard models, for NOAC and warfarin users after stabilized inverse probability of treatment weighting.

Supplement Table 1. Specification and emulation of a target trial evaluating the effect of NOAC versus warfarin on hazards of diabetes complications using real-world data from Taiwan's NHIRD

Component	Target trial	Emulated trial using real-world data
Aim	To estimate the relative effect of NOAC versus warfarin on hazards of diabetes complications and mortality in AF patients with DM	Same
Eligibility	Adult patients aged ≥ 20 years previously diagnosed with AF and DM without severe valvular heart disease or end stage renal disease No prior use of oral anticoagulants.	Same, but with the exclusion of patients with a previous diagnosis of rheumatic heart disease, congenital heart disease, or who had received valve replacement surgery, because severe valvular heart disease is hard to define using diagnostic codes in NHIRD directly
Treatment strategies	1. Receiving NOAC treatment 2. Receiving warfarin treatment	Same
Treatment assignment	Eligible patients are randomly assigned to either treatment group (the same probability of treatment assignment between the two groups)	Using propensity score approaches to generate a study population with similar probability of treatment assignment between the two groups.
Follow-up	Follow-up begins at treatment assignment and ends at occurrence of diabetes complications, at death, at loss to follow-up, or on 31 December 2018, whichever occurs first	Same (the assignment and initiation of the treatment occur at the same time in the real-world scenario)
Outcome	Macrovascular complications, microvascular complications, glycemic emergency, and mortality	Same
Causal contrast	Primary analysis: ITT effect (i.e., effect of being assigned to NOAC versus warfarin at baseline, regardless of whether patients continue following the assigned treatment after baseline)	Same (using as-started analysis, analog of ITT)

	Sensitivity analysis: per-protocol effect (i.e., effect of following the treatment strategies in the study protocol at baseline and after baseline)	Same (using on-treatment analysis, analog of per-protocol)
Statistical analysis	Cox proportional hazards model	Same (except we further applied the shared frailty model accounting for potential cluster-specific random effects from each individual hospital/clinic)

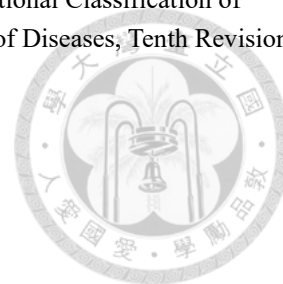


Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulant; IPTW, inverse probability of treatment weighting; ITT, intention-to-treat

Supplement Table 2. Diagnosis and procedure codes for each study outcome

Diseases	ICD-9-CM codes	ICD-10-CM codes	Procedure codes
Coronary artery diseases	410–414	I20–I25	
Stroke	430–438	I60–I69	
Peripheral vascular disease	250.7, 443.9, 440.2	E08.5, E10.5, E11.5, E13.5, I73.9, I70.2	
Retinopathy	250.5, 362.0	E08.31–E08.35, E08.37 E10.31–E10.35, E10.37 E11.31–E11.35, E11.37 E13.31–E13.35, E13.37	
Neuropathy	250.6, 357.2	E08.4, E10.4, E11.4, E13.4	
Dialysis			Case type: 05 or procedure codes: 58001C, 58002C, 58002CB, 58011AB, 58014C, 58017B, 58018C, 58019C, 58020C, 58021C, 58022C, 58023C, 58024C, 58025C, 58026C, 58027C, 58029C, 58030B in Taiwan's NHIRD
Lower extremity amputation			ICD-9-CM procedure code: 84.1 or ICD-10-CM procedure code: 0Y6
Diabetic ketoacidosis	250.1	E08.1, E10.1, E11.1, E13.1	
Hyperosmolar hyperglycemic state	250.2	E08.0, E11.0, E13.0	
Hypoglycemia	251.0–251.2	E16.0–E16.2 E08.64, E10.64, E11.64, E13.64	
Cardiovascular mortality	390–459 (using the primary diagnosis for the cause of death in National	I00–I99 (using the primary diagnosis for the cause of death in National Register of	

Abbreviations: NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification



Supplement Table 3. Baseline characteristics of NOAC and warfarin users in the original population before applying propensity score methods

	Original population		SMD [†]
	NOAC (N = 19847)	Warfarin (N = 10372)	
Age (years) [‡]	74.9 ± 9.7	71.8 ± 10.9	0.292
Sex			
Male	53.7	55.1	0.028
Female	46.3	44.9	0.028
Income level (NTD)			
Financially dependent	29.1	28.0	0.024
15840–29999	46.8	46.3	0.009
30000–44999	12.6	15.2	0.074
≥ 45000	11.5	10.5	0.032
Charlson comorbidity index ^{‡§}	2.8 ± 1.9	2.9 ± 1.9	0.062
CHA2DS2-VASc score ^{‡#}	4.4 ± 1.6	4.3 ± 1.8	0.077
Comorbidities			
Hypertension	77.7	77.5	0.006
Coronary artery disease	34.6	36.6	0.000
Congestive heart failure	26.2	30.2	0.089
COPD	14.4	14.2	0.007
Chronic kidney disease	13.1	15.5	0.070
Liver cirrhosis	4.8	6.7	0.084
Hyperlipidemia	37.2	36.3	0.017
Stroke	31.0	31.7	0.000
Rheumatoid arthritis	0.7	0.8	0.004
Gout	9.8	11.3	0.048
Dementia	6.8	5.5	0.054
Malignancy	8.6	7.8	0.030
Medication use			
Statins	37.9	33.8	0.085
ACEI or ARB	63.3	61.6	0.037
β blockers	45.9	47.3	0.027
Calcium channel blockers	46.4	47.4	0.020
Diuretics	30.7	35.5	0.104
NSAID	34.8	33.6	0.025
Corticosteroids	8.9	9.4	0.018
Antipsychotics	4.9	5.1	0.008
Proton pump inhibitors	7.8	8.5	0.023
Baseline diabetes medications			

Metformin	49.9	46.9	0.059
Sulfonylurea	33.2	36.9	0.076
Meglitinide	6.0	8.4	0.093
AGI	8.3	9.7	0.050
TZD	4.6	4.8	0.007
DPP-4i	29.2	23.8	0.122
SGLT-2i	1.2	0.2	0.111
GLP-1	0.1	0.1	0.010
Insulin	11.4	13.8	0.072
Numbers of baseline diabetes medications			
Without medications	31.2	28.5	0.059
1 type	24.1	26.6	0.058
2 types	22.4	23.7	0.033
≥ 3 types	22.3	21.1	0.029
Index year			
2012–2013	11.1	44.1	0.793
2014–2015	35.1	36.5	0.030
2016–2017	53.8	19.4	0.765
Hospital level of OAC initiation			
Medical center	40.0	32.8	0.150
Regional hospital	44.5	45.7	0.024
District hospital or clinic	15.4	21.5	0.156
Physician specialty			
Cardiologist	66.9	61.9	0.104
Neurologist	16.4	13.6	0.077
Others	16.7	24.5	0.192

Data are presented as percentages unless otherwise noted.

[†]A standardized mean difference of <0.1 indicates a negligible difference.

[‡]Presented as mean ± standard deviation.

[§]Calculated without including scores for age.

[#]Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Supplement Table 4. Baseline characteristics of NOAC and warfarin users in the population after inverse probability of treatment weighting or propensity score matching for the analysis of macrovascular complications

	Population after IPTW*			Population after PSM*		
	NOAC (N = 6914)	Warfarin (N = 3325)	SMD [†]	NOAC (N = 2594)	Warfarin (N = 2594)	SMD [†]
Age (years) [‡]	72.5 ± 10.2	72.6 ± 11.1	0.009	70.9 ± 10.1	71.0 ± 11.1	0.008
Sex						
Male	52.9	52.7	0.003	55.3	55.1	0.004
Female	47.1	47.3	0.003	44.7	44.9	0.004
Income level (NTD)						
Financially dependent	27.2	26.9	0.007	25.1	25.7	0.013
15840–29999	46.5	47.5	0.020	47.2	46.7	0.011
30000–44999	14.8	14.1	0.020	16.1	16.2	0.001
≥ 45000	11.5	11.5	0.001	11.6	11.5	0.002
Charlson comorbidity index ^{‡§}	2.2 ± 1.6	2.2 ± 1.7	0.003	2.2 ± 1.7	2.2 ± 1.7	0.015
CHA2DS2-VASc score ^{‡#}	3.5 ± 1.3	3.5 ± 1.4	0.021	3.3 ± 1.3	3.3 ± 1.4	0.008
Comorbidities						
Hypertension	72.8	73.0	0.004	72.2	71.1	0.023
Coronary artery disease	0.0	0.0	0.000	0.0	0.0	0.000
Congestive heart failure	24.0	25.6	0.038	24.3	24.2	0.003
COPD	12.5	12.8	0.009	11.3	11.4	0.005
Chronic kidney disease	12.3	12.2	0.002	12.9	13.3	0.011
Liver cirrhosis	5.8	5.7	0.003	6.4	6.6	0.009
Hyperlipidemia	35.6	35.6	0.000	36.0	34.3	0.036
Stroke	0.0	0.0	0.000	0.0	0.0	0.000
Rheumatoid arthritis	0.9	0.9	0.000	1.0	1.0	0.004
Gout	10.2	10.5	0.008	11.2	10.5	0.022
Dementia	3.8	3.2	0.031	3.0	2.9	0.007
Malignancy	9.0	8.7	0.013	8.4	9.0	0.021
Medication use						
Statins	33.5	33.8	0.006	32.3	31.3	0.022
ACEI or ARB	60.5	60.1	0.009	59.8	59.0	0.016
β blockers	41.7	41.9	0.004	42.8	42.5	0.005
Calcium channel blockers	43.8	44.5	0.014	44.3	43.4	0.018
Diuretics	28.9	30.1	0.025	29.5	30.2	0.016
NSAID	33.1	33.2	0.002	33.0	33.3	0.006
Corticosteroids	8.3	8.3	0.001	8.4	8.6	0.006
Antipsychotics	3.6	3.3	0.016	3.0	2.9	0.007
Proton pump inhibitors	7.1	6.7	0.016	7.4	7.1	0.015

Baseline diabetes						
medications						
Metformin	49.8	49.8	0.000	49.2	49.1	0.001
Sulfonylurea	35.2	34.9	0.006	37.0	36.7	0.006
Meglitinide	6.2	5.8	0.017	6.4	6.3	0.006
AGI	8.5	8.2	0.013	8.8	9.0	0.005
TZD	5.5	5.3	0.008	5.6	5.7	0.003
DPP-4i	26.6	25.8	0.018	25.6	24.9	0.016
SGLT-2i	0.8	0.7	0.012	0.3	0.4	0.013
GLP-1	0.1	0.1	0.005	0.1	0.1	0.012
Insulin	9.9	10.3	0.013	10.3	10.4	0.003
Numbers of baseline diabetes						
medications						
Without medications	32.0	30.0	0.041	31.8	30.0	0.040
1 type	23.5	27.3	0.088	23.1	26.1	0.069
2 types	22.5	22.1	0.012	22.8	22.9	0.003
≥ 3 types	22.0	20.6	0.035	22.2	21.0	0.030
Index year						
2012–2013	19.0	19.2	0.005	25.7	25.7	0.000
2014–2015	35.0	35.7	0.015	43.1	43.1	0.000
2016–2017	46.0	45.1	0.018	31.2	31.2	0.000
Hospital level of OAC						
initiation						
Medical center	37.7	37.3	0.010	34.8	35.5	0.014
Regional hospital	42.6	42.9	0.005	43.9	43.6	0.008
District hospital or clinic	19.6	19.8	0.005	21.2	20.9	0.007
Physician specialty						
Cardiologist	78.3	78.4	0.002	78.3	77.9	0.008
Neurologist	2.8	2.5	0.014	2.1	1.9	0.017
Others	18.9	19.1	0.004	19.6	20.2	0.014

Data are presented as percentages unless otherwise noted.

*All the covariates listed in the table were used to calculate the propensity score for weighting or matching.

†A standardized mean difference of <0.1 indicates a negligible difference.

‡Presented as mean ± standard deviation.

§Calculated without including scores for age.

#Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Supplement Table 5. Baseline characteristics of NOAC and warfarin users in the population after inverse probability of treatment weighting or propensity score matching for the analysis of microvascular complications

	Population after IPTW*			Population after PSM*		
	NOAC (N = 16835)	Warfarin (N = 8506)	SMD [†]	NOAC (N = 6403)	Warfarin (N = 6403)	SMD [†]
Age (years) [‡]	73.8 ± 10.1	73.9 ± 11.0	0.010	72.9 ± 10.1	72.8 ± 11.0	0.018
Sex						
Male	54.6	54.5	0.002	54.9	54.9	0.000
Female	45.4	45.5	0.002	45.1	45.1	0.000
Income level (NTD)						
Financially dependent	28.4	28.3	0.001	27.8	28.0	0.004
15840–29999	47.1	47.6	0.009	47.8	46.9	0.018
30000–44999	13.3	13.2	0.003	13.9	14.2	0.008
≥ 45000	11.2	10.8	0.010	10.5	10.9	0.014
Charlson comorbidity index ^{‡§}	2.6 ± 1.8	2.6 ± 1.8	0.002	2.6 ± 1.8	2.6 ± 1.8	0.017
CHA2DS2-VASc score ^{‡#}	4.3 ± 1.6	4.3 ± 1.8	0.007	4.2 ± 1.7	4.2 ± 1.8	0.010
Comorbidities						
Hypertension	76.9	76.9	0.001	76.6	76.3	0.006
Coronary artery disease	34.9	34.7	0.000	34.8	34.6	0.000
Congestive heart failure	27.7	28.5	0.017	28.5	28.2	0.006
COPD	14.2	14.5	0.007	14.2	13.8	0.012
Chronic kidney disease	13.2	13.2	0.001	14.1	13.7	0.011
Liver cirrhosis	5.4	5.5	0.004	6.1	6.3	0.008
Hyperlipidemia	35.5	35.2	0.008	34.7	34.6	0.001
Stroke	29.8	29.6	0.000	27.8	27.9	0.000
Rheumatoid arthritis	0.7	0.7	0.007	0.8	0.7	0.012
Gout	10.4	10.5	0.003	10.6	10.7	0.005
Dementia	6.3	6.1	0.010	5.9	5.6	0.013
Malignancy	8.2	8.1	0.004	8.3	7.8	0.018
Medication use						
Statins	35.2	35.3	0.002	34.1	33.5	0.012
ACEI or ARB	61.6	61.5	0.002	61.0	61.1	0.002
β blockers	46.2	46.3	0.001	46.8	46.9	0.002
Calcium channel blockers	46.6	47.1	0.009	47.0	46.9	0.002
Diuretics	32.0	32.4	0.009	33.5	33.7	0.005
NSAID	33.6	33.8	0.003	34.0	33.4	0.013
Corticosteroids	8.9	9.1	0.007	8.9	8.8	0.005
Antipsychotics	5.0	5.0	0.000	4.9	4.6	0.014
Proton pump inhibitors	7.8	7.5	0.010	7.4	7.9	0.019

Baseline diabetes						
medications						
Metformin	46.4	46.0	0.008	44.7	44.8	0.003
Sulfonylurea	32.2	32.6	0.009	33.2	33.2	0.001
Meglitinide	6.2	6.1	0.006	6.6	6.7	0.003
AGI	7.9	7.8	0.005	8.4	8.2	0.008
TZD	4.1	4.3	0.008	4.4	4.2	0.009
DPP-4i	25.3	25.2	0.000	23.7	24.1	0.009
SGLT-2i	0.8	0.8	0.004	0.3	0.3	0.014
GLP-1	0.0	0.1	0.002	0.1	0.1	0.000
Insulin	9.6	9.9	0.010	10.7	10.1	0.018
Numbers of baseline diabetes						
medications						
Without medications	34.9	32.7	0.046	35.8	33.2	0.056
1 type	24.1	26.8	0.061	23.3	26.5	0.075
2 types	21.2	21.6	0.011	20.8	21.8	0.025
≥ 3 types	19.7	18.8	0.023	20.1	18.5	0.040
Index year						
2012–2013	22.3	22.3	0.002	27.9	27.9	0.000
2014–2015	35.3	36.0	0.014	45.7	45.7	0.000
2016–2017	42.5	41.7	0.015	26.4	26.4	0.000
Hospital level of OAC						
initiation						
Medical center	37.1	36.0	0.022	34.0	34.4	0.010
Regional hospital	44.9	46.0	0.023	45.5	45.2	0.006
District hospital or clinic	18.0	18.0	0.002	20.6	20.4	0.004
Physician specialty						
Cardiologist	66.2	66.1	0.002	66.3	66.6	0.006
Neurologist	14.4	14.0	0.013	12.4	12.2	0.008
Others	19.4	19.9	0.014	21.2	21.2	0.001

Data are presented as percentages unless otherwise noted.

*All the covariates listed in the table were used to calculate the propensity score for weighting or matching.

†A standardized mean difference of <0.1 indicates a negligible difference.

‡Presented as mean ± standard deviation.

§Calculated without including scores for age.

#Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Supplement Table 6. Baseline characteristics of NOAC and warfarin users in the population after inverse probability of treatment weighting or propensity score matching for the analysis of glycemic emergency

	Population after IPTW*			Population after PSM*		
	NOAC (N = 19358)	Warfarin (N = 9934)	SMD [†]	NOAC (N = 7426)	Warfarin (N = 7426)	SMD [†]
Age (years) [‡]	73.7 ± 10.0	73.9 ± 10.8	0.012	72.7 ± 10.0	72.7 ± 10.8	0.005
Sex						
Male	54.6	54.4	0.003	55.1	55.2	0.003
Female	45.4	45.6	0.003	44.9	44.8	0.003
Income level (NTD)						
Financially dependent	28.6	28.8	0.003	28.1	28.3	0.005
15840–29999	46.8	47.2	0.008	46.6	46.7	0.002
30000–44999	13.5	13.3	0.008	14.7	14.5	0.006
≥ 45000	11.1	10.8	0.009	10.6	10.5	0.004
Charlson comorbidity index ^{‡§}	2.8 ± 1.9	2.8 ± 1.9	0.003	2.8 ± 1.9	2.8 ± 1.9	0.019
CHA2DS2-VASc score ^{‡#}	4.3 ± 1.6	4.3 ± 1.8	0.009	4.2 ± 1.6	4.2 ± 1.8	0.020
Comorbidities						
Hypertension	77.5	77.6	0.003	77.2	76.8	0.010
Coronary artery disease	35.1	34.8	0.000	35.8	35.1	0.000
Congestive heart failure	27.4	28.0	0.014	28.4	27.7	0.016
COPD	14.1	14.4	0.007	14.2	14.1	0.003
Chronic kidney disease	13.9	13.8	0.001	15.3	15.0	0.009
Liver cirrhosis	5.5	5.6	0.006	6.1	6.5	0.014
Hyperlipidemia	36.9	36.7	0.003	36.7	36.2	0.010
Stroke	30.9	30.7	0.000	29.6	28.7	0.000
Rheumatoid arthritis	0.7	0.7	0.003	0.8	0.8	0.000
Gout	10.4	10.4	0.000	10.9	10.9	0.000
Dementia	6.2	5.9	0.015	5.6	5.7	0.004
Malignancy	8.1	8.0	0.004	7.8	7.9	0.005
Medication use						
Statins	36.5	36.7	0.003	35.1	34.6	0.011
ACEI or ARB	62.9	62.8	0.001	63.1	62.3	0.016
β blockers	46.6	46.7	0.001	46.9	47.1	0.005
Calcium channel blockers	46.8	47.2	0.009	47.8	47.6	0.005
Diuretics	32.3	32.7	0.008	34.3	33.7	0.013
NSAID	34.3	34.7	0.008	34.6	34.3	0.007
Corticosteroids	8.9	9.1	0.008	9.1	9.0	0.005
Antipsychotics	5.0	5.1	0.004	4.9	4.8	0.008
Proton pump inhibitors	8.0	7.7	0.009	8.3	8.3	0.002

Baseline diabetes						
medications						
Metformin	48.6	48.4	0.004	46.7	46.4	0.006
Sulfonylurea	34.5	34.8	0.006	35.9	35.6	0.006
Meglitinide	6.7	6.5	0.010	6.9	7.2	0.013
AGI	8.7	8.7	0.000	8.9	8.7	0.008
TZD	4.6	4.8	0.009	4.7	4.8	0.001
DPP-4i	27.2	27.3	0.003	25.6	26.0	0.010
SGLT-2i	0.9	0.9	0.005	0.4	0.3	0.007
GLP-1	0.1	0.1	0.005	0.1	0.1	0.005
Insulin	11.4	11.5	0.003	11.9	12.1	0.005
Numbers of baseline diabetes						
medications						
Without medications	31.5	29.4	0.044	32.2	30.4	0.039
1 type	24.2	26.4	0.051	24.1	26.0	0.044
2 types	22.4	23.0	0.013	21.7	22.8	0.026
≥ 3 types	21.9	21.2	0.018	22.0	20.9	0.028
Index year						
2012–2013	22.7	22.7	0.000	28.3	28.3	0.000
2014–2015	35.5	36.1	0.013	45.6	45.6	0.000
2016–2017	41.8	41.2	0.012	26.1	26.1	0.000
Hospital level of OAC						
initiation						
Medical center	37.4	36.6	0.016	35.5	35.3	0.005
Regional hospital	44.7	45.6	0.018	45.0	44.9	0.001
District hospital or clinic	17.9	17.7	0.004	19.5	19.8	0.007
Physician specialty						
Cardiologist	65.6	65.7	0.001	65.5	65.7	0.005
Neurologist	15.2	14.8	0.011	13.5	13.1	0.013
Others	19.1	19.5	0.009	21.0	21.2	0.005

Data are presented as percentages unless otherwise noted.

*All the covariates listed in the table were used to calculate the propensity score for weighting or matching.

†A standardized mean difference of <0.1 indicates a negligible difference.

‡Presented as mean ± standard deviation.

§Calculated without including scores for age.

#Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PSM, propensity score matching; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione

Supplement Table 7. The hospital level of treatment initiation in NOAC and warfarin users among each index year period, after stabilized IPTW and propensity score matching

A. Population after stabilized IPTW

Index year	Treatment	Hospital level, N (%)		
		Medical center	Regional hospital	District hospital or clinic
2012-2013	NOAC	1802 (39.8)	1904 (42.1)	821 (18.1)
	Warfarin	941 (40.2)	1023 (43.7)	377 (16.1)
2014-2015	NOAC	2606 (36.9)	3275 (46.4)	1182 (16.7)
	Warfarin	1406 (37.9)	1691 (45.6)	614 (16.6)
2016-2017	NOAC	3033 (36.5)	3742 (45.0)	1544 (18.6)
	Warfarin	1432 (33.7)	1990 (46.8)	826 (19.5)

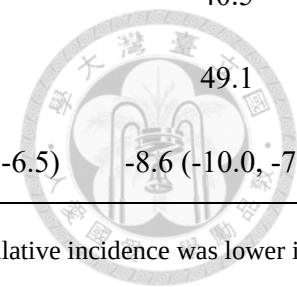
B. Population after propensity score matching

Index year	Treatment	Hospital level, N (%)		
		Medical center	Regional hospital	District hospital or clinic
2012-2013	NOAC	1022 (47.2)	879 (40.6)	265 (12.2)
	Warfarin	1021 (47.1)	881 (40.7)	264 (12.2)
2014-2015	NOAC	1150 (32.8)	1681 (48.0)	672 (19.2)
	Warfarin	1158 (33.1)	1660 (47.4)	685 (19.6)
2016-2017	NOAC	539 (26.8)	933 (46.5)	536 (26.7)
	Warfarin	543 (27.0)	918 (45.7)	547 (27.2)

Abbreviations: NOAC, non-vitamin K antagonist oral anticoagulant; IPTW, inverse probability of treatment weighting

Supplement Table 8. Cumulative incidences and their differences with 95% CI between treatment groups at each year since treatment commencement after stabilized IPTW

Macrovascular complication	Time since treatment commencement, year					
	1	2	3	4	5	6
Cumulative incidence in NOAC users, %	16.0	23.9	30.0	34.6	39.1	42.2
Cumulative incidence in warfarin users, %	18.8	27.7	34.6	39.7	44.6	48.0
Difference in cumulative incidences* (95% CI), %	-2.8 (-4.0, -1.6)	-3.9 (-5.5, -2.2)	-4.6 (-6.6, -2.6)	-5.1 (-7.3, -2.9)	-5.5 (-7.9, -3.1)	-5.7 (-8.2, -3.3)
Microvascular complication	Time since treatment commencement, year					
	1	2	3	4	5	6
Cumulative incidence in NOAC users, %	4.8	7.8	10.4	12.7	15.1	16.4
Cumulative incidence in warfarin users, %	6.0	9.7	12.8	15.6	18.5	20.1
Difference in cumulative incidences* (95% CI), %	-1.2 (-1.6, -0.7)	-1.9 (-2.5, -1.2)	-2.4 (-3.3, -1.6)	-2.9 (-4.0, -1.9)	-3.4 (-4.6, -2.2)	-3.7 (-5.0, -2.4)
Glycemic emergency	Time since treatment commencement, year					
	1	2	3	4	5	6
Cumulative incidence in NOAC users, %	2.9	4.9	6.7	8.8	10.5	12.2
Cumulative incidence in warfarin users, %	3.3	5.5	7.4	9.8	11.7	13.6
Difference in cumulative incidences* (95% CI), %	-0.4 (-0.6, -0.1)	-0.6 (-1.1, -0.1)	-0.8 (-1.4, -0.2)	-1.0 (-1.8, -0.2)	-1.2 (-2.2, -0.2)	-1.4 (-2.5, -0.3)
Mortality	Time since treatment commencement, year					
	1	2	3	4	5	6



Cumulative incidence in NOAC users, %	9.4	16.6	22.9	29.1	34.7	40.5
Cumulative incidence in warfarin users, %	12.0	21.0	28.6	36.1	42.5	49.1
Difference in cumulative incidences* (95% CI), %	-2.6 (-3.1, -2.2)	-4.4 (-5.2, -3.6)	-5.8 (-6.7, -4.8)	-6.9 (-8.1, -5.8)	-7.8 (-9.1, -6.5)	-8.6 (-10.0, -7.1)

The cumulative incidences were estimated by cause-specific Cox proportional hazard model.

*The difference in cumulative incidences was calculated by using the warfarin group as the reference group; the negative value indicated that the cumulative incidence was lower in NOAC users than warfarin users.

Abbreviations: NOAC, non-vitamin K antagonist oral anticoagulant; IPTW, inverse probability of treatment weighting

Supplement Table 9. Hazards of diabetes complications and mortality associated with each NOAC versus warfarin

Outcome	Population after IPTW [†]		Population after PSM	
	HR [‡] (95% CI)	p-value	HR [‡] (95% CI)	p-value
Dabigatran vs. warfarin				
Macrovascular complication	0.81 (0.74-0.89)	<0.001	0.78 (0.70-0.88)	<0.001
Microvascular complication	0.81 (0.74-0.89)	<0.001	0.84 (0.74-0.94)	0.003
Glycemic emergency	0.96 (0.86-1.08)	0.53	0.93 (0.81-1.07)	0.29
Mortality	0.78 (0.73-0.83)	<0.001	0.79 (0.73-0.84)	<0.001
Rivaroxaban vs. warfarin				
Macrovascular complication	0.90 (0.82-0.99)	0.029	0.94 (0.83-1.06)	0.28
Microvascular complication	0.83 (0.75-0.91)	<0.001	0.81 (0.71-0.92)	0.002
Glycemic emergency	0.95 (0.85-1.06)	0.37	0.98 (0.84-1.14)	0.79
Mortality	0.83 (0.78-0.88)	<0.001	0.81 (0.75-0.87)	<0.001
Apixaban vs. warfarin				
Macrovascular complication	0.81 (0.68-0.96)	0.013	0.82 (0.66-1.03)	0.082
Microvascular complication	0.84 (0.70-1.00)	0.045	0.83 (0.66-1.04)	0.104
Glycemic emergency	0.83 (0.66-1.04)	0.107	0.88 (0.66-1.17)	0.38
Mortality	0.85 (0.76-0.94)	0.003	0.80 (0.70-0.91)	0.001
Edoxaban vs. warfarin				
Macrovascular complication	0.74 (0.51-1.08)	0.119	0.90 (0.65-1.24)	0.51
Microvascular complication	0.56 (0.33-0.96)	0.036	0.59 (0.40-0.87)	0.008
Glycemic emergency	0.68 (0.36-1.32)	0.26	0.62 (0.39-0.99)	0.047
Mortality	0.86 (0.65-1.15)	0.32	0.68 (0.55-0.84)	<0.001

In each outcome analysis, patients who had already experienced the corresponding outcome event before the index date were excluded.

[†]A pseudo-population constructed by stabilized IPTW for analyses

[‡]The HR is calculated by a cause-specific Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; PSM, propensity score matching.

Supplement Table 10. Hazards of diabetes complications and mortality in atrial fibrillation patients with diabetes taking NOACs versus warfarin, stratified by age, sex, and hospital levels

Outcome and stratification	Population after IPTW [†]		Population after PSM	
	HR [‡] (95% CI)	p-value	HR [‡] (95% CI)	p-value
Age < 65 years				
Macrovascular complication	0.93 (0.79-1.11)	0.43	1.00 (0.81-1.25)	0.98
Microvascular complication	0.86 (0.72-1.03)	0.101	0.90 (0.72-1.14)	0.39
Glycemic emergency	1.11 (0.85-1.47)	0.44	1.10 (0.76-1.60)	0.61
Mortality	0.89 (0.76-1.03)	0.124	0.84 (0.68-1.02)	0.084
Age ≥ 65 years				
Macrovascular complication	0.82 (0.75-0.89)	<0.001	0.78 (0.69-0.87)	<0.001
Microvascular complication	0.75 (0.69-0.83)	<0.001	0.76 (0.68-0.85)	<0.001
Glycemic emergency	0.91 (0.82-1.01)	0.066	0.87 (0.77-0.99)	0.037
Mortality	0.82 (0.78-0.86)	<0.001	0.81 (0.76-0.86)	<0.001
Male				
Macrovascular complication	0.85 (0.77-0.95)	0.003	0.98 (0.86-1.12)	0.73
Microvascular complication	0.81 (0.73-0.91)	<0.001	0.89 (0.78-1.01)	0.079
Glycemic emergency	0.93 (0.81-1.06)	0.27	1.08 (0.91-1.29)	0.36
Mortality	0.80 (0.75-0.86)	<0.001	0.84 (0.78-0.91)	<0.001
Female				
Macrovascular complication	0.82 (0.73-0.92)	0.001	0.77 (0.67-0.89)	<0.001
Microvascular complication	0.76 (0.67-0.86)	<0.001	0.78 (0.67-0.91)	0.002
Glycemic emergency	0.88 (0.77-1.00)	0.056	0.94 (0.80-1.11)	0.470
Mortality	0.77 (0.72-0.82)	<0.001	0.78 (0.71-0.85)	<0.001
Medical center				
Macrovascular complication	0.83 (0.73-0.95)	0.006	0.77 (0.65-0.92)	0.003
Microvascular complication	0.77 (0.67-0.88)	<0.001	0.80 (0.67-0.94)	0.008
Glycemic emergency	0.91 (0.77-1.07)	0.24	1.12 (0.91-1.38)	0.27
Mortality	0.74 (0.68-0.80)	<0.001	0.78 (0.71-0.86)	<0.001
Regional hospital				
Macrovascular complication	0.84 (0.75-0.94)	0.003	0.80 (0.69-0.93)	0.004
Microvascular complication	0.80 (0.71-0.90)	<0.001	0.79 (0.68-0.92)	0.002
Glycemic emergency	0.89 (0.78-1.02)	0.105	0.93 (0.78-1.10)	0.39
Mortality	0.83 (0.78-0.89)	<0.001	0.86 (0.79-0.94)	0.001
District hospital or clinic				
Macrovascular complication	0.89 (0.75-1.06)	0.176	0.89 (0.72-1.11)	0.31
Microvascular complication	0.87 (0.71-1.06)	0.153	0.94 (0.74-1.19)	0.60
Glycemic emergency	0.92 (0.73-1.17)	0.52	0.91 (0.68-1.21)	0.51
Mortality	0.72 (0.64-0.81)	<0.001	0.76 (0.65-0.89)	<0.001

[†]A pseudo-population constructed by stabilized IPTW for analyses

[‡]The HR is calculated by a cause-specific Cox proportional hazard model with shared frailty model

considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; PSM, propensity score matching.



Supplement Table 11. Hazards of diabetes complications and mortality associated with NOAC versus warfarin in the sensitivity analysis excluding patients with chronic kidney diseases at baseline

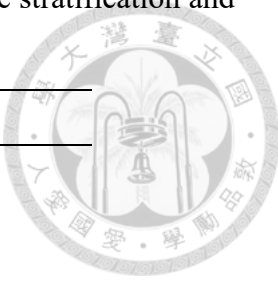
Outcome	Population after IPTW [†]		Population after PSM	
	HR [‡] (95% CI)	p-value	HR [‡] (95% CI)	p-value
Macrovascular complication	0.83 (0.77-0.90)	<0.001	0.85 (0.76-0.94)	0.002
Coronary artery disease	0.90 (0.83-0.97)	0.009	0.86 (0.78-0.96)	0.005
Stroke	0.77 (0.71-0.84)	<0.001	0.82 (0.74-0.92)	<0.001
Peripheral vascular disease	0.87 (0.75-1.01)	0.074	0.87 (0.72-1.05)	0.141
Microvascular complication	0.89 (0.81-0.97)	0.011	0.97 (0.86-1.08)	0.57
Retinopathy	1.09 (0.94-1.28)	0.27	1.10 (0.91-1.33)	0.31
Neuropathy	0.96 (0.84-1.10)	0.57	0.94 (0.80-1.11)	0.47
Dialysis	0.63 (0.55-0.72)	<0.001	0.69 (0.58-0.83)	<0.001
Lower extremity amputation	0.74 (0.55-1.00)	0.053	0.60 (0.41-0.88)	0.009
Glycemic emergency	0.91 (0.82-1.01)	0.063	0.98 (0.86-1.12)	0.78
Diabetic ketoacidosis	1.04 (0.68-1.58)	0.87	1.02 (0.61-1.72)	0.93
Hyperosmolar hyperglycemic state	0.89 (0.73-1.08)	0.24	0.82 (0.63-1.06)	0.131
Hypoglycemia	0.92 (0.81-1.04)	0.168	0.96 (0.82-1.11)	0.55
Mortality	0.78 (0.74-0.82)	<0.001	0.80 (0.75-0.86)	<0.001
Cardiovascular mortality	0.68 (0.63-0.74)	<0.001	0.73 (0.65-0.81)	<0.001
Non-cardiovascular mortality	0.85 (0.79-0.90)	<0.001	0.85 (0.78-0.93)	<0.001

[†]A pseudo-population constructed by stabilized IPTW for analyses

[‡]The HR is calculated by a cause-specific Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; PSM, propensity score matching.

Supplement Table 12. Hazards of diabetes complications and mortality associated with NOAC versus warfarin in the sensitivity analyses after applying propensity score fine stratification and without using propensity score methods



Outcome	HR [†] (95% CI)	p-value
Propensity score fine stratification with 50 strata		
Macrovascular complication	0.85 (0.79-0.92)	<0.001
Microvascular complication	0.79 (0.73-0.86)	<0.001
Glycemic emergency	0.91 (0.83-0.99)	0.046
Mortality	0.78 (0.75-0.82)	<0.001
Multivariable regression model without applying propensity score methods [‡]		
Macrovascular complication	0.85 (0.78-0.92)	<0.001
Microvascular complication	0.80 (0.73-0.87)	<0.001
Glycemic emergency	0.91 (0.82-1.01)	0.086
Mortality	0.80 (0.76-0.84)	<0.001

[†]The HR is calculated by a cause-specific Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

[‡]All variables listed in Table 1 are adjusted for in the multivariable regression model.

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant

Supplement Table 13. Analyses for negative control outcomes

Negative control outcome	Population after IPTW [†]		Population after PSM	
	HR [‡] (95% CI)	p-value	HR [‡] (95% CI)	p-value
Cancer				
NOAC	0.96 (0.88-1.04)	0.297	1.02 (0.92-1.14)	0.669
Warfarin	1.00 (ref.)		1.00 (ref.)	
COPD				
NOAC	0.98 (0.92-1.04)	0.431	0.97 (0.90-1.04)	0.345
Warfarin	1.00 (ref.)		1.00 (ref.)	
Suicide				
NOAC	1.35 (0.76-2.41)	0.302	1.12 (0.59-2.15)	0.728
Warfarin	1.00 (ref.)		1.00 (ref.)	

[†]A pseudo-population constructed by stabilized IPTW for analyses

[‡]The HR is calculated by a cause-specific Cox proportional hazard model with shared frailty model considering cluster-specific random effects of individual hospital/clinic; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; PSM, propensity score matching.

Supplement Table 14. Hazards of diabetes complications and mortality associated with NOAC versus warfarin in the analyses using Fine–Gray proportional subdistribution hazards models to calculate the subdistribution hazard ratio in the propensity score-matched population *

Outcome	SHR [†] (95% CI)	p-value
Macrovascular complication	0.91 (0.83-1.00)	0.045
Coronary artery disease	0.94 (0.85-1.03)	0.176
Stroke	0.83 (0.75-0.91)	<0.001
Peripheral vascular disease	0.92 (0.78-1.09)	0.34
Microvascular complication	0.84 (0.76- 0.93)	0.001
Retinopathy	1.15 (0.96-1.37)	0.124
Neuropathy	0.99 (0.85-1.15)	0.91
Dialysis	0.60 (0.52-0.69)	<0.001
Lower extremity amputation	0.68 (0.47-0.97)	0.031
Glycemic emergency	1.00 (0.88-1.12)	0.94
Diabetic ketoacidosis	0.83 (0.53-1.30)	0.41
Hyperosmolar hyperglycemic state	1.01 (0.80-1.29)	0.91
Hypoglycemia	0.94 (0.82-1.07)	0.23

*The analyses were not performed in the population after stabilized IPTW, since, to our knowledge, the current analytic codes (using SAS and R) do not simultaneously support the functions of weighting and clustering (by shared frailty model) in the Fine–Gray proportional subdistribution hazards regression model.

[†]The SHR is calculated by Fine–Gray proportional subdistribution hazards models with shared frailty model considering the cluster-specific random effect of individual hospital/clinic and treating death as a competing event; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; CV, cardiovascular; SHR, subdistribution hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant



Supplement Table 15. Hazards of diabetes complications and mortality associated with NOAC versus warfarin in two sensitivity analyses using Fine–Gray proportional subdistribution hazards models to calculate the subdistribution hazard ratio in the propensity score-matched population*

Outcome	Analyses using on-treatment design (analog of per-protocol)		Analyses limited to patients with MPR $\geq$ 80%	
	SHR [†] (95% CI)	p-value	SHR [†] (95% CI)	p-value
Macrovascular complication	0.88 (0.77-1.01)	0.077	0.71 (0.62-0.82)	<0.001
Coronary artery disease	0.94 (0.83-1.07)	0.33	0.77 (0.68-0.87)	<0.001
Stroke	0.74 (0.65-0.86)	0.005	0.56 (0.48-0.66)	<0.001
Peripheral vascular disease	0.89 (0.68-1.17)	0.41	0.71 (0.54-0.93)	0.014
Microvascular complication	0.74 (0.65-0.84)	<0.001	0.60 (0.52-0.69)	<0.001
Retinopathy	1.00 (0.80-1.25)	0.99	0.78 (0.61-0.99)	0.041
Neuropathy	1.03 (0.84-1.26)	0.81	0.83 (0.67-1.03)	0.090
Dialysis	0.33 (0.26-0.42)	<0.001	0.27 (0.21-0.35)	<0.001
Lower extremity amputation	0.57 (0.34-0.95)	0.032	0.44 (0.26-0.76)	0.003
Glycemic emergency	0.91 (0.76-1.09)	0.29	0.75 (0.62-0.92)	0.005
Diabetic ketoacidosis	0.86 (0.52-1.41)	0.54	0.81 (0.43-1.51)	0.50
Hyperosmolar hyperglycemic state	1.04 (0.72-1.50)	0.83	0.83 (0.56-1.23)	0.35
Hypoglycemia	0.79 (0.64-0.96)	0.020	0.63 (0.51-0.77)	<0.001

*The analyses were not performed in the population after stabilized IPTW, since, to our knowledge, the current analytic codes (using SAS and R) do not simultaneously support the functions of weighting and clustering (by shared frailty model) in the Fine–Gray proportional subdistribution hazards regression model.

[†]The SHR is calculated by Fine–Gray proportional subdistribution hazards models with shared frailty model considering the cluster-specific random effect of individual hospital/clinic and treating death as a competing event; the HR is calculated using the warfarin group as the reference.

Abbreviations: CI, confidence interval; CV, cardiovascular; SHR, subdistribution hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant

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Statistical Code

1. Statistical software information

Our study used SAS for executing data management and the following analytic methods/procedures: propensity score calculation, stabilized inverse probability of treatment weighting (IPTW), propensity score matching, cause-specific Cox proportional hazard model, Fine-Gray competing risk regression model, and estimation of cumulative incidences and difference in cumulative incidences. The software R was applied to estimate the sub-distribution hazard ratio which clustered within an individual hospital using the *crrSC* package. All figures were graphed using STATA software. Detailed statistical software information is described below:

- SAS Version: 9.4; Statistical module: SAS/STAT 15.2
- STATA Version: 15
- R Version: 4.1.1; additional packages *crrSC* v.1.1

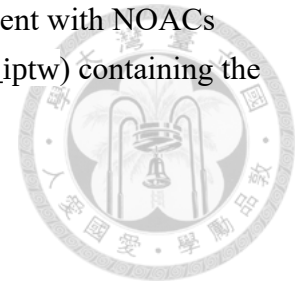
2. Data snapshot

Here, we demonstrate a dataset that includes the major variables we used. The variables *id* and *hosp_id* represent the unique identified numbers of patients' and hospitals', respectively. Our comparison groups, NOAC and warfarin, were coded in the *noac* column, with *noac* = 1 and *noac* = 0. The data include some of the following covariates: *age* (years old), *female* (0 = male, 1 = female), *cci* (range: 0-18), and *yg* (group label of index year, 1213 = 2012-2013, 1415 = 2014-2015, 1617 = 2016-2017) for demonstration. Other covariates were suppressed in the explanation below to avoid the program line being too long to read. In this scenario, macrovascular events were the primary outcome, and the *macrovas_ft* variable represented the years from the index date to the end of follow-up. If the *macrovas_crr* variable was coded 1, it means that the macrovascular composite outcome occurred; otherwise, 0 and 2 represent either that the endpoint was censored or a competing event (death) occurred.

id	noac	age	female	cci	yg	hosp_id	...	macrovas_ft	macrovas_crr
A1	1	84	0	2	1213	H55	...	2.26	0
A2	1	77	1	5	1415	H75	...	3.72	2
...	...	...	...	...		...	...	...	...
B1	0	69	0	4	1213	H37		1.51	1
B2	0	50	1	3	1617	H19		4.33	0
...	...	...	...	...		...		...	...

3. Calculating propensity score

We used the **LOGISTIC** procedure to calculate the probability of treatment with NOACs using all baseline covariates. Following this, SAS outputs a dataset (dt_iptw) containing the predicted probability variable (**predicted** = ps).



SAS code:

```
proc logistic data = dt_original;
  class noac(ref = '0');
  model noac = age female cci;
  output out = dt_iptw predicted = ps;
run;
```

4. Inverse probability of treatment weighting (IPTW)

We implemented stabilized inverse probability of treatment weighting (IPTW) to adjust for confounders (Stürmer et al., 2014 *J Intern Med*). In contrast to traditional IPTW, the stabilized process multiplies the weight by the overall marginal prevalence of the treatment exposure. First, we calculated the marginal prevalence of the NOAC as *prev_noac* column; in this case, the value was 0.6747. Then, *iptw* variables were generated for the following weighting in the analysis.

Reference: Stürmer *et al* (2014). Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med*. 275(6):570-80. Doi: 10.1111/joim.12197.

SAS code:

```
proc sql;
  create table dt_iptw as
  select *, sum(noac) / count(*) as prev_noac
  from dt_iptw;
quit;

data dt_iptw;
  set dt_iptw;
  iptw =
    ((noac * prev_noac) / ps) +
    (((1 - noac) * (1 - prev_noac)) / (1 - ps));
Run;
```

Then, we had a complete dataset with the *iptw* variable.

id	noac	age	sex	cci	yg	hosp_id	ps	prev_noac	iptw	macrovas_ft	macrovas_crr
A1	1	84	1	2	1213	H55	0.8714	0.6747	0.7743	2.26	0
A2	1	77	2	5	1415	H75	0.5881	0.6747	1.1473	3.72	2
...	...	...	...	...		...	...	...	...	...	...
B1	0	69	1	4	1213	H37	0.5363	0.6747	0.7015	1.51	1
B2	0	50	2	3	1617	H19	0.4456	0.6747	0.5868	4.33	0
...	...	...	...	...		...	...	...	...	...	...

5. Propensity score matching (PSM)

Another well-established method for adjusting for confounders is propensity score matching (PSM). We used the **PSMATCH** procedure to calculate the propensity score of prescription NOAC, followed by a 1:1 nearest neighbor matching (`method = greedy(k = 1)`) within 0.2 caliper of logit of the propensity score (`distance = lps caliper = 0.2`) by index year stratum (`by yg`).

SAS code:

```
proc psmatch data = dt_original region = treated;
  class noac;
  psmodel noac(Treated = '1') = age sex cci;
  by yg;
  match
    method = greedy(k = 1 order = random(seed = 1019))
    distance = lps caliper = 0.2;
  output out(obs = match) = dt_psm matchid = _MatchID;
run;
```

6. Cause-specific Cox proportional hazard model

The **PHREG** procedure performs regression analysis of survival data based on the Cox proportional hazards model. The time-to-macrovascular event model was set in the `model` statement (`macrovas_ft * macrovas_crr(0, 2)`) using *noac* as an independent variable. When we used the IPTW method to adjust for confounders, a `weight iptw` statement was included. To consider the cluster effect within the individual hospital/cluster, `class hosp_id` and `random hosp_id` statements were declared to fit a shared frailty model for clustered data.

SAS code:

```
proc phreg data = dt_iptw;
  class hosp_id;
  model macrovas_ft * macrovas_crr(0, 2) = noac / rl;
```

```
weight iptw;
random hosp_id;
run;
```



7. Fine-Gray competing risk regression model (FG model)

We used the R software `crrSC` package developed by Zhou et al. (2012) to develop a Fine-Gray competing risk regression model (FG model) which considered the cluster effect of individual hospitals. The `crrc` function was adapted to model the sub-distribution hazard ratio of the outcome event that compared NOAC with warfarin (`cov1 = dt_psm$noac`), with mortality treated as a competing event (`ftime = dt_psm$macrovas_ft`, `fstatus = dt_psm$macrovas_crr`). We also considered individual hospital as a cluster (`cluster = dt_psm$hosp_id`).

Reference: Zhou et al. (2012). Competing risks regression for clustered data. *Biostatistics*. 13(3):371-83. doi: 10.1093/biostatistics/kxr032. Epub 2011 Oct 31.

R code:

```
crrResult <- crrc(ftime = dt_psm$macrovas_ft, fstatus =
dt_psm$macrovas_crr, cov1 = dt_psm$noac, cluster = dt_psm $hosp_id)
summary(crrResult)
```

8. Cumulative incidence and difference of cumulative incidence calculated using Cox model

We created a temporary dataset, `Risk`, including the variable presented in our major comparison sets: NOAC (`noac = 1`) and warfarin (`noac = 0`). After modeling the Cox model using the **PHREG** procedure, the `Risk` dataset was used to estimate the cumulative incidence and the difference in cumulative incidence.

The output dataset `dt_cif` had the pointwise cumulative incidence, and the `dt_diff` dataset contained the pairwise difference and the corresponding 95% confidence interval in the cumulative incidence.

SAS code:

```
data Risk;
  noac = 0; output;
  noac = 1; output;
run;

proc phreg data = dt_iptw;
  model macrovas_ft*macrovas_crr(0, 2) = noac / rl;
```

```

weight iptw;
baseline
  covariates = Risk
  out = dt_cif
  outdiff = dt_diff
  survival = _all_ / diradj group = noac;
run;

```



9. Cumulative incidence calculated using Fine-Gray competing risk model

When we estimated the cumulative incidence, which considered the mortality as a competing event, we used the Fine-Gray competing risk model (FG model). After fitting the FG model using the PHREG procedure, the Risk dataset was used to estimate the cumulative incidence. The output dataset dt_cif had the pointwise cumulative incidence.

SAS code

```

proc phreg data = dt_iptw plots(overlay = stratum) = cif;
  model macrovas_ft*macrovas_crr(0) = noac / rl eventcode = 1;
  weight iptw;
  baseline
    covariates = Risk
    out = dt_cif cif = _all;
run;

```



Risk of serious hypoglycaemia in patients with atrial fibrillation and diabetes concurrently taking antidiabetic drugs and oral anticoagulants: a nationwide cohort study

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Aims

Evidence regarding the risks of serious hypoglycaemia for patients with atrial fibrillation (AF) and diabetes mellitus (DM) taking antidiabetic medications with concurrent non-vitamin K antagonist oral anticoagulants (NOACs) vs. warfarin is limited. This study aimed to investigate this knowledge gap.

Methods and results

This retrospective cohort study used nationwide data from Taiwan's National Health Insurance Research Database and included a total of 56 774 adult patients treated with antidiabetic medications and oral anticoagulants between 1 January 2012 and 31 December 2020. The incidence rate ratios (IRRs) of serious hypoglycaemia were estimated for patients taking antidiabetic drugs with NOACs vs. warfarin. Poisson regression models with generalized estimating equations accounting for intra-individual correlation across follow-up periods were used. Stabilized inverse probability of treatment weighting was used to create treatment groups with balanced characteristics for comparisons. Compared to concurrent use of antidiabetic drugs with warfarin, those with NOACs showed a significantly lower risk of serious hypoglycaemia (IRR = 0.73, 95% CI: 0.63–0.85, $P < 0.001$). In the analyses of each NOAC, patients taking dabigatran (IRR = 0.76, 95% CI: 0.63–0.91, $P = 0.002$), rivaroxaban (IRR = 0.72, 95% CI: 0.61–0.86, $P < 0.001$), and apixaban (IRR = 0.71, 95% CI: 0.57–0.89, $P = 0.003$) showed a significantly lower risk of serious hypoglycaemia than those taking warfarin.

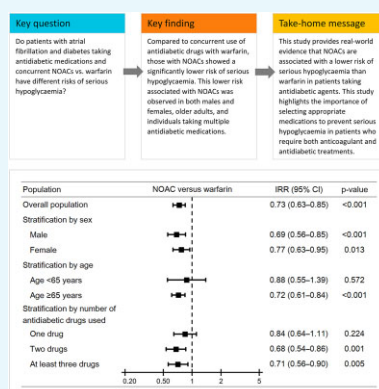
Conclusion

In patients with AF and DM taking antidiabetic drugs, concurrent use of NOACs was associated with a lower risk of serious hypoglycaemia than concurrent use of warfarin.

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Graphical Abstract



Keywords

Hypoglycaemia • Oral anticoagulant • Diabetes mellitus • Antidiabetic drugs • Warfarin • NOAC

Introduction

Both atrial fibrillation (AF) and diabetes mellitus (DM) are major global health issues in the world's aging populations.¹⁻³ These two conditions have a high prevalence and incidence in older adults, and DM is also a major risk factor for AF. Many patients are diagnosed with both conditions. In most diabetes patients with atrial fibrillation, long-term oral anticoagulant treatment is required for stroke prevention. Warfarin, a vitamin K antagonist, is a traditional and cornerstone oral anticoagulant used for decades. Non-vitamin K antagonist oral anticoagulants (NOACs) have been approved as alternatives to warfarin in recent years.⁴⁻⁶

Hypoglycaemia is a dangerous side-effect of diabetes treatment. Hypoglycaemia is linked to an increased risk of cardiovascular events, central nervous system damage, and mortality in patients with DM.^{7,8} It could also affect cardiac autonomic tone and cause abnormal repolarization. This can further lead to cardiac arrhythmias and sudden cardiac death.^{9,10} Recent studies have also shown that in diabetes patients with AF, severe hypoglycaemia leads to a worsened prognosis and premature death; thus, it is crucial to find strategies to minimize the risk of hypoglycaemia for this vulnerable population.¹¹

Recent evidence suggests that vitamin K has a beneficial effect on insulin sensitivity and glycaemic control through several mechanisms.¹²⁻¹⁴ Warfarin, but not NOACs, may interfere with glycaemic control by antagonizing vitamin K function, increasing the risk of DM and its complications, such as hypoglycaemia.¹⁵⁻¹⁷ Moreover, previous studies have reported that concurrent use of warfarin compared with non-use may increase the risk of serious hypoglycaemic events in patients treated with specific antidiabetic drugs (e.g. sulfonylureas) owing to the potential drug-drug interactions.^{18,19} Since DM and AF commonly co-exist in aging populations, many patients need to take antidiabetic drugs and anticoagulants concurrently. Therefore, choosing an optimal oral anticoagulant that reduces the risk of serious hypoglycaemia in patients with diabetes treatment becomes a crucial clinical issue.

However, there is limited evidence comparing the effects of NOACs vs. warfarin on serious hypoglycaemia risk in patients taking antidiabetic drugs. This study used a nationwide cohort to address the knowledge gap on whether patients taking various antidiabetic medications and concurrent NOACs vs. warfarin would have different risks of serious hypoglycaemia.

Methods

Data sources

This nationwide retrospective cohort study was conducted using data from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD comprises healthcare data from approximately 23.6 million individuals, representing the entire population of Taiwan. A brief description of NHIRD is provided in Supplementary Note 1, and the details of NHIRD have been reported elsewhere.^{20,21} The Research Ethics Committee of Hualien Tzu Chi Hospital approved this study (REC No: IRB110-170-C); the requirement for informed consent was waived.

Study population, exposure, and follow-up time

The data were initially retrieved from all adult patients aged ≥20 years who had been diagnosed with both DM (ICD-9-CM code 250 or ICD-10-CM codes E08–E13) and AF (ICD-9-CM code 427.31 or ICD-10-CM codes I48.0, I48.1, I48.2, and I48.91) at least once in an inpatient service or twice in outpatient services between 2012 and 2020 in NHIRD. Our study population was limited to patients treated with antidiabetic medications concurrently with any oral anticoagulant.

In clinical practice, the use of diabetes medications and anticoagulants often changes over time; it is unreasonable to limit patients to being exposed to the same drug use status during several years of the follow-up. Therefore, we divided each patient's follow-up time into different periods (unit of time: day) according to the combination of specific antidiabetic medication and oral anticoagulant types used concurrently. Each period of concurrent use of the same combination of oral anticoagulants and antidiabetic drugs in each patient was used as the unit of analysis. In other words, each patient's follow-up time was divided into several separate periods for analysis based on each specific combination of the oral anticoagulant and antidiabetic drug; if the oral anticoagulant or antidiabetic drug changed, then the periods before and after the change were considered different samples for analysis. Each period of concurrent use of oral anticoagulants and antidiabetic drugs was then classified into the warfarin or NOAC group based on the type of oral anticoagulant prescribed. This design helped decrease the likelihood of exposure misclassification for patients who had changed their antidiabetic medications and oral anticoagulants during long-term follow-up.

We excluded follow-up periods during which patients did not possess any antidiabetic drugs or oral anticoagulants, as determined by prescription

data, from our analysis. Other exclusion criteria included those without any diagnosis of AF before the follow-up periods, as well as those with end-stage renal disease (ESRD), rheumatic heart disease, congenital heart disease, or having valve replacement surgery to avoid potential confounding by indications.^{22,23}

Study outcome

The outcome event was serious hypoglycaemia, ascertained when a patient was admitted to the hospital or treated in the emergency department with a diagnosis of hypoglycaemia (ICD-9-CM codes: 251.0–251.2 or ICD-10-CM codes: E16.0–E16.2, E08.64, E10.64, E11.64, E13.64) accompanied with prescriptions of intravenous high concentration glucose solution (e.g. 50% glucose solution). The incidence rates of serious hypoglycaemia were compared between the periods with NOAC use and those with warfarin use.

Covariates and confounders

Patient demographics, comorbidities, medications, and healthcare utilization were retrieved as covariates for each period. Medical conditions diagnosed at least once in an inpatient or twice in outpatient services within the year before each period were considered pre-existing baseline comorbidities. The Charlson Comorbidity Index and CHA2DS2-VASc score were calculated. Medical utilization (numbers of outpatient visits, emergency room visits, and hospitalizations) in the previous year of each period were retrieved as covariates. Baseline medications were defined as a drug prescribed for at least 30 days within the year prior to the corresponding period. Current diabetes medications indicated the antidiabetic drugs used during the corresponding period; and the number of antidiabetic drugs used was also calculated. Whether there was a history of serious hypoglycaemia within the year before each period was also treated as a covariate. The index year, DM and AF diagnosis duration, monthly income, and hospital level, where oral anticoagulants were prescribed were also retrieved.

Subgroup and stratified analyses

In addition to the main analysis comparing the use of NOAC vs. warfarin for overall patients taking any antidiabetic drugs, also they were compared in the subgroups according to each type of antidiabetic drug, including metformin, sulfonylurea, meglitinide, α -glucosidase inhibitors (AGI), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonist (GLP-1 RA), and insulin. Periods with concurrent prescriptions of a specific antidiabetic drug were included in the subgroup analysis for that antidiabetic drug. We classified the NOACs into four subgroups (dabigatran, rivaroxaban, apixaban, and edoxaban) and compared each NOAC with warfarin regarding their risks of serious hypoglycaemia. Stratified analyses were performed according to age (<65 and ≥ 65 years), sex, and numbers of antidiabetic drugs. Interaction tests were conducted to determine whether differences in the risk of hypoglycaemia between NOACs and warfarin were moderated by age, sex, and the number of antidiabetic drugs.

Inverse probability of treatment weighting using propensity score

Propensity scores were calculated to estimate the probability of prescribing NOACs for each period using a multivariable logistic regression model, including all covariates in Table 1. We then applied stabilized inverse probability of treatment weighting (IPTW) with truncating the extreme weights to construct a weighted dataset with balanced characteristics between treatment groups. Any weight > 5 was considered large, and we reduced any weight > 5 down to this threshold.²⁴ The stabilization and truncation of weights helped avoid unstable or extreme weights for subjects with a very low probability of receiving the treatment administered.^{24–26} Inverse probability of treatment weighting was used to generate the comparison

Table 1 Characteristics and comorbidities at baseline among patients with atrial fibrillation and diabetes taking oral anticoagulants and antidiabetic drugs

	Overall population (N = 56 774)	
	N	%
Age (years) [†]	73.5 $\pm$ 10.2	
Sex		
Male	31 482	55.5
Female	25 292	44.6
Income level (NTD)		
Financially dependent	15 912	28.0
15 840–29 999	26 222	46.2
30 000–44 999	7519	13.2
$\geq 45 000$	7121	12.5
Charlson comorbidity index ^{†,‡}	3.1 $\pm$ 2.1	
CHA2DS2-VASc score ^{†,§}	4.2 $\pm$ 1.7	
Comorbidities		
Hypertension	43 546	76.7
Coronary artery disease	19 490	34.3
Congestive heart failure	15 381	27.1
COPD	7738	13.6
Asthma	4025	7.1
Chronic kidney disease	8438	14.9
Cirrhosis	2123	3.7
Hyperlipidemia	22 329	39.3
Stroke	17 381	30.6
Rheumatoid arthritis	441	0.8
Dementia	3755	6.6
Depression	2036	3.6
Malignancy	4749	8.4
Baseline medication use		
Statins	25 558	45.0
ACEI/ARB	38 277	67.4
β -blocker	29 583	52.1
CCB	25 738	45.3
Diuretics	20 159	35.5
NSAID	17 024	30.0
Corticosteroids	3694	6.5
Antipsychotics	2999	5.3
PPI	5184	9.1
Current diabetes medications		
Metformin	39 033	68.8
Sulfonylurea	21 210	37.4
Meglitinide	4047	7.1
AGI	5300	9.3
TZD	2972	5.2
DPP-4i	20 713	36.5
SGLT-2i	2538	4.5
GLP-1 RA	183	0.3
Insulin	7720	13.6

Table 1 Continued

	Overall population (N = 56 774)	
	N	%
No. of current diabetes medication types		
1	26 407	46.5
2	17 359	30.6
≥3	13 008	22.9
Duration of diabetes		
<2 years	12 427	21.9
≥2 years	44 347	78.1
Duration of AF		
<2 years	37 691	66.4
≥2 years	19 083	33.6
History of serious hypoglycaemia	819	1.4
Index year		
2012–2014	15 727	27.7
2015–2017	19 547	34.4
2018–2020	21 500	37.9
Medical utilization in the previous year		
No. of outpatient visits [†]	29.8 ± 19.0	
No. of ER visits [‡]	1.3 ± 2.0	
No. of hospitalizations [‡]	1.0 ± 1.4	

Data are presented as percentages unless otherwise noted.

[†] Presented as mean ± standard deviation.

[‡] Calculated without including scores for age.

[§] Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category (CHA2DS2-VASc) score.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; AF, atrial fibrillation; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; ER, emergency room; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PPI, proton pump inhibitors; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; and TZD, thiazolidinedione.

set (weighted dataset) before performing each analysis, including the overall and subgroup/stratified/sensitivity analyses.

Statistical analysis

The difference in baseline characteristics between the treatment groups was evaluated using standardized mean difference, with a value of <0.1 indicating a negligible difference. Because the outcome event, serious hypoglycaemia, can occur more than once during each of the follow-up periods within a patient, we used Poisson regression models to estimate the incidence rate ratios (IRRs) of serious hypoglycaemia for patients taking antidiabetics with NOACs vs. warfarin.²⁷ The regression models were weighted by IPTW to control potential confounders; generalized estimating equations were applied to account for intra-individual correlation, because the follow-up periods from the same patient were not entirely independent.²⁸ The risk of serious hypoglycaemia during periods prescribed with warfarin was used as the reference category. The

details and statistical codes for how we performed Poisson regression models weighted by IPTW and applied generalized estimating equations accounting for intra-individual correlation are described in Supplementary Materials (Statistical Code section). A two-tailed *P* value < 0.05 was considered statistically significant. Data management and statistical analyses were performed using R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Sensitivity analyses

We did a sensitivity analysis by excluding patients with any diagnosis of chronic kidney disease (CKD) since the renal function may influence the choice of oral anticoagulants, but we could not obtain the renal function data in the claims-based dataset. In addition, three negative control outcomes (occurrence of influenza, urinary tract infection, and suicide death) were evaluated, for which no causal effect was expected, to indirectly investigate whether potential unmeasured/unknown confounders existed.²⁹

Results

Patient characteristics

A total of 56 774 patients with AF and DM taking antidiabetic drugs with concurrent use of NOACs or warfarin were included in the study population. Their characteristics at baseline (according to their first observed follow-up periods) are shown in Table 1. The mean age was 73.5 years, and females accounted for 44.6% of the study population. We identified 800 691 and 286 384 periods attributable to concurrent use of antidiabetic agents with NOACs and warfarin, respectively. After IPTW, all characteristics were appropriately balanced between the NOAC and warfarin groups, with a standardized mean difference of <0.1 for all variables (see Supplementary material online, Table S1). The flow diagram of patient selection is shown in Supplementary Figure S1.

Risk of serious hypoglycaemia in those with concurrent use of NOACs vs. warfarin

Overall, concurrent use of NOACs with antidiabetic drugs had a significantly lower risk of serious hypoglycaemia than that of warfarin with antidiabetic drugs (IRR = 0.73, 95% CI: 0.63–0.85, *P* < 0.001) (Figure 1). The detailed results (e.g. the follow-up time, event numbers, and incidence rates) are provided in Supplementary Table S2.

Stratified analyses revealed that, in both male and female subgroups, concurrent use of NOACs was associated with a significantly lower risk of serious hypoglycaemia compared to warfarin use. The significantly lower risk of serious hypoglycaemia linked to concurrent NOAC use was observed only in older patients aged ≥65 years and those taking two or more antidiabetic drugs (see Figure 1 and Supplementary material online, Table S2). However, none of the interaction tests reached statistical significance (*P* for interaction with sex = 0.661; *P* for interaction with age = 0.977; and *P* for interaction with antidiabetic drug numbers = 0.219).

In the subgroup analyses of each individual NOAC, a significantly lower risk of serious hypoglycaemia was found in dabigatran (IRR = 0.76, 95% CI: 0.63–0.91, *P* = 0.002), rivaroxaban (IRR = 0.72, 95% CI: 0.61–0.86, *P* < 0.001), and apixaban (IRR = 0.71, 95% CI: 0.57–0.89, *P* = 0.003) users. Although the analysis for edoxaban did not reach statistical significance, a similar trend of lower hypoglycaemia risk in edoxaban users was observed (IRR = 0.77, 95% CI: 0.57–1.03, *P* = 0.078) (see Figure 2 and Supplementary material online, Table S3).

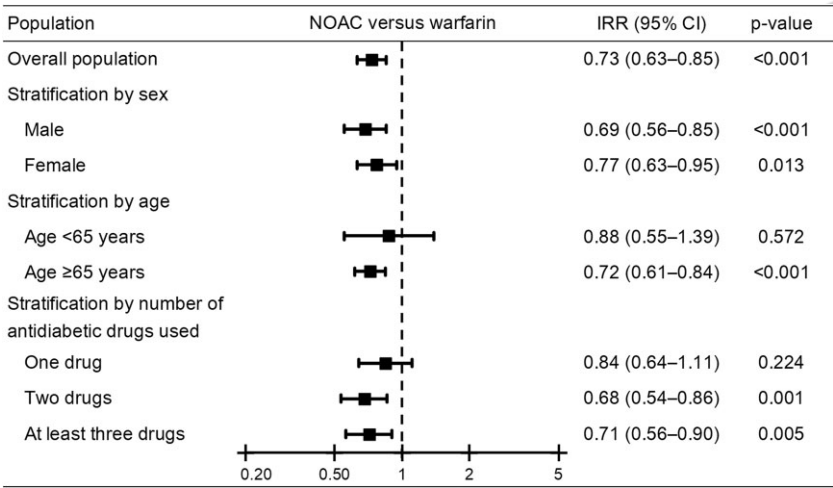


Figure 1 Risk of serious hypoglycaemia in patients taking antidiabetic drugs with concurrent use of NOACs vs. warfarin. Abbreviations: CI, confidence interval; IRR, incidence rate ratio; and NOAC, non-vitamin K antagonist oral anticoagulant.

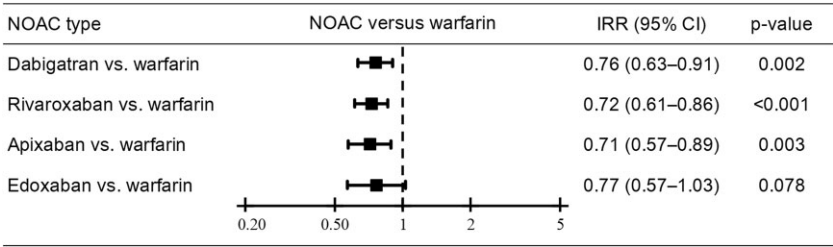


Figure 2 Risk of serious hypoglycaemia in patients taking antidiabetic drugs with concurrent use of each NOAC vs. warfarin. Abbreviations: CI, confidence interval; IRR, incidence rate ratio; and NOAC, non-vitamin K antagonist oral anticoagulant.

Risk of serious hypoglycaemia according to each antidiabetic drug with concurrent use of NOACs vs. warfarin

The significantly lower risk of serious hypoglycaemia associated with concurrent NOAC use was found in patients taking metformin (IRR = 0.73, 95% CI: 0.59–0.89, $P = 0.002$), DPP-4i (IRR = 0.73, 95% CI: 0.59–0.92, $P = 0.007$), or sulfonylurea (IRR = 0.68, 95% CI: 0.56–0.81, $P < 0.001$). The difference in serious hypoglycaemia risks between NOAC and warfarin was not statistically significant in patients taking other antidiabetic drugs (see [Figure 3](#) and Supplementary material online, [Table S4](#)).

Results of sensitivity analyses

The sensitivity analysis excluding patients with CKD demonstrated findings consistent with the primary analysis (see Supplementary material online, [Figure S2](#)); these results suggest that this study's findings were not confounded by CKD status. Regarding the analysis of negative control outcomes (occurrence of influenza, urinary tract infection, and suicide death), none of the outcomes demonstrated a significant association with concurrent use of NOACs compared

with warfarin (see Supplementary material online, [Figure S3](#)). These sensitivity analyses supported the robustness of the study's findings.

Discussion

This nationwide retrospective cohort study demonstrated that patients with DM and AF taking antidiabetic drugs with concurrent use of NOACs had a significantly lower risk of serious hypoglycaemia than those with concurrent use of warfarin. Each NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) had a similar trend of lower hypoglycaemia risk compared with warfarin.

Two previous observational studies have evaluated the risk of serious hypoglycaemia associated with warfarin use vs. non-use in patients taking antidiabetic medications and suggested an increased risk of serious hypoglycaemia in patients taking sulfonylureas with concurrent use of warfarin.^{18,19} However, the comparison in those studies was made only between warfarin use and non-use, without an active comparator. Those findings are more prone to confounding by indication bias as patients/periods with or without anticoagulant treatment may represent different populations or patient conditions (e.g. different disease severity or comorbidity status). Furthermore, if patients are indicated for an oral anticoagulant treatment to

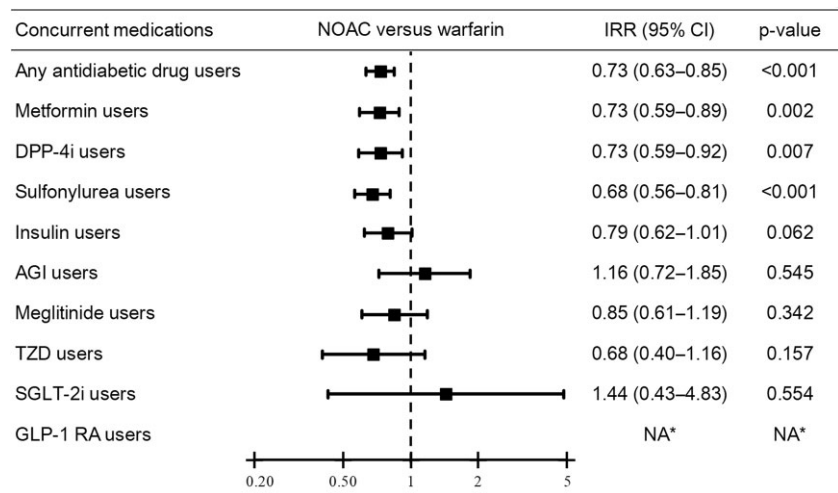


Figure 3 Risk of serious hypoglycaemia in patients taking various antidiabetic drugs with concurrent use of NOACs vs. warfarin. *Not applicable because of the limited sample size. Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; and TZD, thiazolidinedione.

prevent or treat stroke/thromboembolism, such treatment would be prescribed regardless of the potential risk of hypoglycaemia in clinical practice. Therefore, selecting an appropriate oral anticoagulant with lower hypoglycaemia risk is a more clinically important issue for patients with diabetes requiring anticoagulant treatment. As NOACs have been introduced as alternatives to warfarin, evidence comparing hypoglycaemia risk between NOACs and warfarin in this specific population is needed. However, limited evidence regarding this issue has been reported to date. A previous study in 2020 was the first to suggest that NOACs may lead to a lower risk of hypoglycaemia than warfarin in AF patients with diabetes in its sensitivity analysis.¹⁷ However, the study made no distinction between various concurrent antidiabetic medications,¹⁷ which is crucial as the underlying mechanisms may be related to potential drug–drug interactions.¹⁸ Furthermore, the study design did not consider the potential time-varying exposures and confounders, which is a critical issue as the use of medications, especially oral anticoagulants and antidiabetic drugs, can change during several years of follow-up.¹⁷ In addition, a recent observational study focusing exclusively on patients taking sulfonylureas reported an increased risk of severe hypoglycaemia in those taking both sulfonylureas and warfarin compared to sulfonylurea alone,³⁰ consistent with prior literature.^{18,19} However, the authors proposed residual confounding as a potential issue, as no significant difference in hypoglycaemia risk between warfarin and NOACs was observed in their supplementary analyses.³⁰ Nonetheless, only a limited number of hypoglycaemia events in the NOAC group (43 events) were observed. A larger study with a greater number of events is therefore needed. Our present study focused on patients with AF and DM and used an active-comparator design to compare the risk of serious hypoglycaemia between different oral anticoagulants (NOACs vs. warfarin) in patients taking different antidiabetic drugs. Here, the design of partitioning each patient's follow-up time into different periods according to the antidiabetic medication and oral anticoagulant use and retrieving information on exposures and covariates according to each period considered the time-varying exposures and confounders. Additionally, more comprehensive analyses were performed (including various subgroup, stratified, and sensitivity analyses) than those in previous studies.^{17–19} Therefore, this study addressed the previous knowl-

edge gaps and provided more robust findings on this crucial clinical issue.

Patients with certain diseases such as severe valvular heart disease and end-stage renal disease tend to be prescribed warfarin during our study period. To avoid potential confounding by indication, our study population has excluded these patients. Also, we have made efforts to control for various potential confounders, such as the index year, age, sex, income level, Charlson Comorbidity Index, CHA2DS2-VASc score, various comorbidities, baseline medications, current diabetes medications, medical utilization, duration of diabetes and atrial fibrillation, and hypoglycaemia history. In our analysis, all these potential confounding factors were well-balanced after IPTW was undertaken. Thus, the difference in the probabilities of being prescribed to patients with clinically complex situations has been minimized. Indeed, our subgroup analyses revealed that the hypoglycaemia risk was lower in NOAC users compared to warfarin users particularly in elderly patients and those taking multiple antidiabetic drugs who are more likely to have a clinically complex situation. These observations suggest that clinical complexity of patients is unlikely to be a confounding factor for our findings.

While the precise mechanisms remain undetermined, some hypotheses have been proposed. First, warfarin is a vitamin K antagonist, whereas NOACs have no such effect. Accumulated evidence has suggested the beneficial effects of vitamin K on insulin sensitivity and diabetes control.^{12–14} In fact, recent clinical studies suggested that NOACs may offer better glycemic control and lower diabetes complication risks compared to warfarin.^{16,17,31} Patients with poorly controlled diabetes have heightened risk of hypoglycaemia events.^{8,32} Thus, the difference in the drug effects on vitamin K may account for the findings observed in this study. Second, warfarin and certain antidiabetic medications (e.g. sulfonylureas) are both primarily metabolized through the cytochrome P450 2C9 hepatic pathway.^{18,19,33} The shared pathway and a potential drug–drug interaction may hinder sulfonylurea metabolism and increase hypoglycaemia risk. Our study detected the lowest IRR of serious hypoglycaemia within the sulfonylurea subgroup (Figure 3), aligning with the hypothesis that interactions between warfarin and sulfonylureas may precipitate hypoglycaemia events. However, the exact biological mechanisms involved in our

study findings remain uncertain, necessitating further investigation in future research.

In clinical practice, it is essential to achieve an optimal time in the therapeutic range (TTR) for patients using warfarin. A previous study from our hospital in Taiwan reported the mean and distribution of TTR among patients receiving warfarin as follows: mean TTR = 0.70; TTR < 0.6: 29.6%; TTR 0.6–0.9: 36.1%; and TTR > 0.9: 34.2%.³⁴ An increase in dose of warfarin may be needed in some warfarin users who do not achieve the optimal TTR; in these cases, the potential negative impact of warfarin on hypoglycaemia risk may be enhanced.

The present study has important clinical implications. Hypoglycaemia, a dangerous but common side effect of diabetes treatment, can cause neurologic damage, cardiovascular events, and death. Prevention of serious hypoglycaemia is crucial for reducing the personal, healthcare, and socioeconomic burden.^{7,35} This study provides direct, real-world evidence that NOACs are associated with a lower risk of serious hypoglycaemia than warfarin in patients taking antidiabetic agents. Such findings suggest that clinicians should select appropriate medications to prevent serious hypoglycaemia in patients with AF and DM indicated for both anticoagulant and antidiabetic treatment. In patients treated with antidiabetic drugs, NOACs may be used instead of warfarin to decrease the risk of serious hypoglycaemia.

The present study was strengthened by its large-scale, nationwide design using real-world data. The design using periods as the unit of analysis and collecting patient characteristics based on each period helps control potential time-sensitive factors. Nevertheless, several limitations should be addressed. First, the detailed data on patient lifestyle, substance use, and laboratory examination results could not be retrieved from the database. The database also does not contain information regarding patients' medical compliance, disease severity, clinical complexity, and social and domestic factors. While IPTW was applied to balance various patient characteristics between the study groups, it is still possible that there was imbalance in unmeasured confounder between these two groups that may account for our observed results. Second, our study focuses on serious hypoglycaemic events with the need of administration of high-concentration intravenous glucose in the emergency department or during hospitalization. However, some patients, especially those with mild symptoms, might not seek medical assistance and the present study did not include these mild events. As such, our findings cannot be generalized to patients with mild hypoglycaemia. Third, only a few patients were prescribed SGLT-2i and GLP-1 RA in the database because these medications were introduced and covered by Taiwan's National Health Insurance relatively late. The small sample sizes with few event numbers in the subgroup analyses for SGLT-2i and GLP-1 RA resulted in a wide confidence interval or the unavailability to estimate the study outcome. Further studies are required to address this issue. Fourth, given the nature of an observational study, we could not reliably determine whether the modest treatment effect found in our study was causal. Further research is required to confirm our findings. Lastly, our findings were based on the analyses of data in Taiwan, and certain patient groups (e.g. those with ESRD or undergoing valve replacement surgery) were not included. As such, our results may not be generalized to different populations or other areas/countries.

In conclusion, this real-world nationwide cohort study demonstrated that patients with AF and DM taking antidiabetic drugs with concurrent use of NOACs had a significantly lower risk of serious hypoglycaemia than those with concurrent use of warfarin. These findings are based on more evidence from the patients using relatively old antidiabetic agents, but less from the users with modern antidiabetic agents. It is still necessary to further evaluate whether the findings are consistent across patients using different antidiabetic drugs, especially for the most modern antidiabetic agents. Further studies, particularly randomized controlled trials, are needed to validate our findings.

Supplementary Material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Conflict of interest: None declared.

Ethics approval and consent to participate

The Research Ethics Committee of Hualien Tzu Chi Hospital approved our study (REC No: IRB110-170-C); the requirement for informed consent was waived.

Consent for publication

Not applicable.

Data availability statement

The dataset used in this study is managed by the Taiwan Ministry of Health and Welfare and thus cannot be made available publicly. Researchers interested in accessing this dataset can submit a formal application to the Ministry of Health and Welfare to request access (Taiwan Ministry of Health and Welfare, No. 488, Section 6, Zhongxiao E Rd, Nangang District, Taipei 115, Taiwan; website: <https://dep.mohw.gov.tw/DOS/cp-2516-59203-113.html>).

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Supplementary Materials

Risk of serious hypoglycemia in patients with atrial fibrillation and diabetes concurrently taking antidiabetic drugs and oral anticoagulants: A nationwide cohort study



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Supplemental Note 1: A brief introduction to Taiwan's National Health Insurance Research Database (NHIRD)

The National Health Insurance program is a mandatory single-payer program administered by the government of Taiwan since 1995 and covers more than 99% of the population of Taiwan. The NHIRD comprises healthcare data from approximately 23.6 million individuals, representing the entire population of Taiwan. The NHIRD includes patient demographic information and medical claims for inpatient, outpatient, and emergency care services. The diagnostic and procedure codes in the NHIRD were derived using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes before 2016 and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes after 2016. The NHIRD is maintained by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. For research purposes, anonymized data was made available.

Table S1. Baseline characteristics according to each period with concurrent use of specific oral anticoagulants and antidiabetic drugs that were used as an analytic unit*

	Before IPTW			After IPTW [†]		
	NOAC (N=800,691)	Warfarin (N=286,384)	SMD [‡]	NOAC (N=801,404)	Warfarin (N=279,368)	SMD [‡]
Age (years) [§]	74.9±9.5	72.3±10.5	0.260	74.3±9.7	74.0±10.3	0.030
Sex						
Male	56.4	56.8	0.008	56.7	56.9	0.004
Female	43.6	43.2	0.008	43.3	43.1	0.004
Income level (NTD)						
Financially dependent	28.7	29.2	0.011	28.9	29.2	0.007
15,840–29,999	45.2	43.5	0.034	44.6	44.5	0.002
30,000–44,999	12.3	14.5	0.065	13.0	13.0	0.000
≥45,000	13.7	12.8	0.027	13.5	13.3	0.006
Charlson Comorbidity Index ^{§¶}	3.3±2.1	3.3±2.1	0.000	3.3±2.1	3.3±2.1	0.000
CHA2DS2-VASc score ^{§#}	4.3±1.6	4.2±1.7	0.061	4.3±1.6	4.3±1.7	0.000
Comorbidities						
Hypertension	73.6	72.5	0.025	73.4	73.5	0.002
Coronary artery disease	33.5	33.2	0.006	33.4	33.2	0.004
Congestive heart failure	27.9	30.0	0.046	28.3	28.3	0.000
COPD	13.7	13.0	0.021	13.5	13.5	0.000
Asthma	6.6	6.4	0.008	6.6	6.6	0.000
Chronic kidney disease	17.4	18.4	0.026	17.7	18.1	0.010
Cirrhosis	2.4	4.5	0.115	3.0	3.1	0.006
Hyperlipidemia	38.6	36.2	0.050	38.1	38.5	0.008
Stroke	31.5	32.0	0.011	31.7	31.0	0.015
Rheumatoid arthritis	0.7	0.6	0.012	0.7	0.6	0.012
Dementia	8.1	5.9	0.086	7.5	7.2	0.011
Depression	3.8	3.6	0.011	3.8	3.8	0.000
Malignancy	9.1	7.7	0.050	8.7	8.5	0.007
Baseline medications						
Statins	54.5	47.7	0.136	52.7	52.3	0.008
ACEI/ARB	70.5	69.7	0.017	70.3	70.3	0.000
β-blocker	61.5	58.9	0.053	60.8	60.5	0.006
CCB	43.8	47.5	0.074	44.8	44.6	0.004
Diuretics	41.0	48.3	0.147	42.8	42.9	0.002
NSAID	27.6	26.1	0.034	27.2	27.2	0.000
Corticosteroids	6.4	5.9	0.021	6.2	6.2	0.000
Antipsychotics	7.2	6.0	0.048	6.9	6.6	0.012

PPI	11.3	9.5	0.059	10.9	11.0	0.003
Current diabetes medications						
Metformin	69.4	61.7	0.163	67.1	66.4	0.015
Sulfonylurea	37.1	44.9	0.159	39.2	39.6	0.008
Meglitinide	7.3	9.9	0.093	8.1	8.2	0.004
AGI	10.5	12.7	0.069	11.0	11.3	0.010
TZD	6.1	5.7	0.017	6.1	6.0	0.004
DPP-4i	46.7	38.2	0.173	44.6	44.7	0.002
SGLT-2i	8.7	2.2	0.289	7.0	6.4	0.024
GLP-1 RA	0.9	0.4	0.062	0.8	0.7	0.012
Insulin	16.0	17.6	0.043	16.6	16.8	0.005
No. of current diabetes medication types						
1	36.5	40.5	0.082	37.4	37.6	0.004
2	33.3	33.1	0.004	33.3	33.3	0.000
≥3	30.2	26.5	0.082	29.3	29.1	0.004
Duration of diabetes				6.1±2.8	6.0±2.9	0.035
< 2 years	8.9	13.5	0.146	10.3	8.8	0.051
≥ 2 years	91.1	86.5	0.146	89.7	91.2	0.051
Duration of AF						
< 2 years	34.3	34.7	0.008	34.8	32.3	0.053
≥ 2 years	65.7	65.3	0.008	65.2	67.7	0.053
History of serious hypoglycemia	1.6	1.9	0.023	1.7	1.7	0.000
Index year						
2012–2014	7.1	44.5	0.945	17.0	17.4	0.011
2015–2017	33.1	36.0	0.061	33.8	34.8	0.021
2018–2020	59.9	19.5	0.907	49.2	47.8	0.028
Medical utilization in the previous year						
No. of outpatient visits [§]	32.0±19.0	32.5±19.2	0.026	32.1±19.2	32.1±18.6	0.000
No. of ER visits [§]	1.2±2.0	1.2±2.1	0.000	1.2±2.0	1.1±2.1	0.049
No. of hospitalizations [§]	0.8±1.4	0.8±1.3	0.000	0.8±1.3	0.8±1.3	0.000

Data are presented as percentages unless otherwise noted.

* Each period with concurrent use of the same combination of oral anticoagulants and antidiabetic drugs in each patient was used as the unit of analysis.

† All covariates listed in the table were used to calculate the propensity score for IPTW.

‡ A standardized mean difference of <0.1 indicates a negligible difference.

§ Presented as mean±standard deviation.

¶ Calculated without including scores for age.

Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category (CHA2DS2-VASc) score

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AGI, alpha-glucosidase inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl

peptidase-4 inhibitors; ER, emergency room; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drugs; NTD, New Taiwan Dollar; OAC, oral anticoagulant; PPI, proton pump inhibitors; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference; TZD, thiazolidinedione



Table S2. The event number, incidence rate and incidence rate ratio of serious hypoglycemia in patients taking antidiabetic drugs with concurrent use of NOAC versus warfarin

Population		Person-day	Event number	Incidence rate *	IRR [†] (95% CI)	p-value
Overall population	NOAC	26,807,039	1,276	4.8	0.73 (0.63–0.85)	<0.001
	Warfarin	8,707,347	565	6.5	1.00 (Reference)	
Stratification by sex	Male					
	NOAC	15,343,655	550	3.6	0.69 (0.56–0.85)	<0.001
	Warfarin	5,019,131	264	5.3	1.00 (Reference)	
	Female					
	NOAC	11,462,888	732	6.4	0.77 (0.63–0.95)	0.013
	Warfarin	3,676,946	300	8.2	1.00 (Reference)	
Stratification by age	Age <65 years					
	NOAC	3,404,949	72	2.1	0.88 (0.55–1.39)	0.572
	Warfarin	2,164,743	56	2.6	1.00 (Reference)	
	Age ≥65 years					
	NOAC	23,332,873	1,233	5.3	0.72 (0.61–0.84)	<0.001
	Warfarin	6,595,230	480	7.3	1.00 (Reference)	
Stratification by number of antidiabetic drugs used	One drug					
	NOAC	9,977,459	292	2.9	0.84 (0.64–1.11)	0.224
	Warfarin	3,609,741	126	3.5	1.00 (Reference)	
	Two drugs					
	NOAC	9,062,289	439	4.8	0.68 (0.54–0.86)	0.001
	Warfarin	2,884,916	204	7.1	1.00 (Reference)	
	At least three drugs					
	NOAC	7,749,286	557	7.2	0.71 (0.56–0.90)	0.005
	Warfarin	2,220,737	224	10.1	1.00 (Reference)	

* Per 100,000 person-days

† The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NOAC, non-vitamin K antagonist oral anticoagulant

Table S3. The event number, incidence rate and incidence rate ratio of serious hypoglycemia in patients taking antidiabetic medications with concurrent use of each NOAC versus warfarin

Medication	Person-day	Event number	Incidence rate*	IRR [†] (95% CI)	<i>p</i> -value
Dabigatran	7,654,348	356	4.7	0.76 (0.63–0.91)	0.002
Warfarin	8,785,662	547	6.2	1.00 (Reference)	
Rivaroxaban	10,461,826	502	4.8	0.72 (0.61–0.86)	<0.001
Warfarin	7,862,802	520	6.6	1.00 (Reference)	
Apixaban	4,390,716	226	5.1	0.71 (0.57–0.89)	0.003
Warfarin	6,334,269	451	7.1	1.00 (Reference)	
Edoxaban	3,298,918	167	5.1	0.77 (0.57–1.03)	0.078
Warfarin	3,713,313	243	6.5	1.00 (Reference)	

* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NOAC, non-vitamin K antagonist oral anticoagulant

Table S4. The event number, incidence rate and incidence rate ratio of serious hypoglycemia according to antidiabetic drugs with concurrent use of NOAC versus warfarin

Concurrent medications	Person-day	Event number	Incidence rate [*]	IRR [†] (95% CI)	<i>p</i> -value
Any antidiabetic drugs					
NOAC	26,807,039	1,276	4.8	0.73 (0.63–0.85)	<0.001
Warfarin	8,707,347	565	6.5	1.00 (Reference)	
Metformin					
NOAC	19,352,161	748	3.9	0.73 (0.59–0.89)	0.002
Warfarin	5,578,463	295	5.3	1.00 (Reference)	
DPP-4i					
NOAC	12,706,701	614	4.8	0.73 (0.59–0.92)	0.007
Warfarin	3,388,180	224	6.6	1.00 (Reference)	
Sulfonylurea					
NOAC	9,796,663	724	7.4	0.68 (0.56–0.81)	<0.001
Warfarin	3,890,754	420	10.8	1.00 (Reference)	
Insulin					
NOAC	3,267,086	386	11.8	0.79 (0.62–1.01)	0.062
Warfarin	1,202,730	179	14.9	1.00 (Reference)	
AGI					
NOAC	2,612,129	152	5.8	1.16 (0.72–1.85)	0.545
Warfarin	1,022,866	54	5.2	1.00 (Reference)	
Meglitinide					
NOAC	1,683,623	175	10.4	0.85 (0.61–1.19)	0.342
Warfarin	743,696	97	13.1	1.00 (Reference)	
TZD					
NOAC	1,551,623	87	5.6	0.68 (0.40–1.16)	0.157
Warfarin	459,988	38	8.2	1.00 (Reference)	
SGLT-2i					
NOAC	2,493,693	64	2.5	1.44 (0.43–4.83)	0.554
Warfarin	209,069	4	1.8	1.00 (Reference)	
GLP-1 RA					
NOAC	199,827	0	0.0	NA [‡]	NA [‡]
Warfarin	25,391	4	15.0	NA [‡]	

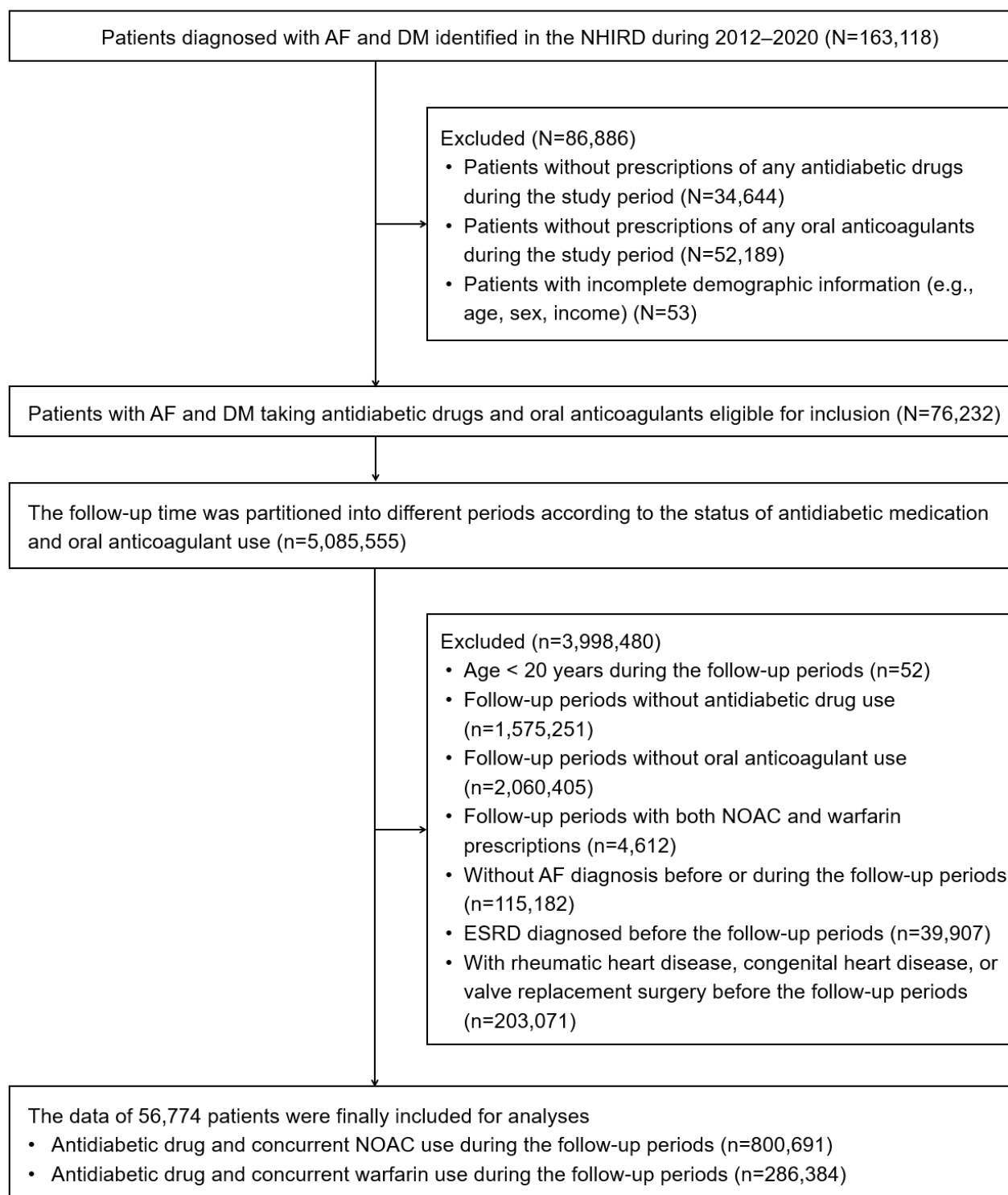
* Per 100,000 person-days

[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.

[‡] Not applicable because of the limited sample size.

Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione

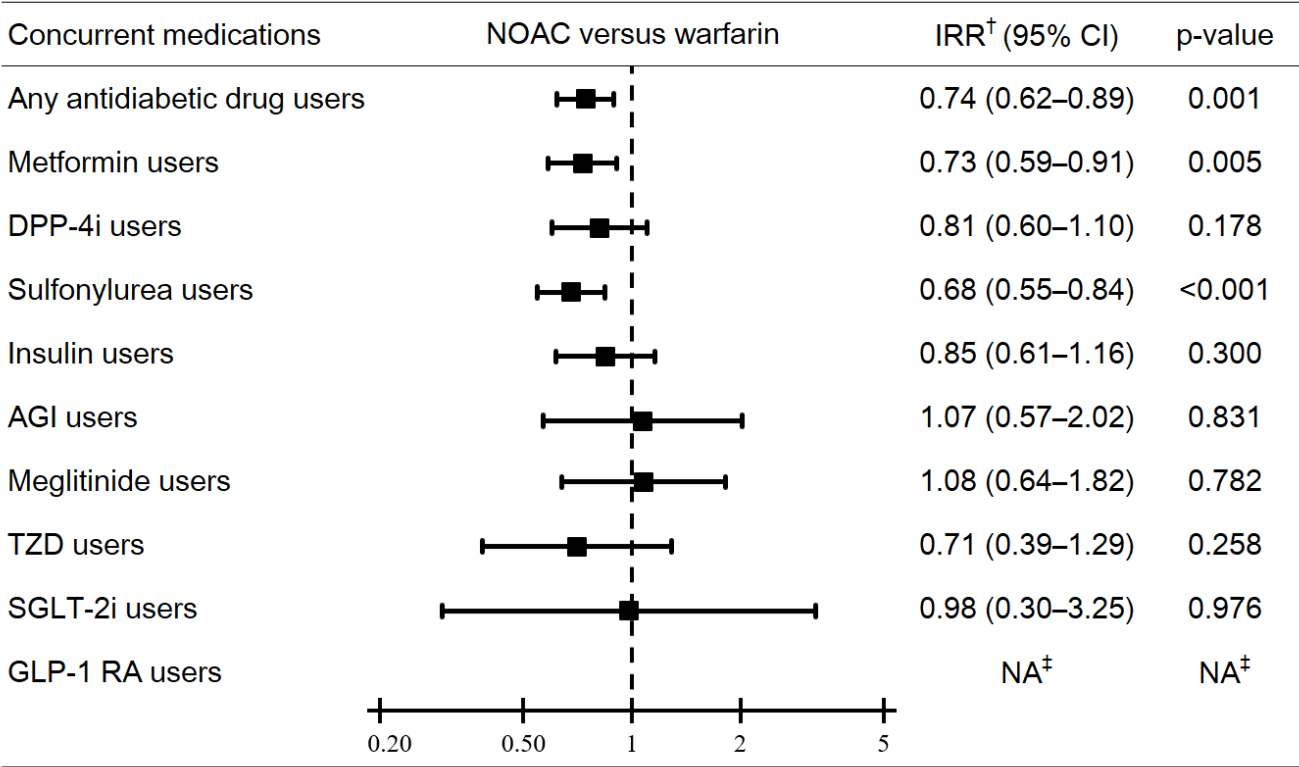
Figure S1. Flow diagram of patient selection



Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; ESRD, end-stage renal disease; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulant

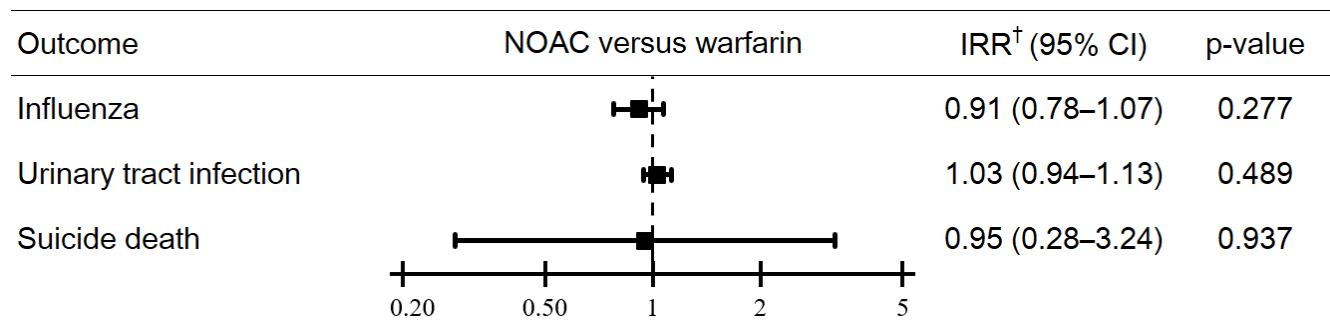


Figure S2. Risk of serious hypoglycemia in patients taking various antidiabetic drugs with concurrent use of NOACs versus warfarin in the sensitivity analysis excluding patients with chronic kidney diseases



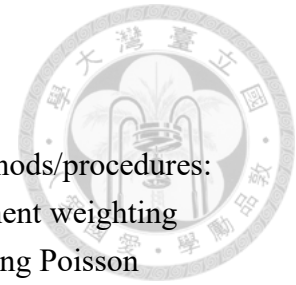
[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.
[‡] Not applicable because of the limited sample size.
Abbreviations: AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TZD, thiazolidinedione

Figure S3. Risk of negative control outcomes in patients taking antidiabetic drugs with concurrent use of NOAC versus warfarin



[†] The IRR was calculated using Poisson regression models weighted by IPTW and estimated by generalized estimating equations to account for potential intra-individual correlation.
Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; NOAC, non-vitamin K antagonist oral anticoagulant

Appendix - Statistical Codes



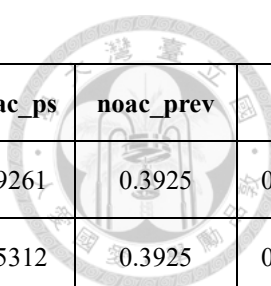
1. Statistical software information

We used R to execute data management and the following analytic methods/procedures: propensity score calculation and stabilized inverse probability of treatment weighting (IPTW). We used SAS software to estimate the incidence rate ratios using Poisson regression models with IPTW and the generalized estimating equations (GEE) approach. The statistical software used is described below.

- SAS Version: 9.4; Statistical module: SAS/STAT 15.2
- R Version: 4.1.3

2. Data snapshot

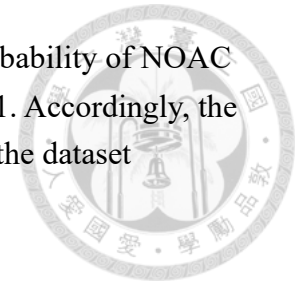
Here, we demonstrate a dataset that includes the major variables used as an example. Variable *id* represents the unique number used to identify each patient. We divided each patient's follow-up time into different periods according to the combination of specific antidiabetic medications and oral anticoagulants used concurrently. Each period for each patient was used as the unit of analysis. The start and end dates for each observation period were coded as *obs_date_start* and *obs_date_end*, respectively. The variable *obs_days* represents the observed number of days in each period. The variable *hg_count* recorded the count of hypoglycemia events during each observation period. Our comparison groups, NOAC and warfarin, were coded in the variable *noac*, with *noac* = 1 and *noac* = 0, respectively. The data also included the following covariates: *age* (years), *female* (0 = male, 1 = female), and concurrent DM medication dummies (*metformin*, *su*, *dpp4i*) for the demonstration. The other covariates shown in Table 1 were suppressed to avoid the program line being too long to read.



Id	obs_date_start	obs_date_end	obs_days	hg_count	noac	age	female	metformin	su	dpp4i	...	noac_ps	noac_prev	iptw
S00033201	2014-03-12	2014-06-03	84	1	1	75	0	1	0	0	...	0.9261	0.3925	0.4238
S00033201	2014-06-04	2014-08-26	84	0	1	75	0	1	1	0	...	0.5312	0.3925	0.7389
S00033201	2014-09-25	2014-12-17	84	2	1	75	0	1	1	1	...	0.7082	0.3925	0.5543
S00033201	2014-12-18	2015-02-11	56	0	0	75	0	1	1	1	...	0.6776	0.3925	0.5793
S00033201	2015-02-15	2015-03-14	28	0	0	76	0	1	0	1	...	0.4365	0.3925	0.8992
S00049025	2014-04-25	2014-05-08	14	0	0	52	1	1	0	1	...	0.3403	0.3925	0.9208
S00049025	2014-05-09	2014-05-22	14	1	0	52	1	1	0	0	...	0.2434	0.3925	0.8029
S00049025	2014-05-23	2014-07-17	56	0	1	52	1	1	0	0	...	0.5762	0.3925	1.4335

3. Calculating propensity score

We used the `glm()` and `predict()` functions in R to calculate the probability of NOAC treatment for each follow-up period using all covariates listed in Table 1. Accordingly, the predicted probability variable (`type = "response"`) is contained in the dataset (`dt$noac_ps`).



R code:

```
noac_psmodel <- glm(  
  formula = treated ~ female + age + metformin + su + dpp4i,  
  data = dt,  
  family = binomial("logit"))  
  
dt$noac_ps <- predict(  
  object = noac_psmodel,  
  data = dt,  
  type = "response")
```

4. Inverse probability of treatment weighting (IPTW)

We implemented stabilized inverse probability of treatment weighting (IPTW) to control confounders (Sturmer et al., 2014, *J Intern Med*). In contrast to traditional IPTW, the stabilized process multiplies the weight by the overall marginal prevalence of the treatment exposure. First, we calculated the marginal prevalence of the NOAC as `noac_prev` column. In this case, the value was 0.3925. Then, the `iptw` variable was generated for the following weighting in the analysis.

R code:

```
dt$noac_prev <- mean(dt$noac)  
dt <- dt [noac == 1, `:=`(iptw = noac_prev / noac_ps)]  
dt <- dt [noac == 0, `:=`(iptw = (1 - noac_prev) / (1 - noac_ps))]
```

As a result, we had a complete dataset with the `iptw` variable.

Reference: Stürmer *et al* (2014). Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med*. 275(6):570-80. Doi: 10.1111/joim.12197.

5. Generalized linear model

The **GENMOD** procedure in the SAS software performs a regression analysis using a generalized linear model. With our repeated measurement study design and data structure, we accounted for the self-correlation between different observed periods of the same subject using the GEE approach. The hypoglycemia event count (*hg_count*) was set in the **model** statement using *noac* as an independent variable. We used the Poisson distribution (**dist = poisson**) to model the distribution of event counts and estimate incidence rate ratios. We used an offset variable (**ln_obs_days = ln(obs_days)**) to deal with the varied lengths between the different observed periods. To consider the cluster effect within the individuals, we first declared **class id** statement and **repeated subject = id** to identify clustered data. Second, the **corr = exch** option was used to design a correlation matrix in an exchangeable structure. When the IPTW method was used to control for confounders, a **weight iptw** statement was included.

SAS code:

```
proc genmod data = dt;
  class id;
  model hg_count = noac / dist = poisson offset = ln_obs_days;
  repeated subject = id / corr = exch;
  weight iptw;
run;
```