國立臺灣大學公共衛生學院流行病學與預防醫學研究所

博士論文

Institute of Epidemiology and Preventive Medicine
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Doctoral Dissertation

利用世代研究探討心血管疾病患者在不同治療方針與各項風險因子之預後

Applying the Cohort Studies to Explore the Outcomes in Patients with Cardiovascular Diseases under Various Treatment Strategies and Risk Factors

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博士生涯的三年時光一晃而過，回首過往求學、研究途中風風雨雨的歲月，心中備感充實、感慨良多。首先我要誠摯地感謝我的導師-簡國龍教授，無論在我的求學、研究、和生活上，都給予我最充足的教導、關懷和支援。簡老師以嚴謹的治學之道、積極樂觀的生活態度，為我樹立科學和教育道路上的典範。再來，我要感謝我在臺北榮民總醫院心臟內科的人生導師-陳適安教授和林彥璋教授。陳適安教授和林彥璋教授是鼓勵我前往博士學路上精進的貴人，如果沒有他們提供我充足的學術資源和指導，我的求學道路就不會如此地順遂。另外，我也要感謝臺北榮民總醫院心臟內科的鐘法博醫師，我們一起並肩執行過許多研究和發表，我並從中獲得許多受益的學術思路。

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中文摘要

背景：心血管疾病是全球主要的死亡原因，造成心血管疾病患者死亡的主要因素為冠狀動脈疾病、心臟衰竭、和中風。探討風險因子與心血管疾病風險之間的關聯性很重要，透過風險評估可以改善治療策略，而世代研究可以衡量特定暴露在心血管結局的發生率和危險因子。

方法：我們使用世代研究來探討心血管疾病的危險因素和臨床結果。本博士論文包含三個研究：(1) 第一個研究利用金山社區心血管世代研究調查，探討一般民眾心因性猝死的危險因子 (針對年紀大於 35 歲、沒有冠心病、和左心室收縮功能< 35%者)。研究重點放在 12 導程心電圖、標準心臟超音波、和頸動脈超音波等篩檢工具的異常，利用佛萊明風險分數方法來發展預測十年內心因性猝死的評分系統，並使用自助抽樣法驗證。(2) 第二個研究針對心房顫動患者，我們使用臺灣全民健康保險研究資料庫的醫療資料，來發展預測一年內中風評分系統，並進行內部驗證。(3) 第三個研究基於全國大型世代資料，探討臺灣地區罕見疾病類澱粉性沉積症患者的發生率，以及評估長期心室頻脈和心因性死亡的風險。

結果：(1) 嶄新心因性猝死預測分數系統 (CCCC-SCD-Score) 具有良好的十年內心因性猝死預測能力 (高風險切點: > 5; 一致性指數 [C 指數]: 0.881, 95 % 信賴區間: 0.805-0.958; Hosmer-Lemeshow 適合度檢定: P 值 = 0.82)，分數依年齡組別 (最高 4 分)、左心室肥大 (1 分)、高血壓 (1 分)、左心室射出分量 < 40% (1 分)、主動脈瓣流速 > 190 cm/s (1 分)、以及頸動脈斑塊分數 ≥ 5 (1 分) 計算。(2) 透過評估電燒狀態新發展的心房顫動預測中風評分系統 (AF-CA-Stroke: 高風險切點: > 5; 一致性指數 [C 指標]: 0.658, 95 % 信賴區間: 0.644-0.675; Hosmer-Lemeshow 適合度檢定: P 值 = 0.81)，在預測一年內中風風險方面比傳統評分系統 ($CHADS_2$，一致性指數 [C 指數]: 0.577, 95 % 信賴區間: 0.570-0.584) 具有更好的辨別能力 (DeLong 測試: P 值 < 0.001)，分數依年齡組別 (最高 5 分)、未接受心房顫動電燒手術 (1 分)、過去中風史 (1 分)、慢性腎臟病 (1 分)、其他過去心臟 (冠心症) 或周邊血管疾病 (1 分) 計算。(3) 類澱粉性沉積症患者在臺灣的發生率為每十萬人年 6.54 人，心臟型類澱粉性沉積症患者在臺灣的發生率為每十萬人年 0.61 人。罹患有類澱粉性沉積症的患者未來發生心室頻脈的風險 (調整後風險函數比: 7.90, 95% 信賴區間: 4.49-13.9) 和心血管死亡風險 (調整後風險函數比: 5.09, 95 % 信賴區間: 4.23-6.12) 都較沒有罹患類澱粉性沉積症的患者高。

結論：瞭解各種心血管疾病患者的危險因子很重要，可以針對具有心血管事件高風險的患者，進行長期追蹤，以助於提供初級預防處置和治療的策略。

關鍵字：類澱粉性沉積症、心房纖維顫動、心血管疾病、風險評估、心因性猝死、中風。

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English Abstract

Background:

Cardiovascular diseases (CVDs) are among the leading causes of death worldwide. The main causes of death in CVD patients are coronary artery disease (CAD), heart failure, and stroke. Cohort studies are used to measure incidence rates for cardiovascular (CV) outcomes based on a specific exposure, as well as to examine the risk factors and clinical outcomes associated with CVDs. By assessing risk, the treatment strategies can be improved for patients with CVDs.

Methods:

We investigated several factors and outcomes of CVDs in the cohort studies. The doctoral dissertation includes three projects: (1) The objective of the first project was to investigate risk factors for sudden cardiac death (SCD) in a general population aged ≤ 35 years without a prior history of CAD or left ventricular ejection fraction < 35 based on the Chin Shan Community Cardiovascular Cohort, focusing on the screening tools of 12-lead electrogram, standard echocardiography, and carotid artery duplex sonography. By using the Framingham risk score methods, we developed a novel CCCC-SCD-Score to predict incident 10-year SCD. The CCCC-SCD-Score was internally validated using bootstrapping method. (2) The objective of the second project was to develop a novel model-based point scoring system for 1-year stroke prediction in patients with atrial fibrillation (AF) using Taiwan's National Health Insurance Research Database. An internal validation study was performed. (3) The objective of the third project was to investigate the risks of new-onset ventricular tachycardia and CV outcomes in patients with amyloidosis after a long-term follow-up based on a representative national cohort.

Results:

(1) A CCCC-SCD-Score score is calculated using age groups (maximum points = 4), left ventricular hypertrophy, hypertension, left ventricular ejection fraction < 40%, aortic flow rate > 190 cm/s, and carotid plaque scores ≥ 5 (point = 1 for each risk factor). In predicting 10-year SCD risk, the CCCC-SCD-Score had good prediction performance (cut-off point: > 5; C-index: 0.881, 95% confidence interval [CI]: 0.805-0.958; Hosmer-Lemeshow test: P-value = 0.82). (2) The AF-CA-Stroke scoring system includes important clinical risk factors: age (maximum

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points = 5), the status of not having undergone AF ablation (point = 1), prior stroke history (point = 1), chronic kidney disease (point = 1), and prior CAD or vascular disease (point = 1). The novel AF-CA-Stroke scoring system using the status of AF ablation (cut-off point: > 5; C-index: 0.658, 95% CI: 0.644-675; Hosmer-Lemeshow test: P-value = 0.81) predicted incident 1-year stroke risk more accurately than conventional $CHADS_2$ scoring system (C-index: 0.577, 95% CI: 0.570-584) (P-value = 0.001, using the DeLong test). (3) The incidence rates of amyloidosis and cardiac amyloidosis were 6.54 and 0.61 per 100000 person-years, respectively. Amyloidosis was associated with higher rates of ventricular tachycardia (adjusted HR: 7.90, 95% CI: 4.49-13.9) and CV deaths (adjusted HR: 5.09, 95% CI: 4.23-6.12).

Conclusions:

Knowledge of risk factors in patients with various CVDs is essential, and long-term follow-up of patients at high risk for cardiovascular events can aid in primary prevention and guide treatment strategies.

Key words:

Amyloidosis, atrial fibrillation, cardiovascular diseases, risk assessment, sudden cardiac death, stroke.

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Abbreviations

AAD：anti-arrhythmic drugs;
AF：atrial fibrillation;
AFFIRM study：Atrial Fibrillation Follow-up Investigation of Rhythm Management study;
ALT：alanine aminotransferase;
ARIC study: Atherosclerosis Risk in Communities study;
AST：aspartate aminotransferase;
AUC: area under curve;
BUN：blood urea nitrogen;
CABANA study：Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation study;
CAD：coronary artery disease;
CCA：common carotid artery;
CCCC study：Chin-Shan Community Cardiovascular Cohort study;
CHF AF trial：Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial.
CHD study: Coronary Heart Disease study;
CHS study: Cardiovascular Health study;
CI：confidence interval;
CIMT：carotid intima-media thickness;
CV：cardiovascular;
CVDs：cardiovascular diseases;
CSH: cause-specific hazard function;
ECA：external carotid artery;
ECG：electrogram (electrocardiography);
HDL：high-density lipoprotein;
HF: heart failure;
HR：hazard ratio;
ICA：internal carotid artery;
ICD-9-CM：International Classification of Diseases, Ninth Revision, Clinical Modification;
ICD implantation: implantable cardioverter-defibrillators implantation;
IRB：Institutional Review Board;
LDL：low-density lipoprotein;
LV：left ventricular/ventricle;
LVEF：left ventricular ejection fraction;
LVH：left ventricular hypertrophy;
NHIRD：National Health Insurance Database;
NOAC: non-vitamin K antagonist oral anticoagulant;
NRI: net reclassification index;
PYs：person-years;
PS：propensity-score;
RACE trial：RAte Control versus Electrical cardioversion for persistent atrial fibrillation trial.
ROC: receiver operating characteristic curve;
SCD：sudden cardiac death;
SD：standard deviation;
TVGH：Taipei Veterans General Hospital;
VT: ventricular tachycardia;
WHO：World Health Organization.

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Chapter 1：Introduction

1.1 Overview of Cardiovascular Diseases

Cardiovascular diseases (CVDs) are disorders of the heart and systemic tissues, including coronary artery disease (CAD), heart failure (HF), cardiac arrhythmia, cerebrovascular disease, cardiomyopathy, aorta disease, heart valve disease, pericarditis, subclinical atherosclerosis, and peripheral vascular disease [1,2]. CVDs result in huge economic burdens, and CVDs are the leading causes of death globally [1]. The main causes of death in CVD patients (80%) are due to CAD, HF, and stroke [2,3].

A number of factors contribute to CVD, such as age, gender, hypertension, chronic kidney disease, diabetes mellitus, high cholesterol, obesity, metabolic syndrome, physical inactivity, and smoking. According to the 2017 USA National Health Interview Survey, the age-adjusted prevalence of all types of heart disease was 10.6%, and the prevalence of CVD varied among different racial groups [2]. It is important to investigate how risk factors affect cardiovascular (CV) and death outcomes. Preventive medicine requires a thorough assessment of CV risks [4].

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1.2 Risk Assessment on Clinical Outcomes based on Cohort Studies

Health caregivers can identify or calculate risk factors via risk assessment, which may help people recognize their health condition and improve their management strategy and decision-making [4,5]. Several cardiovascular risk scoring systems were identified based on the cohort studies [4,6-8]. The cohort study design represents one of the fundamental designs in the field of the epidemiology. The observation of a risk or time of a specific event requires that a whole cohort remains at risk and under observation for the entire follow-up period. Hence, a cohort study can be used to measure incidence rates for CV and death outcomes in relation to a specific exposure [9]. For example, the Framingham calculator is the most commonly used risk scoring system to identify risks of CVD or death developing from the Framingham cohort study [7].

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1.3 Study Projects

The cohort studies were used to explore the risk factors of CVDs and clinical outcomes. This doctoral dissertation includes three study projects (**Figure 0**):

Project 1: Risk Assessment of Sudden Cardiac Death

Applying the Chin-Shan Community Cardiovascular Cohort Study to Explore the Risk Factors of Sudden Cardiac Death: A Novel Point-Based Prediction Model for General Population

Project 2: Risk Assessment of Stroke in Patients with Atrial Fibrillation

Novel Model-Based Point Scoring System for Predicting Stroke Risk in Atrial Fibrillation Patients: Results from a Nationwide Cohort Study with Validation

Project 3: Clinical Outcomes in Patients with Amyloidosis

Risks of Ventricular Tachyarrhythmia and Deaths in Patients with Amyloidosis– A Long-term Cohort Study

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1.4 Project 1: Risk Assessment of Sudden Cardiac Death

1.4.1 Definition and Importance of Sudden Cardiac Death

Sudden cardiac death (SCD) is a leading cause of death in the CV sector, accounting for approximately 15-20% of all deaths annually [10]. SCD is a non-traumatic and unexpected fatality resulting from sudden cardiac arrest caused by loss of heart function within 6 hours of previously witnessed normal health [11]. While modern medicine has made tremendous advances, SCD remains one of the greatest challenges for physicians all over the world. The age-adjusted annual SCD rate is 0.971 (95% confidence interval [95% CI] of 0.968 to 0. 974) per 1000 population in the United States in 2017 [2]. The causes of SCD differ among age groups: In the younger population < 35 years, SCD is often due to congenital heart defects, while in the general population ≥ 35 years, the cause is more often associated with CAD [12,13].

Determining the etiology of a SCD is dependent on autopsy findings, and the causes can be grouped into structural (e.g. CAD, non-ischemic cardiomyopathies, valvular heart disease, and other structural causes) and non-structural pathologies (e.g. arrhythmic causes) [12]. Today, structural heart diseases such as HF, valvular heart disease, and CAD are common causes of SCD. The leading cause of SCD in the western world is CAD, which accounts for 70– 80% of

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SCD cases [2,12]. In addition, acute stroke can disturb central autonomic control, resulting in myocardial injury, cardiac arrhythmia, electrocardiographic abnormalities, and ultimately sudden death [14].

1.4.2 Examination of the Risk Factors of Cardiovascular Diseases

To exam the risks of CVDs is important in identifying the causes of SCD. Traditional risk factors include physical factors of age, gender, obesity, and various races; underlying diseases of CAD, HF, atrial fibrillation (AF), hypertension, diabetes mellitus, left ventricular hypertrophy (LVH), and renal dysfunction, individuals with these factors may be at risks of SCD. In addition, abnormal biological markers (e.g. elevated serum cholesterol, glucose intolerance) and unhealthy behaviors of smoking, alcohol intake, and physical activity, were reported as independent risk factors of SCD [15,16].

SCDs are primarily caused by cardiac arrhythmias [17]. The most common life-threatening arrhythmia is ventricular tachycardia (VT) or ventricular fibrillation, which is caused by CAD, HF, or cardiomyopathy [18,19]. AF shares similar risk factors with VT, CAD, and HF, and emerging evidence suggests that it may be associated with an increased risk of SCD [20,21]. Hypertension is the most common cause of hypertensive heart disease (e.g. LVH, enlarged left

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atrial enlargement, and diastolic dysfunction) [19]. LVH is a common adverse cardiovascular consequence of hypertension, aortic valve stenosis, diabetes mellitus, obesity, and a variety of inherited disorders, it can play as a secondary cause for hypertrophic cardiomyopathy. LVH and abnormal ventricular configuration result in dynamic left ventricular (LV) outflow obstruction in most patients [22]. The association between LVH and SCD were reported in prior studies, especially in the presence of CAD, heart with fibrosis and scar tissue [19]. In addition, in patients with aortic stenosis, the incidence of SCD remains a particular concern. Previous observational studies reported that severe aortic stenosis was related to high mortality rate, and early intervention may improve the prognosis, irrespective of the symptoms [23]

It is of paramount importance to predict the risk of SCD in the general population. Comprehensive autopsy examination in cases of sudden death can exclude non-cardiac causes of death, such as pulmonary embolism, aortic dissection and intracranial hemorrhage [11,12]. Cardiac imaging may help to identify subjects who are at risk of SCD [24]. Imaging technology of electrogram (ECG) and echocardiography can be applied to improve the diagnosis and treatment of fatal cardiac disease [17,25,26]. ECG and Echocardiography have been widely validated as classifiers for certain populations to detect low ejection fraction and structural abnormalities in high-risk patients. Previous studies regarding the associations of abnormal cardiac imaging and SCD were summarized in **Table 1-1**. A. Holkeri and colleagues

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demonstrated that ECG risk score combining using abnormal ECG (including: heart rate > 80 bpm, PP > 220 ms, QRS > 110 ms, LVH, and T-wave inversion) may predict SCD risk in general population subjects in Finland during 9.3 ± 2.0 follow-up years [26]. The Fingesture study revealed that ECG abnormalities in terms of longer QRS duration > 110 ms, left bundle branch block, pathological Q waves, and T-wave inversion were associated with myocardial fibrosis among SCD victims in Northern Finland and Lapland [27]. The results provide potentially early non-invasive risk assessment of SCD using ECG for patients with fibrotic cardiomyopathy.

The most widely used marker of LV dysfunction is reduced LV ejection fraction (EF), and severe LV dysfunction is an independent risk factor for SCD [18]. Echocardiography is an excellent method for evaluating myocardial function and structure [24]. As shown in **Table 1-1**, the Atherosclerosis Risk in Communities (ARIC) Study (mean follow-up: 7.3 years) and the Cardiovascular Health Study (CHS) (mean follow-up: 13.1 years) found that echocardiographic-derived variables for predicting SCD that provided incremental value over clinical risk factors, e.g. mitral annular calcification, reduced left ventricular ejection fraction (LVEF), LV mass index, mitral E to A < 0.7, and mitral E to A > 1.5, after adjusting for Framingham risk scores and renal function [28].

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The carotid artery duplex may provide additional information for CV risk prediction because plaque score reflects the severity of narrowing in the carotid artery [29,30]. Study results showed that carotid plaque score and carotid intima-media thickness (CIMT) were associated with coronary heart disease and stroke in the Chin-Shan Community Cardiovascular Cohort (CCCC) study [29]. In the ARIC Study and the CHS Study, an increment of CIMT (HR: 1.64, 95% CI: 1.15-2.63) and the presence of plaque (HR: 1.37, 95% CI: 1.13-1.67) were associated with increased SCD risks (the results were summarized in **Table 1-2**) [31].

On the whole, the use of several imaging technologies (e.g. echocardiography, carotid artery duplex) and ECG may improve the diagnosis and treatment of fetal cardiac diseases. The use of a population-based risk score system may be helpful in predicting SCD risk (**Table 1-3**) [26,32].

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1.4.3 Study Gaps, Study Hypotheses, and Study Aims – Project 1

How to predict SCD risk is of paramount importance in preventive medicine. To our knowledge, although several risk factors and prediction model of SCD were reported previously, there are several study gaps: (1) Most of the factors and models were proposed beyond Asia population. However, racial differences in SCD was reported, the risk factors shall be assessed based on various races [33]. The data on general epidemiology, causes, and risk factors of SCD in Taiwan is still lacking. (2) The 12-lead ECG remain the hallmark of initial non-invasive evaluation [26,27]. Nevertheless, the abnormalities of ECG have not yet proven to be useful enough in SCD risk stratification on clinical decision making. (3) While LV function acquired from echocardiography is currently the primary parameter for risk stratification for SCD, it is a poor marker with a low sensitivity and specificity. (4) The current clinical guidelines emphasize primary prevention of SCD in the population with high-risk features of SCD risk, such as those with CAD and HF [18,34,35]. For example, individuals with LVEF < 35% are indicated for implantation of prophylactic implantable cardioverter-defibrillators (ICDs). Nevertheless, current clinical guideline of risk stratification fails to identify individuals in the general population who are at risk of SCD, encompassing a greater number of potential SCD victims. (5) The population-based risk prediction model of SCD has not been well constructed in Taiwan.

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The hypotheses in this study are as following: (1) The incidence rate and risk factors of SCD in Taiwan are different from European and American countries. (2) Abnormal values of imagines in terms of ECG, echocardiography, and carotid artery duplex sonography are associated with higher risks of SCD. (3) Higher scores based on an integrated scoring system for predicting SCD are associated with higher risks of SCD.

In the first project, we aimed to investigate the incidence rate of SCD in a Taiwanese community-based population, identify several risk factors for SCD, and construct a novel point-based prediction model of SCD for general populations in Asia.

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1.5 Project 2: Risk Assessment of Stroke in Patients with Atrial Fibrillation

1.5.1 Stroke Risk and Various Managements in Atrial Fibrillation Patients

Stroke is a leading cause of death and disability, the burden of stroke is increasing due to aging, CVDs, and unhealthy lifestyle [36]. AF is a common cardiac arrhythmia that increases the risks of stroke and death in adults, approximately 25% of individuals aged 40 years or older will develop AF during their lifetime, and AF is associated with 5-fold increased risks of stroke [37,38]. The stroke risk in AF patients varies greatly (ranging from 1%-15% per year), and dependents on several demographic and clinical factors (**Figure 2-1**) [39].

1.5.2 Managing for Atrial Fibrillation Patients

Pharmacologic therapies for AF management includes rate control, rhythm control, and thromboembolic prevention (**Figure 2-1**) [40]. Rhythm control therapy of AF from major clinical studies (AFFIRM, RACE, and CHF AF) failed to demonstrate significant benefit relative to rate control with respect to cardiovascular and mortality outcomes [41], except for patients with paroxysmal or persistent AF receiving dronedarone, dronedarone is associated with reduced risk of stroke in AF [42]. However, data from patients who attained and maintained sinus rhythm in a number of clinical studies demonstrated that the achievement of normal sinus rhythm can reduce AF-associated morbidity and mortality [41].

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As compared with rhythm control therapy, catheter ablation was associated with reduced subsequent AF episodes [43]. Catheter ablation in AF patients has become an alternative therapy for AF, which was associated with reduced CV risks of HF, stroke, and mortality in patients with paroxysmal or persistent AF [44-46]. A prior study using the Taiwan National Health Insurance Database (NHIRD) demonstrated that AF catheter ablation was associated with lower stroke risk [47]. A recent meta-analysis (analyzing one randomized clinical trial- the Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation [CABANA] and other eight large matched population studies) exhibited reduced stroke risk in AF patients with catheter ablation than medical therapy [48].

1.5.3 Risk Assessment of Stroke for Atrial Fibrillation

Several stroke prediction models have been developed and validated by previous studies [49-53]. Currently, the $CHADS_2$ and CHA_2DS_2-VASc scores as the conventional scoring systems are commonly used to identify stroke risk and determine antithrombotic therapies in patients with AF [49,50]. Previous studies suggested that AF patients with $CHADS_2$ score of "0" or CHA_2DS_2-VASc score of < 2 were indeed classified as low stroke risk [54], especially in AF patients undergoing catheter ablation [44,54,55]. Chao, TF, et al. also demonstrated that AF patients in Asian with CHA_2DS_2-VASc score of 0 had a truly low stoke risk than $CHADS_2$ score, and CHA_2DS_2-VASc score might be used for stroke risk stratification in Asians as with

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Caucasians [53].

Effective risk stratification of stroke is a cornerstone for AF management [56]. Age and comorbidities mutually impact the stroke risks in patients with AF [56-58]. Evidences revealed that the incidence of AF increased with aging, which also led to worse prognosis, incident stroke events, and higher risk of death in patients with AF [59]. Most developed countries have accepted the age of 65 years as a definition of elderly. Ages 60 and 65 years are often used, despite its arbitrary nature. Currently, the $CHADS_2$ system includes age ≥ 75 years as 1 point [49], the CHA_2DS_2-VASc set age ≥ 65 years as 1 point and ≥ 75 years as 2 points in predicting future stroke risk in patients with AF [49]. However, to identify the risk of stroke in patients with AF, aging and incident comorbidities are generally a complex issue, and previous studies had difficulties in discussing this issue. A meta-analysis concluded that age as a criterion in patients with AF shall not be simply considered based on gender or age stratifications of ≥ 65 / ≥ 75 years [60]. Taipei Group described that a younger age of > 50 years had an increased stroke risk even without comorbidity based on the NHIRD analysis in Taiwan, and stroke risks vary based on the status of comorbidities in various age groups [58,61].

Hypertension is an important risk factor of hemorrhagic stroke, because it may contribute to atherosclerotic diseases that can lead to ischemic stroke [62]. In the CCCC study, higher blood

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pressures were associated with stroke risks regardless the AF diagnosis in Taiwan [63]. In addition, prior studies reported that AF and renal function seemed to be correlated with each other with bidirectional relationship. AF leads to the progression of chronic kidney disease while impaired renal function may cause the onset of AF, and AF patients with impaired renal function were at higher risks of stroke and deaths [64]. Hence, stroke prevention of oral anticoagulants in AF patients requires more detailed evaluations on renal function.

In the era of catheter ablation, several observational studies in different countries have reported that AF ablation was an effective therapy in AF patients at various ages with multiple co-morbidities [65,66]. In AF patients receiving ablation, they had significantly decreased risks of stroke, AF-related complications, and deaths than AF patients receiving antiarrhythmic drugs but without AF ablation [67,68]. In the largest randomized (CABANA) trial for comparing the effects between antiarrhythmic drugs and AF ablation by using intention-to-treat analysis, AF ablation did not significantly reduce stroke risks in AF ablation group [69]. The reason of non-significant ablation effect on reducing stroke risk could be the crossovers between antiarrhythmic drugs and AF ablation during follow-up, which may affect the final outcomes.

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1.5.4 Study Gaps, Study Hypotheses, and Study Aims – Project 2

There are several study gaps: For the management of stroke risks in patients with AF, both European and American guidelines recommend to use $CHADS_2$ and CHA_2DS_2-VASc scoring systems to determine an optimal strategy of stroke prevention [49,50]. However, the stroke risk scoring systems for AF patients can vary considerably based on the status while receiving the AF ablation and was not considered in the conventional scoring systems.

The study hypothesis in this study are as following: (1) The status of not receiving AF ablation is associated with higher stroke risk in AF patients. (2) Higher stroke-risk scores are related to higher stroke risk in AF patients.

In the second project, we aimed to develop a novel scoring system for stroke risk stratification for AF patients using the conventional risk factors plus the status of catheter ablation. Then, we compared the discrimination abilities among the novel scoring system and the conventional scoring systems.

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1.6 Project 3: Clinical Outcomes in Patients with Amyloidosis

1.6.1 Amyloidosis and Cardiac Amyloidosis

Amyloidosis refers to a group of diseases caused by deposits of abnormal proteins of amyloid, in one or more organs of the body, it is a rare disorder of protein misfolding that is characterized by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs [70]. The main classification of systemic amyloidosis is determined by the amyloid precursor proteins causing a heterogeneous spectrum. Patients with a slower amyloidogenic process may develop symptoms gradually and be diagnosed after several years. Patients with a fast amyloidogenic process may develop severe symptoms and die rapidly, or be undiagnosed.

Cardiac amyloidosis is a restrictive cardiomyopathy determined by the accumulation of amyloid, which is represented by misfolded protein fragments in the heart. However, not every misfolded protein fibril deposit in the heart of an individual with amyloidosis [71]. Cardiac amyloidosis has a poor prognosis which is aggravated by diagnostic delay. Most cases of cardiac amyloidosis are caused by one of two proteins, including: the light chain (AL) or the transthyretin (ATTR). Embedded amyloid fibrils in the heart cause stiffness and exhibit proteotoxicity to the myocardium, which results in HF, arrhythmia (e.g. AF or VT), and SCD [72]. Protein of AL is represented by misfolded immunoglobulin light chains, which can involve almost any system carrying the worst prognosis among amyloidosis patients [71].

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1.6.2 Incidence of Amyloidosis and Cardiac Amyloidosis

Amyloidosis is a relatively rare disease. Currently, there are no data on the nationwide epidemiology of amyloidosis. Most international epidemiological studies are based on death certificate data and are highly selected on specific types of amyloidosis [73-78]. The first study to identify the incidence and prevalence of cardiac amyloidosis among Medicare beneficiaries in the United States was reported by Gilstrap and colleagues, who found that among hospitalized patients over 65 years of age, the incidence rate of cardiac amyloidosis was 17 per 100000 person-years [73]. A Danish Nationwide Study reported that the incidence of cardiac amyloidosis rose from 0.88 to 3.56 per 100000 person-years in the Danish population aged ≥ 65 years [77]. Prior reports investing the incidence of amyloidosis were summarized in **Table 3-1**.

1.6.3 Amyloidosis and Risk of Cardiac Arrhythmia

Amyloidosis is a systemic illness that affects multiple organ systems, including the CV systems. Common manifestations include restrictive cardiomyopathy and cardiac arrhythmias [79]. AF is associated with increased risk of ventricular arrhythmias [80]. In one case series, 62% of ATTR amyloidosis patients had AF [81]. Falk et al. reported that patients with amyloidosis who present with VT are more likely to have a history of HF and abnormal echocardiographic findings [82]. An enlarged LV chamber and impaired LV systolic function could result in structural remodeling and

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diseased substrate formation, which may explain the occurrence of VT at the late stage of amyloidosis with cardiac involvement [83]. Moreover, people with structural heart disease are prone to have incident VT, which can be associated with an increased risk of sudden death [84].

1.6.4 Study Gaps, Study Hypotheses, and Study Aims – Project 3

There are several study gaps: (1) Currently, there are no data on the nationwide epidemiology of amyloidosis. (2) The incidence of VT and the associated outcomes in patients with amyloidosis are not well-documented. (3) The risk factors contributing to VT were also evaluated in patients with amyloidosis, which has not been explored in previous studies.

The study hypotheses in this study are as following: The long-term risks of VT and CV deaths were higher in patients with amyloidosis and cardiac amyloidosis.

In the third project, we aimed to explore the incidence of new-onset VT and CV outcomes in patients with amyloidosis after a long-term follow-up using a representative national cohort. In addition, we assessed the risk factors of VT and CV deaths in patients with amyloidosis.

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Chapter 2：Methods

2.1 Project 1: Risk Assessment of Sudden Cardiac Death

2.1.1 Study Design and Study Population

The CCCC study is a community-based longitudinal cohort conducted since 1990-1991 in Chin-Shan. Originally, a total of 3602 inhabitants (response rate: 82.8%, 47.3% men) aged 35 years and older were included for a prospective observation of the cardiovascular events and related parameters. We re-assessed all cases biennially for CV risk factors, physical examinations, biochemical data, lipid profiles, and 12-lead ECGs **(Figure 1-1**) [6]. Participants without all of the data of 12-lead ECG, echocardiography, and carotid artery duplex sonography were excluded from this study **(Figure 1-2**). Lastly, this study evaluated 2105 participants (44.7% men) without a prior history of CAD or HF with reduced EF (HFrEF: LVEF < 35%). The Institutional Review Board (IRB Number: 2011003001R) of the National Taiwan University Hospital approved this study according to Good Clinical Practice guidelines. Individual informed consents were obtained from each participant (**Appendix 1**).

2.1.2 Ascertainment of Baseline Data

The baseline data of the recruited study population have been reported previously [6,85,86]. As part of the questionnaire, the following information was collected: identification data (e.g., name and age), levels of education, occupation, family history, personal habits (such as smoking and drinking),

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and physical activity (refer to **Figure 1-1**). Body height, weight, body mass index, thickness of subcutaneous fat over the left triceps, blood pressure, heart rate, and peripheral pulses were measured during the physical examination. The blood examinations included: hematocrit, blood count, blood sugar, serum albumin, uric acid, blood urea nitrogen (BUN), creatinine, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol.

The baseline of systemic underlying diseases such as hypertension and diabetes mellitus were recorded if the patient had been diagnosed and treated for these diseases. Hypertension was defined as resting systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg at baseline [87]. Mean arterial pressure was defined as the sum of 1/3*systolic blood pressure + 2/3*diastolic blood pressure. Chronic kidney disease was defined as estimated glomerular filtration rate < 60 ml/min/1.73m^2 for more than 3 months. Smoking was defined as current smoking of more than 10 cigarettes per day or within 30 days of the cessation of smoking. Family history of coronary artery disease was considered a risk factor if the first relatives of the case aged less than 55 years in men and less than 65 years in women had coronary events or were diagnosed as coronary artery disease. Hypercholesterolemia and hypertriglyceridemia were defined as levels exceeding 240 and 200 mg/dl respectively.

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The flow chart for data collection of ECG, echocardiography, and carotid artery duplex sonography was summarized in **Figure 1-1**. The measurements of 12-lead ECG were corrected by a physician using a standard value or deviation, and the abnormalities detected by 12-lead ECG were based on three examinations during biannual follow-ups (since 1994-1995).

The ECG risk score was calculated as [26]:

(Heart rate > 80) + (PR > 220 ms) + (QRS > 110 ms) + LVH + T wave inversion.

Standard echocardiography was performed between 1992-1993 (first follow-up) and 1994-1995 (second follow-up). Carotid artery duplex sonography was performed once for study participant between 1994-1995. Qualified cardiologists measured M-mode echocardiography in accordance with the recommendations of the American Society of Echocardiography, measurements were repeated twice for calculating the average values. LVEF, LV mass, aortic (valve) flow rate (jet velocity), wall thickness, and any associated abnormalities were assessed using echocardiography. The values of intra-class correlation reliability were between 0.70 and 0.85 in the various measurements and had been reported [88]. On the basis of echocardiography, significant LV systolic dysfunction was defined as LVEF less than 40% [89]. LV mass index was defined as LV mass / body surface area. The aortic flow rate is a direct measurement of the highest antegrade systolic velocity signal across the aortic valve, and defined as the highest velocity signal obtained from any window after a careful examination. A resting aortic flow rate of ≥ 260 cm/s (2.6 m/s) was associated with aortic stenosis

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[90]. Both echocardiography and ECG were applied to define LVH (echocardiography: LV mass index ≥ 132 g/m^2 in men, LV mass index ≥ 109 g/m^2 in women; ECG: S wave depth in V1 + tallest R wave height in V5-V6 > 35 mm [Sokolov-Lyon criteria]) [91,92].

Duplex carotid artery sonography was used to detect the intima thickness near the bulb of the carotid artery, and to determine the carotid plaque score using a Hewlett-Packard SONO 1500 ultrasound system with a 7.5 MHz real-time B-mode scanner. Carotid plaque score was measured within the extracranial carotid bed based on the sum of sub-scores calculating from 10 segments (bilateral proximal/distal common carotid arteries, internal carotid arteries, external carotid arteries, and bulbs) using the Sutton's scoring method [29]: A grade was assigned to each chosen segment (Grade 0: normal or no observable plaque; Grade 1: one small plaque with diameter stenosis of 30%; Grade 2: for one medium plaque with 30% to 49% diameter stenosis or multiple small plaques; Grade 3: for one large plaque with 50% to 99% diameter stenosis or multiple plaques with at least one medium plaque; and Grade 4: for 100% occlusion). Reproducibility of carotid plaque score was good (kappa: 0.70).

The Atherosclerosis Risk in Communities (ARIC)-Framingham score was calculated as [32]:

(0.067*age) + (-1.262*male) + (0.008*cholesterol) + (0.444*lipid-lowing medication use) + (0.307*anti-hypertensive medication use) + (0.025*systolic blood pressure) + (-0.024*diastolic

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blood pressure) + (0.617*current smoker) + (0.787*diabetes mellites) + (0.74*body mass index).

2.1.3 Follow-up Strategy and Outcome Confirmation

Deaths were prospectively collected in CCCC Study from July 1st, 1990 to February 28th, 2005 [6,85]. This study defined sudden death in accordance with the criteria of the World Health Organization (WHO), which defines sudden death as unexpected death that occurs within 1 hour of symptom onset (witnessed) or within 24 hours of having been observed alive and symptom-free (unwitnessed) [93]. SCD was defined as a sudden, unexpected, non-traumatic loss of heart function and vital signs, such as consciousness, palpable arterial pulse, blood pressure, and respiration, without preceding complaints or illness, or within one hour of the onset of the complaints. The victims who were found dead but seen alive and well within 24 hours of the event were also included. Those who suffered from a circulatory arrest because of intoxication or in the terminal phase of a chronic disease were excluded. The information was identified based on the death certificates from the government, combined with the interview of the families or witnesses, and the doctor in charge regarding the onset and mode of death. The interviews were completed by an expert local assistant within one month of the event, and were reviewed by three investigating doctors, especially focusing on the mode of death and the preceding symptoms and signs in correlation to the definition of SCD.

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2.1.4 Framingham Risk Score

A point-based risk scoring system was constructed based on the Framingham risk score methods [63,94]. In the first step, beta coefficients were determined according to a 1-year increment of age ($Beta_{age-1}$), and a 10-year increment of age ($Beta_{age-10}$) was then calculated to be used as a reference for calculating risk scores. Finally, point values were assigned for the selected clinical risk factors based on the model coefficients:

$$\text{Risk points} = Beta_{\text{risk factor}} * (W_{i-j} - W_{i-ref}) / Beta_{age-10}$$

The difference between each value of a risk factor and its reference value is represented as ($W_{i-j} - W_{i-ref}$). As an example, a one-year increase in $Beta_{age}$ was 0.191 ($Beta_{age-1}$) in the CCCC study, $Beta_{age-10}$ was calculated as 1.910. For patients with a history of hypertension (HTN), $Beta_{HTN}$ was 1.105 based on the multivariable regression model, and ($W_{i-j} - W_{i-ref}$) was (Yes: 1-No: 0). Consequently, we obtained a risk score of 1 point.

Second, the probability of SCD in the following 10 years was calculated based on the following formula:

$$\text{Risk} = 1 - S0(t)^{\exp(\Sigma ßX - ß\bar{x})}$$

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S0(t) represents the average survival rate based on time t (e.g. 10 years) at the mean values of the risk factors, ß represents the Cox regression coefficient of the $Beta_{age\text{-}10}$ or $Beta_{risk\ factor}$, X represents the individual's values on the variables, and X-bar ($\bar{x}$) represents the means or proportions of variables.

2.1.5 Statistical Analyses

Normally distributed continuous variables were presented as mean ± standard deviation and compared using Student's t-test. Continuous variables with a non-normal distribution were presented as medians and interquartile ranges (IQR). Categorical values were presented as absolute numbers (N) with percentages (%), and chi-square tests were used for statistical comparisons. Incidence rates of events were calculated as the number of cases per 1000 person-years (PYs) along with 95% confidence intervals (CIs) (SAS programming: **Coding 1-1**).

The event-free survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used to determine statistical significance. Because SCD rate may change over time, competing risk models (cause-specific hazard [CSH] v.s. sub-distribution hazard [Fine and Gray]) based on the Cox proportional hazard models were used to analyze the hazard ratios (HRs) (SAS programming: refer to **Coding 1-2**) [95,96]. When the only competing risk is death (main outcome: SCD), the CSH and traditional Cox models will provide similar estimations. In addition, the estimations derived via

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the sub-distribution hazard model were similar to those obtained via the cause-specific hazard model. However, for prognostic research such as estimating the absolute risk function, applying the sub-distribution hazard model is recommended [95,96].

Due to the limited event rate and over-dispersion in the study data, we also applied the negative binomial regression model to generate the beta coefficients for calculating the risk prediction scores (SAS programming: refer to **Coding 1-2**) [97], and comparing with the competing risk models. To perform the negative binomial regression model, the number of events were summarized by time groups (follow-up years: 0-5, 6-10, > 10 years), baseline age group (< 45, 45-54, 55-64, 65-74, ≥ 75 years), and other important risk groups based on the risk factors selecting from the competing risk models under the weight of log (person-years) as offset variable.

In an attempt to construct a simple point-based SCD prediction model, this study examined the incremental predictive values of adding these variables in the multivariable model-derived coefficients. To assess the conventional risk factors such as age, gender, hypertension, and diabetes mellitus, we selected a factor with a P-value of ≤ 0.1 in the univariate analysis and included it in a multivariable analysis. The abnormal electrocardiographic patterns, echocardiographic data, and carotid artery duplex sonography data was adjusted for baseline age group (< 45, 45-54, 55-64, 65-74, ≥ 75 years), gender, diabetes mellitus, hypertension, LVEF < 40%, and smoking history. After

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obtaining the beta value, it would be applied to the Framingham risk score, and to calculate the probability of SCD over the following 10 years [63,94]. The novel model (CCCC-SCD-Score) has been validated internally by using the bootstrapping method [98]. The training dataset was repeatedly resampled 100 times to produce 5 replicated bootstrap sample sets. Each the bootstrap sample size was the same as the training dataset (**Figure 1-2**) (MATLAB programming: refer to the **Coding 1-3**).

Receiver operating characteristic curves (ROC) and area under curves (AUC) were used to summarize the prediction performance. The best cut-off value for predicting incident events was determined using the Youden index of the AUC (sensitivity + specificity -1). The CCCC-SCD-Score was compared to the ARIC-Framingham score and ECG risk score using the DeLong test (SAS programming: **Coding 1-4)**. We assessed the goodness-of-fit based on the Hosmer-Lemeshow test. The level of statistical significance is set at a 2-tailed alpha level < 0.05. The analyses were performed using SAS version 9.4.

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2.1.6 Sample Size and Power

Sample size and power were calculated by using R package of “"powerSurvEpi"” (**Coding 1-5:** Power and Sample Size Calculations in Survival Data, and Power Calculation for Cox Proportional Hazards Regression with Nonbinary Covariates for Epidemiological Studies). Total sample size in this study was 2105, the power (β) was calculated as 99.2% in this study while setting: (1) a type 1 error (α) of 5%, (2) total SCD events of 13, (3) a proportion of (high-risk group / low-risk group) as 0.01, and (4) a relative hazard (high-risk group v.s. low-risk group) of 15.0 based on the CCCC study.

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2.2 Project 2: Risk Assessment of Stroke in Patients with Atrial Fibrillation

2.2.1 Study Design and Study Population

This study includes a nationwide cohort of the NHIRD as the training dataset and an internal-validation dataset (one-fifth population in the training cohort) (**Figure 2-2**). Participants with prior AF ablation or aged < 18 years before the baseline were excluded from this study. This study was approved by the IRB (IRB Numbers: 201305044W and 2021-09-014BC) (**Appendices 2 and 3**) of the Taipei Veterans General Hospital (TVGH) in accordance with the Good Clinical Practice Guidelines.

2.2.2 Training Cohort and Internal Validation Cohort

The Taiwan Collaboration Centre of Health Information Application, Ministry of Health and Welfare, provided the entire dataset used for this study. Taiwan's National Health Insurance (NHI) program enrolled 27 million people and covered over 99% of the country's population. NHI data included information on outpatient visits, hospitalizations, prescribed medications, and the National Death Registry.

The training cohort was a nationwide cohort generating from the NHIRD in 2003. A total of 147405 patients with AF aged ≥ 18 years were identified. Among them, 2833 drug refractory AF patients from their first diagnosis of AF < 6 months with catheter ablation of pulmonary ablation were

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confirmed according to the procedure codes of AF catheter ablation (**Figure 2-2**). The newly constructed scoring system constructed in the training dataset was validated using one-fifth population in the training cohort as the validation dataset (total number: 29481) (**Figure 2-2**).

2.2.3 Ascertainment of Baseline Data

The NHIRD includes records of outpatient visits, hospital admissions, prescriptions, and disease diagnoses for > 99% of the 23 million population. All patient information was anonymized, and the requirement for written informed consent from patients was officially waived. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding system was used for identifying the disease diagnoses. The diagnoses were confirmed only if the patient had at least one incidence of hospitalization or at least three consecutive outpatient visits with the above listed diseases to improve the accuracy of coding.

Important clinical variables were identified including: age (years), gender, congestive heart failure (ICD-9-CM: 428), hypertension (ICD-9-CM: 401-405), diabetes mellitus (ICD-9-CM: 250), prior stroke (ICD-9-CM: 430-438), vascular diseases (ICD-9-CM: 440-444), CAD (ICD-9-CM: 410-411), chronic kidney disease (ICD-9-CM: 584-585), chronic obstructive pulmonary disease (ICD-9-CM: 490-496), valvular heart diseases (ICD-9-CM: 393-398, 746), hyperlipidemia (ICD-9-CM: 272), and thyroid diseases (ICD-9-CM: 242).

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The diagnostic accuracy of AF (ICD-9-CM: 427.31) using this definition in NHIRD has been validated previously [99]. For the training dataset, the status of receiving AF ablation or not was based on: (1) an AF diagnosis of ICD-9-CM code: 427.31; (2) the procedural codes of AF catheter ablation (33091B, 33139B, 33140B); (3) the procedural codes for trans-septal puncture [47]. Medications were identified using the codes based on the Anatomical Therapeutic Chemical (ATC) Classification System.

The traditional scoring systems for predicting stroke in AF patients including the $CHADS_2$ score and the CHA_2DS_2-VASc score. The $CHADS_2$ scoring system was constructed based on the status of congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke [49], whereas the CHA_2DS_2-VASc scoring system was constructed based on the status of congestive heart failure, hypertension, age ≥ 75 or ≥ 65 years, diabetes mellitus, prior stroke, vascular diseases, and women [50]. The R_2CHADS_2 and $R_2CHA_2DS_2$-VASc scoring systems were calculated by adding renal function as two points on the basis of $CHADS_2$ and CHA_2DS_2-VASc scoring systems [100,101].

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2.2.4 Follow-up Strategy and Outcome Confirmation

This study evaluated the rates of stroke (ICD-9-CM codes: 430-438) using the NHIRD database. The accuracy of identifying ischemic stroke using the NHIRD was approximately 94% [102]. Participants were followed until the occurrence of first stroke event or at the end of 2015. Deaths were recorded to the Death Registry and followed until the end of 2016.

2.2.5 Statistical Analyses

Continuous variables were presented as mean ± standard deviation (SD), whereas categorical variables were presented as proportion. Cox proportional hazard models were used to evaluate stroke risk with HR and 95% CI. This study examined the incremental predictive values of adding these variables into the multivariable Cox model-derived coefficients to construct a simple point-based clinical model using the training dataset. The final risk factors in the multivariable model were selected from the univariable model using a significance level of 0.1. The categorization point model was constructed according to clinical covariates in the training dataset by applying the methods of the Framingham study risk score functions (refer to the section of **2.1.4 Framingham Risk Score**) [63,94] .

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To adjust for the over-optimism in model fitting, the novel model (AF-CA-Stroke score) was validated in the validation dataset. The initial clinical model included age (years), gender, receiving AF ablation or not, congestive heart failure, hypertension, diabetes mellitus, prior stroke, CAD or vascular diseases, chronic kidney disease, chronic obstructive pulmonary disease, valvular heart diseases, hyperlipidemia, and thyroid diseases. The "point" of stroke risk assessment of < 1% at 1 year was set to be "low risk", and ≥ 1% at 1 year was set to be "higher risk".

We compared the performance of the novel AF-CA-Stroke score model with the $CHADS_2$/CHA_2DS_2-VASc scoring systems. The integrated discrimination abilities of AUC under ROC and category-free net reclassification index (NRI) were assessed to compare among all models [103,104] (**Coding 2-1**). The best cut-of-value predicting the incident stroke events was calculated using the Youden index of the AUC (sensitivity + specificity -1). We assessed the goodness-of-fit based on the Hosmer-Lemeshow test. All statistical analyses were performed using the SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at two-tailed $P < 0.05$.

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2.2.6 Sample Size and Power

Sample size and power were calculated by using R package of “"powerSurvEpi"” (**Coding 2-2:** Power and Sample Size Calculations in Survival Data). Total sample size in this study was 147405, the power (β) was calculated as > 99.9% in this study while setting: (1) a type 1 error (α) of 5%, (2) total stroke events of 5583, (3) a proportion of (high-risk group / low-risk group) as 0.2, and (4) a relative hazard (high-risk group v.s. low-risk group) of 5.0.

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2.3 Project 3: Clinical Outcomes in Patients with Amyloidosis

2.3.1 Databases

According to the study, the NHIRD in Taiwan was employed to investigate the risks of VT and CV events in patients with amyloidosis during a long-term follow-up (2000 to 2016). National Death Registry contains information on the primary and contributing causes of death, as well as the date of death for all citizens. Previous studies have verified the accuracy of the coding [105,106]. The protocol was reviewed and approved by our institutional review board (IRB Number: 2021-09-014BC) (**Appendix 3**). Additionally, we obtained permission from the National Research Institute for the Department of Health and the Health Promotion Administration, Ministry of Health and Welfare.

2.3.2 Study Design and Participants

A retrospective cohort study was conducted on a population-based basis. **Figure 3-1** illustrates the study flow chart**.** A total of 12139 patients aged 18-85 years diagnosed with amyloidosis between 2000 and 2006 were identified from the NHIRD, using the ICD-9-CM code 277.3. Co-morbidities were obtained from the medical claims database based on ICD-9-CM codes. Amyloidosis should have been documented at least twice in outpatient records or at least once in inpatient records. Cardiac amyloidosis was defined as amyloidosis coupled with one of the possible cardiac manifestations of amyloidosis, including HF, cardiomyopathy, or AF [77].

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VT was defined as ventricular tachycardia, ventricular flutter and fibrillation, and cardiac arrest (ICD 9-CM codes: 427.1, 427.4, and 427.5, respectively). The study excluded patients with prior implantable cardioverter defibrillator, prior history of tuberculosis (ICD 9-CM code: 011.9), with other systemic inflammatory diseases or connective tissue disorders (ICD-9-CM codes: Reiter's syndrome [099.3], Hodgkin disease [201.9], multiple myeloma [203.0], familial Mediterranean fever [277.31], Crohn's disease [555], ulcerative colitis [556], systemic lupus erythematosus [710], rheumatoid arthritis [714], ankylosing spondylitis [720.0]), and who experienced VT.

An independent control group of 150000 individuals without a diagnosis of amyloidosis during the induction period of five years, without prior structural heart disease, and aged 18-85 years was selected between 2000 and 2006 as a comparison group. The propensity score was used to match the same number of controls with the same number of amyloidosis patients to minimize the impact of imbalanced distributions between cases and controls (**Figure 3-1**).

Furthermore, we collected data regarding the following characteristics: age (years), sex, hypertension (ICD-9-CM codes: 401-405), diabetes mellitus (ICD-9-CM code: 250), chronic obstructive pulmonary disease (ICD-9-CM codes: 490-496), chronic kidney disease (ICD-9-CM codes: 584-585), congestive heart failure (ICD-9-CM code: 428), hyperlipidemia (ICD-9-CM code: 272), thyroid diseases (ICD-9-

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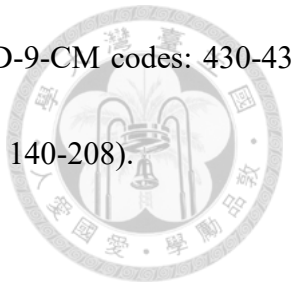
CM code: 242), prior CAD (ICD-9-CM codes: 410-411), prior stroke (ICD-9-CM codes: 430-438), chronic liver disease (ICD-9-CM code: 571), and cancer (ICD-9-CM codes: 140-208).



2.3.3 Study Endpoints During the Follow-up

The follow-up period ended when the subjects died or had CV outcomes beyond 2015. Study outcomes included time to new-onset VT, AF-related hospitalization, HF-related hospitalization, CV deaths (ICD-9-CM codes: 390-450), and all-cause death. HF-related hospitalization is defined as hospitalization for either a primary diagnosis of HF or with HF as one of the first two secondary diagnoses (ICD-9-CM codes: 428, 428.0, 428.1, and 428.9). Time to implantation of a pacemaker or implantable cardioverter-defibrillators (ICD) implantation was checked. A national death registry in Taiwan was used to confirm deaths, and death data was traced until the end of 2016.

2.3.4 Statistical Analyses

The Student's t-test was used to compare normally distributed continuous variables, while the Mann-Whitney U test was used to compare non-normally distributed continuous variables. The categorical values were expressed as absolute numbers (n) and percentages (%), and statistical comparisons were performed using the chi-square test. Incidence rates were calculated as the number of cases per 10000 PYs. In this study, confounders were minimized using the 1:1 PS-matching method. Age, sex, hypertension, and diabetes mellitus were matched 1:1 under identical PS with a 0.15 caliper (refer to

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Coding 3-1 for PS-matching technique in SAS).

Using the Kaplan-Meier method, the event-free survival curve was plotted, and the significance of the results was determined using the log-rank test. A conditional Cox proportional hazards regression was used to compare the HR with 95% CI for the outcomes (**Coding 3-2**). A multivariable analysis was used to identify the independent predictors of new-onset VT and deaths during the long-term follow-up. Two different models were used to adjust for potential confounders (Model 1: age and sex; Model 2: Model 1 plus hypertension, diabetes mellitus, congestive HF, hyperlipidemia, chronic kidney disease, liver disease, chronic obstructive pulmonary disease, thyroid disease, prior CAD, prior stroke, and cancer). A two-tailed alpha level of < 0.05 was considered statistically significant. The analysis was conducted using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

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2.3.5 Sample Size and Power

Sample size and power were calculated by using R package of “"powerSurvEpi"” (**Coding 3-3:** Sample Size Calculation for Conditional Logistic Regression with Binary Covariate). Total sample size in this study was 24278, the power (β) was calculated as > 99.9% in this study while setting: (1) a type 1 error (α) of 5%, (2) total number in the training dataset as 24278 (the number in amyloidosis v.s. non-amyloidosis groups as 12139 v.s. 12139), (3) a population prevalence of amyloidosis as 6 per 100000, (4) a relative hazard (amyloidosis v.s. non-amyloidosis) of 6.5, (5) R^2 of coefficient of determination for the exposure variable and other covariates as 0.01.

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Chapter 3：Results

3.1 Project 1: Risk Assessment of Sudden Cardiac Death

3.1.1 Baseline Characteristics of the Cohort

The study enrolled a total of 2105 participants (44.1% men) (**Figure 1-2**). The baseline characteristics are provided in **Table 1-4**. During a median follow-up period of 16.4 years (IQR: 15.7-16.9), a total of 401 deaths (19.0%) were recorded. Among these, 13 were classified as SCD (3.24% of all deaths, 0.61% of total participants). The incidence of SCD was 0.406 per 1000 person-per years (95% CI: 0.185-0.627). Among SCD victims, 23.1% were attributed to CAD, 7.69% due to valvular heart disease, 7.69% due to arrhythmia, and 61.5% due to other causes.

3.1.2 Clinical History, ECG Patterns, and Sudden Cardiac Deaths

In this study, we analyzed several background factors associated with SCD, including: gender, age, body mass index, smoking status, alcohol consumption, regular exercise, diabetes status, fasting blood glucose, triglyceride levels, total cholesterol levels, HDL, LDL, cholesterol levels, antihypertensive and hypoglycemic medications (refer to **Table 1-4 and Table 1-5**). In comparison to the participants without SCD, SCD victims were only significantly associated with older age (sub-distribution HR: 1.09, 95% CI: 1.04-1.15) and hypertension (sub-distribution HR: 3.50, 95% CI: 1.01-10.9) after multivariable adjustment

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(**Table 1-5**). In addition, the educational differences, marital status, and occupation were not risk factors of SCD in this study. **Table 1-6** summarized the baseline characteristics of ECGs. LVH documented by 12-lead ECG was the only independent risk factor of abnormal ECG pattern for SCD (sub-distribution HR: 6.04, 95% CI: 1.47-24.9) (**Table 1-7**).

3.1.3 Associations between Ultrasonographic Findings and Sudden Cardiac Death

Table 1-8 summarized the findings of carotid artery duplex sonography. Using multivariable adjustment, carotid plaque scoring ≥ 5 (sub-distribution HR: 5.76, 95% CI: 1.15-28.7), aortic flow rate > 190 cm/s (sub-distribution HR: 72.1, 95% CI: 12.4-418.8; cut-off point identifying by the Youden index of the AUC), LV systolic dysfunction (LVEF < 40%) (sub-distribution HR: 23.6, 95% CI: 2.35-237.5), and LVH based on the echocardiography (sub-distribution HR: 5.92, 95% CI: 1.37-25.7) were independent factors for SCD (**Table 1-9**).

3.1.4 CCCC-SCD-Score Construction Using the Training Dataset

CCCC-SCD-Score was developed for the purpose of estimating 10-year SCD risks for the general population after carefully selecting several risk factors associated with SCD occurrence. Two competing risk models (cause-specific approach and sub-distribution approach) and the multivariable negative binomial regression were fit to the selected risk factors for comparisons among various models (**Table 1-10**). Based on the training dataset,

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the points calculated by the three regression models were identical. The points were assigned based on the 1-year increments of adjusted beta coefficient change in age: < 45 years: 0, 45–54 years: 1, 55–64 years: 2, 65–74 years: 3, and ≥ 75 years: 4 points. There were other clinical risk factors included in the simple point-based SCD prediction score, including: hypertension (point =1), LVH (ECG or echocardiography) (point = 1), LVEF < 40% (point = 1), aortic (valve) flow rate >190 cm/s (point = 1), and carotid plaque scores ≥ 5 (point = 1) (**Table 1-10**). In **Table 1-11** and **Figure 1-3A**, the CCCC-SCD-Score was used to illustrate the risk function that predicts 10-year SCD rates on the basis of cause-specific approach, sub-distribution approach, and negative binomial model. The sub-distribution approach is more suitable for estimating 10-year SCD rate in this study.

In the training dataset, analyses of the ROC demonstrated that CCCC-SCD-Score had good predictive performance in predicting incident events of SCD (**Table 1-12**). The AUC was 0.881 (95% CI: 0.805-0.958; sensitivity: 0.923, specificity: 0.955; positive predictive value: 0.172; negative predictive value: 0.999; positive likelihood ratio: 80.1; negative likelihood ratio: 0.92). SCD events were predicted most accurately with a cut-off value of ≥ 6. Kaplan-Meier survival plot demonstrated significant differences between the survival curves for patients stratified according to CCCC-SCD-Score ≥ 6 or < 6 (Log-rank test, P < 0.001)

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(**Figure 1-4**). In fitting the observed and predicted values, the CCCC-SCD-Score had good prediction accuracy (chi-square of Hosmer-Lemeshow test: 0.906; P-value = 0.82; **Figure 1-3B**).

Table 1-12 summarized the predictive performance of various models for risk assessment of SCD according to the flow chart in **Figure 1-5**. The AUCs was significantly lower when only the electrocardiogram (Step 2-0), echocardiography (Step 3-0), and carotid artery duplex examination (Step 4-0) were applied, rather than only "the history" and "clinical examination" (Step 1-0: reference). Excellent predictive performance was shown when adding ECG and echocardiography data together as Step 5-0 (AUC: 0.908), adding ECG, echocardiography, and CIMT data together as Step 6-0 (AUC: 0908), and only applying the CCCC-SCD-Score as Step 7-0 (AUC: 0.888) compared with only taking history & clinical examination as Step 1-0 (AUC: 0.842). By comparing with the ARIC-Framingham score and ECG risk score (Step 8-0 and Step 9-0 in **Table 1-12**), the CCCC-SCD-Score effectively identifies the risk for SCD.

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3.1.5 Bootstrapping Validation

The distribution of the AUCs on the basis of bootstrapping validation with 100 times re-sampling was exhibited in **Figure 1-6A**. The ROC analyses for the CCCC-SCD-Score still had good predictive performance for incident events of SCD (mean AUC: 0.880, 95% CI: 0.874-0.887; **Figure 1-6B**). AUCs for the ARIC-Framingham score (mean AUC: 0.731, 95% CI: 0.715-0.756; **Figure 1-6C**) and ECG risk score (mean AUC: 0.650, 95% CI: 0.637-0.663; **Figure 1-6D**) were lower than AUCs for the CCCC-SCD-Score (**Figure 1-6**).

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3.2 Project 2: Risk Assessment of Stroke in Patients with Atrial Fibrillation

3.2.1 Training Dataset and Selection of Clinical Risk Factors

A total of 147405 patients with AF were identified in the training dataset for constructing a model-based scoring system (**Table 2-1**), including 2833 patients receiving AF ablation and 144572 AF patients without ablation (mean age: 72.3 ± 12.0 years, 45.6% of them were women; see **Figure 2-2** and **Table 2-2**). We identified 5583 stroke events (3.84% in the non-ablation group and 0.92% in the AF ablation group) during a median follow-up duration of 4.3 years (IQR: 1.9-7.1 years).

The significant risk factors in the multivariable Cox regression model were summarized in **Table 2-3**. In the final model, age (HR: 1.088, 95% CI: 1.085-1.092, P < 0.001), the status of not receiving AF ablation (HR: 1.83, 95% CI: 1.24-2.69, P=0.002), prior history of stroke (HR: 2.11, 95% CI: 1.98-2.24, P < 0.001), chronic kidney disease (HR: 1.63, 95% CI: 1.32-2.01, P < 0.001), and prior history of CAD or vascular diseases (HR: 1.62, 95% CI: 1.53-1.72, P < 0.001) were strong predictors of incident stroke events.

A simple point scoring system of "AF-CA-Stroke score" to estimate the stroke risks in AF patients using the survival function at 1-year was developed (**Table 2-4**). Depending on the 1-year increment of baseline beta coefficient change in age, up to 5 points were assigned for the following age groups: <35 years: 0, 35–44 years: 1, 45–54 years: 2, 55–64 years: 3, 65–74 years: 4, and ≥75 years: 5 points

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(**Table 2-4**). The AF-CA-Stroke scoring system includes other important clinical risk factors, such as non-AF ablation status (point = 1), prior history of stroke (point = 1), chronic kidney disease (point = 1), and prior history of CAD or vascular diseases (point = 1) (**Table 2-4**). The absolute risk function that predicts the 1-year stroke rate by calculating the AF-CA-Stroke scores, the 1-year stroke rates of the $CHADS_2$ and CHA_2DS_2-VASc scores are summarized in **Figure 2-3 and Table 2-5**. The estimated 1-year stroke rates (%) by the AF-CA-Stroke score, the observed rates (per 100 person-years) in the training dataset were reported in **Table 2-5**.

The study based on the training dataset revealed that discrimination ability of category-free NRI (NRI: 0.26, $P < 0.001$) was significantly higher in the AF-CA-Stroke score as compared with the $CHADS_2$ score system (**Table 2-6**). The discrimination ability of AF-CA-Stroke score in terms of AUC for predicting the 1-year incident stroke risks was significantly higher than the $CHADS_2$ score system (**Table 2-7**). The estimated AUCs using the AF-CA-Stroke score was 0.637 (95% CI: 0.631–0.644), and the estimated AUCs using the $CHADS_2$ score was 0.577 (95% CI: 0.570–0.584). Youden indices indicated that the best cut-off-values predicting the incident stroke event were > 5, > 0, and > 2 in the AF-CA-Stroke, $CHADS_2$, and CHA_2DS_2-VASc scoring systems, respectively (**Table 2-5**). In fitting the observed and predicted values, the AF-CA-Stroke score had good prediction accuracy (chi-square of Hosmer-Lemeshow test: 0.953; P-value = 0.81).

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3.2.2 Validation Dataset

A total of 29481 patients with AF (one-fifth random selection form the training dataset) were identified in the training dataset (**Table 2-1**), including 566 patients receiving AF ablation and 28915 AF patients without ablation (mean age: 72.2 ± 12.0 years, 45.4% of them were women; see **Figure 2-2** and **Table 2-8**). The estimated 1-year stroke rates (%) by the AF-CA-Stroke score and the observed rates (per 100 person-years) in the validation dataset were reported in **Table 2-5**.

The study based on the validation dataset revealed that discrimination ability of category-free NRI (NRI: 0.32, $P < 0.001$) was significantly higher in the AF-CA-Stroke score as compared with the $CHADS_2$ score system (**Table 2-6**). The discrimination ability of AF-CA-Stroke score in terms of AUC for predicting the 1-year incident stroke risks was significantly higher than the $CHADS_2$ score system (**Table 2-7**). The estimated AUCs using the AF-CA-Stroke score was 0.658 (95% CI: 0.644–0.675), and the estimated AUCs using the $CHADS_2$ score was 0.590 (95% CI: 0.574–0.607). In fitting the observed and predicted values, the AF-CA-Stroke score had good prediction accuracy (chi-square of Hosmer-Lemeshow test: 0.253; P-value = 0.97).

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3.2.3 Distributions among Various Scoring Systems and Incident Stroke Risks in the Training Dataset

The distributions among various scoring systems and incident stroke risks in the training dataset were summarized in **Table 2-9**. In the training dataset, a total of 29361 AF patients (19.9%) were grouped as higher stroke risk based on the AF-CA-Stroke score > 5, however, a total of 131389 (89.1%) and 78744 (53.4%) AF patients were grouped as higher stroke risk based on the $CHADS_2$ score > 0 and the CHA_2DS_2-VASc score > 1, respectively.

The incidence rate was 9.19 per 1000 PYs (95% CI: 8.94-9.43 PYs) for AF patients with the $CHADS_2$ score > 0, and the incidence rate was 9.92 per 1000 PYs (95% CI: 9.60-10.2 PYs) for AF patients with the CHA_2DS_2-VASc score > 1; The incidence rate was 1.54 per 1000 PYs (95% CI: 1.30-1.77 PYs) for AF patients with the $CHADS_2$ score = 0, and the incidence rate was 5.81 per 1000 PYs (95% CI: 5.55-6.07 PYs) for AF patients with the CHA_2DS_2-VASc score < 2.

For AF patients in the lower stroke risk based the AF-CA-Stroke score ≤ 5 but in the higher stroke risk based on the $CHADS_2$ score > 0 (N: 102028), the incidence rate was 7.07 per 1000 PYs (95% CI: 6.84-7.31 PYs); For AF patients in the higher stroke risk based the AF-CA-Stroke score > 5 and in the higher stroke risk based on the $CHADS_2$ score > 0 (N: 29361), the incidence rate was 18.4 per 1000 PYs (95% CI: 17.6-19.2 PYs).

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For AF patients in the lower stroke risk based the AF-CA-Stroke score ≤ 5 but in the higher stroke risk based on the CHA_2DS_2-VASc score > 1 (N: 54145), the incidence rate was 6.79 per 1000 PYs (95% CI: 6.48-7.09 PYs); For AF patients in the higher stroke risk based the AF-CA-Stroke score > 5 and in the higher stroke risk based on the CHA_2DS_2-VASc score > 1 (N: 24599), the incidence rate was 19.4 per 1000 PYs (95% CI: 18.5-20.3 PYs).

The stroke rates based on ablation status and various scoring system in the training dataset were summarized in **Table 2-10**. For AF patients with ablation in the low stroke risk groups based on the CHA_2DS_2-VASc score (< 2) and the AF-CA-Stroke score (< 6), the incidence rates of stroke were low and similar; For AF patients with ablation in the high stroke risk groups based on the CHA_2DS_2-VASc score (> 1), the incidence rate of stroke was 3.74 per 1000 PYs (95% CI: 1.85-5.64 PYs). By contrast, for AF patients with ablation in the high stroke risk groups based on the AF-CA-Stroke score (< 6), the incidence rate was 7.15 per 1000 PYs (95% CI: 3.41-10.9 PYs).

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3.3 Project 3: Clinical Outcomes in Patients with Amyloidosis

3.3.1 Patient Characteristics

In total, 12139 patients with amyloidosis and the same number of non-amyloidosis subjects were identified between 2000 and 2006 (**Figure 3-1**). The incidence rate of amyloidosis was 6.54/100000 person-years. Baseline characteristics are shown in **Table 3-2**. For these 12139 patients, 1130 met the criteria of cardiac amyloidosis, and the incidence rate was 0.61/100000 person-years. In comparison with patients with non-cardiac amyloidosis, patients with cardiac amyloidosis were older, more male, and have a greater number of comorbid conditions (**Table 3-3**).

3.3.2 Incidence of Cardiovascular Events

The incidence rate of VT was 8.57 per 10000 PYs in the amyloidosis group, and 3.37 per 10000 PYs in the control group after a median follow-up of 12 years (interquartile range: 11.3–12.0) (**Table 3-4**). The incidences of AF-related hospitalization (30.2 vs. 11.0 per 10000 PYs), HF-related hospitalization (53.9 vs. 21.2 per 10000 PYs), CV deaths (53.0 vs. 33.1 per 10000 PYs), and all-cause deaths (229.9 vs. 154.5 per 10000 PYs) was higher in patients with amyloidosis than those in the control group (**Table 3-4**).

As compared with patients with non-cardiac amyloidosis, the incidence of VT was significantly higher among patients with cardiac amyloidosis (113.8 vs. 0.69 per 10000 PYs) (**Table 3-5**). The incidences

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of CV deaths (495.2 vs. 31.3 per 10000 PYs), and all-cause deaths (1532.9 vs. 165.9 per 10000 PYs) were also higher in patients with cardiac amyloidosis than those with non-cardiac amyloidosis.

3.3.3 Cardiovascular Outcomes

Figures 3-2A – 3-2E showed the Kaplan-Meier event-free survival curves for new-onset VT events, AF, HF admission, CV death, and all-cause death of patients with and without amyloidosis. In comparison with the control group, the amyloidosis group had a higher rate of new-onset VT events ($P < 0.001$, **Figure 3-2A**), AF ($P < 0.001$, **Figure 3-2B**), HF-related admission ($P < 0.001$, **Figure S3-2C**), CV death ($P < 0.001$, **Figure 3-2D**), and all-cause death ($P < 0.001$, **Figure 3-2E**). Notably, the risk of new-onset VT for the two groups was initially comparable during the first 7.5 years and then diverged later (**Figure 3-2A**).

After multivariable adjustment, an increased risk of VT event was observed in patients with amyloidosis (adjusted HR: 7.90, 95% CI: 4.49-13.9; $P < 0.001$). In addition, patients with amyloidosis had a higher risk of AF (adjusted HR: 6.21, 95% CI: 4.38-8.78; $P < 0.001$), HF-related hospitalization (adjusted HR: 54.7, 95% CI: 37.1-80.7; $P < 0.001$), CV deaths (adjusted HR: 5.09, 95% CI: 4.23-6.12; $P < 0.001$), and all-cause deaths (adjusted HR: 5.11, 95% CI: 4.69-5.57; $P < 0.001$) (**Table 3-6**). The risk of VT in patients with cardiac amyloidosis was significantly higher than those with non-cardiac amyloidosis (adjusted HR: 153.3, 95% CI: 54.3-432.7; $P < 0.001$). Patients

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with cardiac amyloidosis also had a higher risk of CV deaths (adjusted HR: 1.34, 95% CI: 1.02-1.78; P = 0.04) (**Table 3-7**) but not for all-cause deaths (adjusted HR: 1.03, 95% CI: 0.88-1.20; P = 0.75).

There was no ICD implantation in the study population during follow-up. Patients with amyloidosis had a higher incidence of pacemaker implantation than those without amyloidosis (1.26% vs. 0.91%; P = 0.008). In addition, more patients with cardiac amyloidosis had a pacemaker implanted than those with non-cardiac amyloidosis (8.94% vs. 0.47%; P < 0.001).

3.3.4 Cardiovascular Risk Factors within Amyloidosis Patients

After multivariable adjustment, a baseline history of HF (HR: 1.86, 95% CI: 1.22-2.85, P = 0.004), diabetes mellitus (HR: 1.61, 95% CI: 1.08-2.41, P = 0.021), chronic liver disease (HR: 7.33, 95% CI: 2.24-24.0, P = 0.001), and anti-arrhythmic drug use (HR: 1.60, 95% CI: 1.02-2.51, P = 0.043) were independently associated with new-onset VT in patients with amyloidosis (**Table 3-8**). In patients with amyloidosis, new-onset VT was an independent risk factor for CV death after multivariable adjustment (HR: 1.50, 95% CI: 1.07-2.12; P = 0.026) (**Table 3-9**).

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Chapter 4：Discussions

4.1 Project 1: Risk Assessment of Sudden Cardiac Death

4.1.1 Main Findings

In this study, a novel model-based point scoring system was developed for the Asian general population without a history of CAD or LVEF < 35%. The risk function used to predict the 10-year estimated SCD risk was reported. The study revealed several relevant findings, including: (1) Hypertension was significantly associated with a higher risk of SCD; (2) LVH documented by ECG or echocardiography was independently associated with SCD; (3) Medical ultrasound findings of LV systolic dysfunction (LVEF < 40%), increased aortic flow, and evidence of significant carotid plaque were associated with SCD; (4) The newly developed CCCC-SCD-Score system in Asia effectively identifies the risk of SCD with a good predictive performance of 0.88, even after bootstrapping validation with 100 times re-sampling.

4.1.2 Applying Electrogram and Echocardiography to Detect SCD Risk

Echocardiography and ECG can be widely used to improve the diagnosis and treatment of fatal cardiac disease [17,25,26], and to identify subjects who are at risk of SCD [24]. The 12-lead ECG is a widely available, inexpensive, non-invasive tool to all physicians, which may provide definitive clues for establishing the diagnosis. Fingesture study (N=5869, 75% men) reported that abnormal ECG patterns were associated with myocardial fibrosis among SCD victims in Northern Finland and

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Lapland [27]. A. Holkeri and colleagues demonstrated that ECG risk score combining various patterns of abnormal ECG may predict 10-year SCD risk in general population in Finland (N = 6830; aged 30-59 years, 45.5% men) [26]. In this study, we found that abnormal ECG pattern of LVH was strongly associated with SCD, but other abnormal ECG patterns were not selected in the CCCC-SCD-Score. However, the CCCC-SCD-Score is more effective at predicting SCD risk than the ECG risk score.

Aging is associated with increased vascular stiffness and aortic valve flow rate. Hypertension could lead to hypertensive heart disease with clinical manifestations of LVH and diastolic dysfunction [19]. The association between LVH and SCD was reported [107], especially in the presence of myocardial ischemia, fibrosis and scar tissue [19]. In fact, SCD can be caused not only by ischemic heart disease, but also by genetic channelopathies (e.g. hypertrophic cardiomyopathy [108], arrhythmogenic right ventricular dysplasia, or Brugada syndrome [109]). The inherited heart conditions are related to genetic mutations and result in cardiomyopathy, but the incidences of inherited heart conditions are relatively rare in the general population under the age of 35, and often have genetic mutations and result in cardiomyopathy [110]. Approximately 60% of patients with a family history (30% of patients without a family history) of hypertrophic cardiomyopathy will have a positive genetic result. However, genetic screening test is extremely labor-intensive and expensive. In the absence of abnormal conditions or other causes of LVH (e.g. hypertension or

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valvular heart disease), standard 2D echocardiography is the first-line imaging tool for identifying LVH [108]. In this study, participants aged less than 35 were excluded from enrollment initially. The inherited heart conditions and family history were rarely reported in the CCCC cohort.

It has been reported by K. Sutton-Tyrrell and colleagues that elevated aortic pulse is a marker of arterial stiffness that is predictive of cardiovascular and death events [111]. Except for LVH, sudden death in patients with severe aortic stenosis is a clinically important issue. The severity of aortic stenosis is determined by aortic jet velocity and mean gradient (mild: aortic jet velocity ranging from 260-300 cm/s (2.6-3 m/s); moderate: aortic jet velocity ranging from 300-400 cm/s (3-4 m/s); severe: aortic jet velocity > 400 cm/s (4 m/s) [90]. As reported by B. Alcón and colleagues, increased aortic jet velocity (flow rate) ranging from 150–200 cm/s (1.5-2 m/s) was significantly associated with increased cardiovascular and mortality outcomes by analyzing 5994 adults without / with aortic stenosis [112]. In our study, we demonstrated the similar findings that increased aortic flow rate > 190 cm/s (1.9 m/s, cut-off point identifying by the Youden index of the AUC) was independent risk factor of SCD even in patients with normal flow. The possible mechanism could be: (1) Increased aortic flow rate or aortic stenosis may lead to arterial hypotension, stimulation of LV baroreceptors may cause a fall in venous return and consequent bradycardia (abnormal Betzold-Jarisch reflex); (2) Inappropriate hypotension and a low cardiac output provoke coronary hypoperfusion, in patients who already have a predisposition through LVH may lead to VT.

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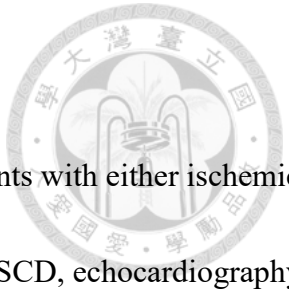

Reduced EF is the most widely used marker for increased SCD risk in patients with either ischemic heart disease or non-ischemic cardiomyopathy [24]. For risk assessment of SCD, echocardiography is highly recommended to assess the structural and functional state of the heart [24]. The ARIC Study and the Cardiovascular Health Study found that echocardiography-derived variables for predicting 10-year SCD provided incremental value for risk stratification after adjustment for Framingham risk scores and renal function in the general population [28]. In agreement with our findings, the echocardiographic evidence of reduced LVEF (< 40%) and LVH were significantly related to incident SCD events in the general population.

4.1.3 Evidence of Carotid Plaque and SCD Risk

In addition, previous study conducted in Japan demonstrated that carotid plaque scores were associated with cardiovascular deaths in the elders with low cardiovascular risk [30]. The ARIC Study and the Cardiovascular Health Study (CHS) reported that the presence of carotid plaque was associated with SCD risk (HR: 1.37, 95% CI: 1.13-1.67) [31]. In order to detect subclinical carotid atherosclerosis, patients without obvious symptoms of cardiovascular events may benefit from carotid artery duplex sonography. Several mechanisms have been proposed regarding the link between early carotid atherosclerosis and SCD. Subclinical atherosclerosis may lead to ischemic

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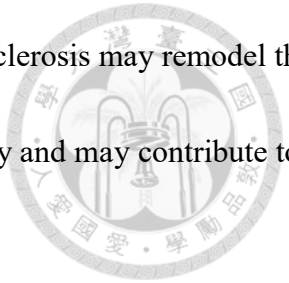
events and inflammatory status, which may result in incident SCD. Atherosclerosis may remodel the LV myocardium in a chronic, subclinical manner, leading to cardiomyopathy and may contribute to fatal arrhythmia and lead to incident SCD consequently [113-115].



4.1.4 Model-based Risk Prediction Score and Traditional Risk Factors

Traditional risk factors include physical factors such as age, gender, obesity, and race, as well as underlying diseases such as CAD, HF, AF, hypertension, diabetes mellitus, and renal dysfunction, which may present a risk for SCD [15,16,116]. Additionally, SCD was associated with abnormal biological markers (e.g. elevated serum cholesterol, glucose intolerance) and unhealthy behaviors (e.g. smoking, alcohol consumption, and physical activity) [15,16].

Given a number of identifiable risk factors, a model-based risk prediction score could be helpful for risk stratification of SCD. Bogle BM and colleagues once developed a simple 10-year risk prediction score based on the ARIC Study (N = 11335) and the Framingham cohort (N = 5626) in the United States (aged 45-65 years, 47.6% men) [32]. This risk score was derived from the following factors: age, sex, total cholesterol, use of lipid-lowering and hypertension medications, blood pressure, smoking status, diabetes, and body mass index, with a C-index of 0.75. The risk of SCD was also higher in blacks than in whites in each risk strata [32]. In contrast, the CCCC-SCD-

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Score did not include diabetes, smoking, lipid profiles, body mass index, renal dysfunction, or cardiac arrhythmias. Nevertheless, the prediction performance of the present score was significantly higher than the ARIC-Framingham score, suggesting that different scoring systems should be applied to risk stratification in different ethnicities.

4.1.5 Clinical Implications

SCD can be caused by structural (e.g. CAD, non-ischemic cardiomyopathies, valvular heart disease, and other structural causes) and non-structural etiologies (e.g. arrhythmic causes) [12]. After excluding prior histories of CAD and LVEF < 35%, 23.1% of the victims in the CCCC study were likely to have a cause of death from CAD. The cause of over 76.9% of SCD in the CCCC study was not attributed to CAD. Identifying the risk factors of SCD that extend beyond CAD is essential for preventive medicine. In this study, we identified several risk factors of SCD associated with structural abnormalities of the heart, and developed a novel CCCC-SCD-Score using the ECG and echocardiography. The CCCC-SCD-Score represents an integrated point-based scoring system as an initial step in developing routine screening for SCD. Since the consequence of SCD is severe, even if the positive predictive value is not so high, patients who are grouped as high-risk group shall be followed routinely, earlier diagnosis and proper prognostic stratification may reduce disease-related mortality by promoting advanced examination (e.g. genetic screening) and timely treatment. Risk-stratification with a resting ECG, echocardiography, and a population-appropriate risk calculator is

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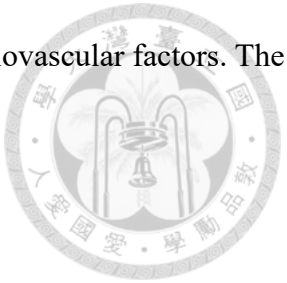
an easy way to begin assessing occult ischemic heart disease and other cardiovascular factors. The CCCC-SCD-Score may be useful in predicting 10-year SCD risk in Asia.



4.1.6 Study Limitations

There are several limitations to this study. First, single measurement at baseline of biomarkers, hemodynamic information, and medical ultrasound data were obtained for the study. The abnormalities detected by 12-lead ECG were also based on three examinations during biannual follow-ups. Time-varying covariance may occur when a covariate changes over time during the follow-up period, which is a common phenomenon in clinical research. Such variable can be analyzed with the Cox regression model to estimate its effect on survival time. However, the CCCC-SCD-Score represents an integrated point-based scoring system based on binary data of abnormalities or diseases as an initial step in developing routine screening for SCD. Due to the status of disease varied with time, the CCCC-SCD-Score is recommended to be re-assessed at least annually for timely risk stratification and treatment. Second, this study was based on the data from a general Chinese population. Interpretations among various races should be cautious, and external validation should be conducted in the future. Third, genetic data and family history of inherited heart conditions were not collected in this study. Genetic screening test is extremely labor-intensive and expensive, but the inherited heart conditions and family history were rare in the CCCC cohort. Finally, medication use, such as lipid-lowering or hypertension medication, may affect outcomes.

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However, since this study was a cohort study, the medications used by patients varied, therefore, the medication history was not well established.

There are several strengths of our study as well. First, CCCC is a valuable study with a large sample size and a long-term follow-up period in Asia. In addition, a community-based population could reduce the possibility of selection bias compared to a hospital-based cohort. Second, we established a comprehensive strategy for identifying the risk factors of SCD and ensuring subjects' follow-up. Integrated analyses based on the ECGs and imaging technology may be applied to improve the diagnosis and treatment of fetal cardiac disease. A proper population-based risk score system is helpful in predicting the risk of SCD in Asia.

4.1.7 Conclusions

The newly constructed clinical model-based point scoring system is useful in identifying the SCD risks among the Asian general population who are at least 35 years of age. In addition to higher age, LV systolic dysfunction, and hypertension, there are significant risk factors associated with SCD, such as LVH, increased aortic flow, and higher carotid plaque score. Early diagnosis using screening

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tools such as ECG, echocardiography, and carotid artery duplex sonography is important for the primary prevention of SCD.

4.1.8 Acknowledgements

The authors express their gratitude to the CCCC participants.

4.1.9 Conflict of Interests

None of the authors have any conflicts of interest or financial relationships related to the study.

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4.2 Project 2: Risk Assessment of Stroke in Patients with Atrial Fibrillation

4.2.1 Main Findings

This study developed a novel model-based point scoring system (AF-CA-Stroke score) to predict incident stroke events in patients with AF based on five clinical variables using a matched AF cohort. Risk functions to predict the 1-year estimated stroke risk was reported. The accurate stroke trends in both training dataset and validation dataset were nearly matched to the 1-year estimated risk function according to the AF-CA-Stroke scores. The AF-CA-Stroke score had significantly higher decimation ability in predicting 1-year incident stroke events than conventional score systems.

4.2.2 Effects of Various Age Groups and Comorbidities on Stroke Risks

Evidences revealed that the incidence of AF increased with aging, which also led to worse prognosis, incident stroke events, and higher risk of deaths in patients with AF [59]. Most developed countries have accepted the age of 65 years as a definition of elderly. Ages 60 and 65 years are often used, despite its arbitrary nature. Currently, the $CHADS_2$ system includes age ≥ 75 years as 1 point [49], the CHA_2DS_2-VASc set age ≥ 65 years as 1 point and ≥ 75 years as 2 points in predicting future stroke risk in patients with AF [49]. However, to identify the risk of stroke in patients with AF, aging and incident comorbidities are generally a complex issue, and previous studies had difficulties in discussing this issue. A meta-analysis concluded that age as a criterion in patients with AF shall not be simply considered based on gender or age stratifications of ≥ 65 / ≥ 75 years [60]. Age and

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comorbidities mutually impact the stroke risks in patients with AF [56-58]. Taipei Group described that a younger age of > 50 years had an increased stroke risk even without comorbidity based on the NHIRD analysis in Taiwan, and stroke risks vary based on the status of comorbidities in various age groups [58,61]. In the current study, the model-based scoring system depending on the baseline beta coefficient changes in age was constructed, with up to 5 points being assigned to the age groups, and a total of 9 points were established in our novel AF-CA-Stroke scoring system. This newly developed AF-CA-Stroke score can provide more flexibility in predicting stroke risks in patients with AF in various age groups and conditions regardless of gender.

4.2.3 Managing Stroke Risks in Patients with AF and the Impact of Catheter Ablation

Several stroke prediction models have been developed and validated by previous studies [49-53]. For the management of stroke risks in patients with AF, both European and American guidelines recommend to use $CHADS_2$ and CHA_2DS_2-VASc scoring systems to determine an optimal strategy of stroke prevention [49,50]. Chao, TF, et al. demonstrated that AF patients in Asian with CHA_2DS_2-VASc score of 0 had a truly low stoke risk than $CHADS_2$ score, and CHA_2DS_2-VASc score might be used for stroke risk stratification in Asians as with Caucasians [53]. Previous studies suggested that patients with AF ablation with $CHADS_2$ score of "0" or CHA_2DS_2-VASc score of < 2 were indeed classified as low stroke risk [54], especially in patients with AF ablation [44,55].

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In the era of catheter ablation, several observational studies in different countries have reported that AF ablation was an effective therapy in AF patients at various ages with multiple co-morbidities [65,66]. In AF patients receiving ablation, they had significantly decreased risks of stroke, AF-related complications, and deaths than AF patients receiving antiarrhythmic drugs but without AF ablation [67,68]. In the largest randomized (CABANA) trial for comparing the effects between antiarrhythmic drugs and AF ablation by using intention-to-treat analysis, AF ablation did not significantly reduce stroke risks in AF ablation group [69]. The reason of non-significant ablation effect on reducing stroke risk could be the crossovers between antiarrhythmic drugs and AF ablation during follow-up, which may affect the final outcomes.

In the current study, we observed that patients with AF ablation with CHA_2DS_2-VASc score of > 1 or AF-CA-Stroke score > 5 (as high risk of stroke) had lower stroke rate than patients without AF ablation. This study firstly showed that the status of receiving AF ablation is a significant factor in the new scoring system with equivalent score of 1 point in the risk stratification of the future stroke risk. Second, when assessing the risk of stroke after an ablation in low-risk patients based on AF-CA-Stroke scores, 68.8% AF patients were classified as higher stroke risk based on CHA_2DS_2-VASc scores, but classified as a lower risk group based on AF-CA-Stroke scores in the training dataset. In this study, both AF-CA-Stroke and CHA_2DS_2-VASc scores can be used for assessing low stroke risk in AF patients in Asia. We suggest that long-term anticoagulants may be discontinued in around 70-

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80% of AF patients in the low-stroke-risk group based on the AF-CA-Stroke scores but originally in the high-risk group based on the $CHADS_2$ or CHA_2DS_2-VASc scores, irrespective of the recurrence state of AF ablation.

4.2.4 Hypertension and Diabetes Mellitus

In addition to the status of receiving AF ablation, most of the clinical risk factors in our novel AF-CA-Stroke scoring system were consistent with the conventional scoring systems for stroke prediction. However, as compared with CHA_2DS_2-VASc or $R_2CHA_2DS_2$-VASc scoring systems [101], it did not include the status of hypertension, diabetes mellitus, and women. Hypertension is an important risk factors of hemorrhagic stroke, because it may contribute to atherosclerotic diseases that can lead to ischemic stroke [62]. In the Chin-Shan Community Cardiovascular Cohort (CCCC) study, higher blood pressures and diabetes mellitus were associated with stroke risks regardless the AF diagnosis in Taiwan [63]. However, in the current study, the risk factors of hypertension and diabetes mellitus were not included in the final model for constructing the novel scoring system.

4.2.5 Gender

The CHA_2DS_2-VASc scoring system includes women as a stroke risk factor. As proposed by J.M. Abraham and colleagues, both $CHADS_2$ and CHA_2DS_2-VASc scoring systems were predictive factor in postmenopausal women with AF [49,50]. In our study, adding the status of women did not

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improve the discrimination ability of stroke prediction. Our study results were in consistent with the results provided by the prior study, which demonstrating that female gender is a “risk modifier” rather than a “risk factor” of stroke in AF patients [117].

4.2.6 Renal Function as a Stroke Risk in Managing Patients with Atrial Fibrillation

Prior studies reported that AF and renal function seemed to be correlated with each other with bidirectional relationship. AF leads to the progression of chronic kidney disease while impaired renal function may cause the onset of AF and hypertension, and AF patients with impaired renal function were at higher risks of stroke and deaths [64]. Hence, stroke prevention of oral anticoagulants in AF patients requires more detailed evaluations on renal function. However, the $CHADS_2$ and CHA_2DS_2-VASc scoring systems did not take the status of chronic kidney disease into consideration for stroke stratification in AF patients. In our study, the status of chronic kidney disease is an important risk factor for constructing the scoring system with one point. In other studies, the R_2CHADS_2 and $R_2CHA_2DS_2$-VASc scoring systems were developed by adding renal function on the basis of $CHADS_2$ and CHA_2DS_2-VASc scoring systems [100,101].

4.2.7 Study Limitations

The large number of population-based AF cohort and long-term follow-up were the strength of our study in constructing a clinical model-based scoring system. This were several limitations in this

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study. First, the diagnoses were based on ICD-9-CM codes, which were established by the physicians and re-confirmed by a certified coding specialist, we could not exclude the possibility of miscoding. Second, information regarding the AF subtypes, AF recurrences, methods of AF ablation were not available in this study. Whether the above-mentioned status might affect the stroke outcome remains unclear. Third, the uses of medications such as anti-coagulation and anti-arrhythmic drugs may affect the stroke outcomes. However, due to this study was a cohort study, medication uses varied among patients. Besides, the study aim was to demonstrate a scoring system using the conventional risk factors plus the status of catheter ablation for stroke management, as a result, we did not consider the effects of medication uses for constructing the scoring system. Finally, changes in therapy may occur over time due to changed status of ablation, underlying diseases, and age, the AF-CA-Stroke score shall be re-assessed annually. Because of lacking data on the comparisons between the novel and conventional scoring systems, it is difficult to conclude that the new scoring system might generate when applied to other populations.

4.2.8 Conclusions

A newly constructed clinical model-based point scoring system is useful in identifying risk stratifications of stroke in patients with AF using clinical factors, including various age stratifications and catheter ablation status. These clinical factors shall be considered as risk stratification for stroke prevention.

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4.2.9 Acknowledgements

The authors express their gratitude to the Taiwan Collaboration Centre of Health Information Application, Ministry of Health and Welfare, for providing the entire dataset used for this study.

4.2.10 Conflict of Interests

None of the authors have any conflicts of interest or financial relationships related to the study.

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4.3 Project 3: Clinical Outcomes in Patients with Amyloidosis

4.3.1 Main Findings

The main findings from this study were: (1) The incidence of amyloidosis and cardiac amyloidosis was 6.54 and 0.61 per 100000 person-years, respectively; (2) Patients with amyloidosis had a significantly higher incidence of VT, AF, HF-related hospitalizations, CV deaths, and all-cause deaths during long-term follow-up; patients with cardiac amyloidosis also had a significantly higher incidence of VT than those with non-cardiac amyloidosis; (3) HF-related hospitalization, diabetes mellitus, and chronic liver disease were associated with new-onset VT in patients with amyloidosis; and (4) new-onset VT was associated with higher risk of CV death in patients with amyloidosis.

4.3.2 Incidence of Amyloidosis and Cardiac Amyloidosis

Most international epidemiological studies for investigating amyloidosis are based on death certificate data and specific types of amyloidosis [74-76,78]. Gilstrap and colleagues reported that the incidence rate of cardiac amyloidosis was 17 per 100000 person-years in the United States [73]. It should be noted that data collected from the Medicare database were highly selective and only included inpatient resources in the study. In our data, the incidence rate of amyloidosis (including both localized and systemic amyloidosis) was 6.54 per 100000 person-years from a nationwide cohort, and the we reported an incidence of 0.61 per 100000 person-years for cardiac amyloidosis. Our study is more in agreement with those published recently in

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the Danish national registries [77]. The difference between our findings and those reported by the Danish national registries may be explained by the selection and age of patients. Additionally, our data was retrieved from 2000 to 2006, a period during which the cardiac amyloidosis was not well diagnosed. Finally, the population from Danish national registries is solely White, whilst our study provides the first nationwide assessment of amyloidosis and cardiac amyloidosis in the Han population.

4.3.3 New-onset VT and CV Events in Patients with Amyloidosis and Cardiac Amyloidosis

There have been few studies to investigate the incidence of VT in patients with amyloidosis. Using Holter monitoring, VT was detected in 18% of 51 and 26.7% of 195 patients with AL amyloidosis, reported by Palladini et al. and Dubrey et al., respectively [118,119]. Goldsmith and colleagues analyzed the types of arrhythmia in 24 patients with AL amyloidosis undergoing stem cell transplantation, and found that sustained VT occurred in 12.5% of patients [120]. A study using implanted loop monitors showed that VT was identifiable only in one patient (5%) with AL amyloidosis during a median follow-up period of 308 days [121]. However, those studies were confined to a small population of highly selected subjects, which rendered the true incidence of ventricular arrhythmia impossible to determine.

To the best of our knowledge, this is the first study to demonstrate the long-term follow-up of CV events in patients with amyloidosis and cardiac amyloidosis using a nationwide cohort.

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Study findings indicate that patients with amyloidosis have a 7.90-fold increased risk of developing VT compared to those without amyloidosis, and patients with cardiac amyloidosis have a 153.3-fold increased risk of new-onset VT compared with patients with non-cardiac amyloidosis. We also demonstrated for the first time that a higher risk of VT was observed 7.5 years after the patients were diagnosed with amyloidosis. Furthermore, our study also demonstrated that VT contributed to a significantly higher CV death rate. In consistent with previous studies [118,120], VT was an independent risk factor with a 1.50-fold increase in CV death after adjusting for other confounders, when compared to amyloidosis patients without VT. Preventing and treating these ventricular arrhythmic events are crucial for improving the prognosis of patients with amyloidosis.

4.3.4 Predictors of Ventricular Tachycardia in Amyloidosis

The current study demonstrated that a history of HF has a predictive value for new-onset VT. Falk and colleagues reported that patients with amyloidosis who present with VT are more likely to have a history of HF and abnormal echocardiographic findings [82], which echoed our findings. An enlarged LV chamber and impaired LV systolic function could result in structural remodeling and diseased substrate formation, which may explain the occurrence of VT at the late stage of amyloidosis with cardiac involvement [83].

There have been some reports that demonstrate that oxidative stress in the presence of liver disease

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and diabetes mellitus was associated with ventricular instability and QT prolongation [122-124], which may contribute to VT. However, the correlation between amyloidosis and diabetes mellitus and the risk of VT remains unclear. There are no published studies linking chronic liver disease, amyloidosis, and VT risk. It is necessary to conduct further studies to demonstrate these relationships.

Furthermore, VT has also been linked to the use of anti-arrhythmic drugs (AADs). According to our data and previous studies, AADs have been used to control the rate or rhythm of AF in patients with amyloidosis [81,124]. Patients receiving AADs may experience more new-onset VT because of amyloidosis affecting both atriums and ventricles. Therefore, the incidence of VT was higher in patients taking AADs for AF. While AADs may reduce the recurrence of VT, their efficacy is rarely promising. Irrespective of the above, AADs are well known to cause proarrhythmic effects because of QTc prolongation, which can also lead to new-onset VT in patients with amyloidosis [125].

4.3.5 Clinical Implications

Our study found that patients with amyloidosis and cardiac amyloidosis had a significantly higher incidence of VT, and they also had a significantly greater incidence of CV death following VT than those without VT. AADs are conventionally used for the treatment of VT. Beta-blockers were widely used to suppress VT, but they may be harmful to patients with

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cardiac amyloidosis because of a consequence loss in cardiac output [125]. Furthermore, our study showed neither protective effects of AADs for VT occurrence nor benefits for CV or all-cause deaths. As previously mentioned, the role of AADs in patients with amyloidosis was not conclusive, and it even posed a risk for VT and CV deaths. Currently, the implantation of an ICD is controversial in patients with amyloidosis. Owing to the lack of survival benefit from an ICD implantation in patients with cardiac amyloidosis with advanced stage of HF [126,127], it is important that these patients should be closely monitored over the long term once amyloidosis has been diagnosed to minimize adverse outcomes. The decisions of pharmacotherapies or an ICD implantation should be carefully considered and discussed between patients and physicians with expertise at the earlier stage, especially for those carrying high-risk features, such as HF, diabetes mellitus, and chronic liver disease.

4.3.6 Study Limitations

There are several limitations in our study. First, the study is retrospective in nature, and therefore there may be inherent bias. Despite PS matching, some variables between non-amyloidosis and amyloidosis groups remained inconsistent. However, we used multivariable regression for doubly confirming the adjusted effect sizes. However, our study findings were analyzed using a large sample size and a long-term follow-up nationwide cohort. In addition, since amyloidosis was diagnosed using an ICD-9 code from the NHIRD, there may have been a diagnosis and procedure coding error. However, amyloidosis is a rare disease, and only physicians who are

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familiar with this disease would be capable of making this diagnosis. A certified coding specialist also confirmed the diagnosis to reduce the possibility of misclassification. Moreover, our medical records should reflect an accurate diagnosis of VT since it is a life-threatening condition. Third, there is no additional information available from the NHIRD that could separate localized from systemic amyloidosis. Fourth, the definition of cardiac amyloidosis was based on the code for amyloidosis plus the codes for one of HF/cardiomyopathy/AF and this definition is neither 100% sensitive or specific, so it will both include patients without cardiac amyloidosis and miss patients with cardiac amyloidosis.

4.3.7 Conclusions

Amyloidosis and cardiac amyloidosis may increase the risk of VT during the follow-up period of over 10 years, and the presence of new-onset VT was an independent risk factor for CV death in patients with amyloidosis. Accordingly, patients with amyloidosis should continue to undergo cardiac evaluations during long-term follow-up. Further investigations to evaluate whether early intervention could improve long-term outcomes is required.

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4.3.8 Acknowledgements

The authors express their gratitude to the Taiwan Collaboration Centre of Health Information Application, Ministry of Health and Welfare, for providing the entire dataset used for this study.

4.3.9 Conflict of Interests

None of the authors have any conflicts of interest or financial relationships related to the study.

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Figures

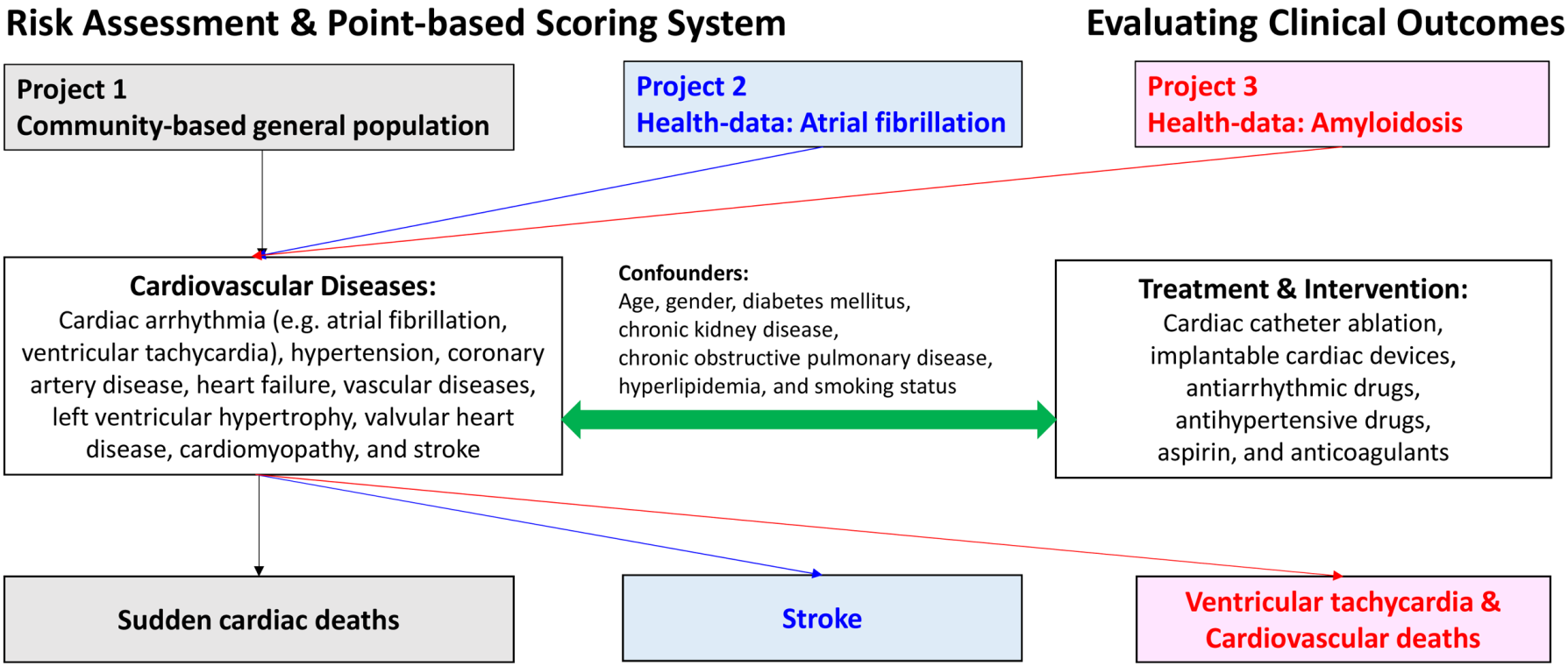

Figure 0: Overview of the three study projects.

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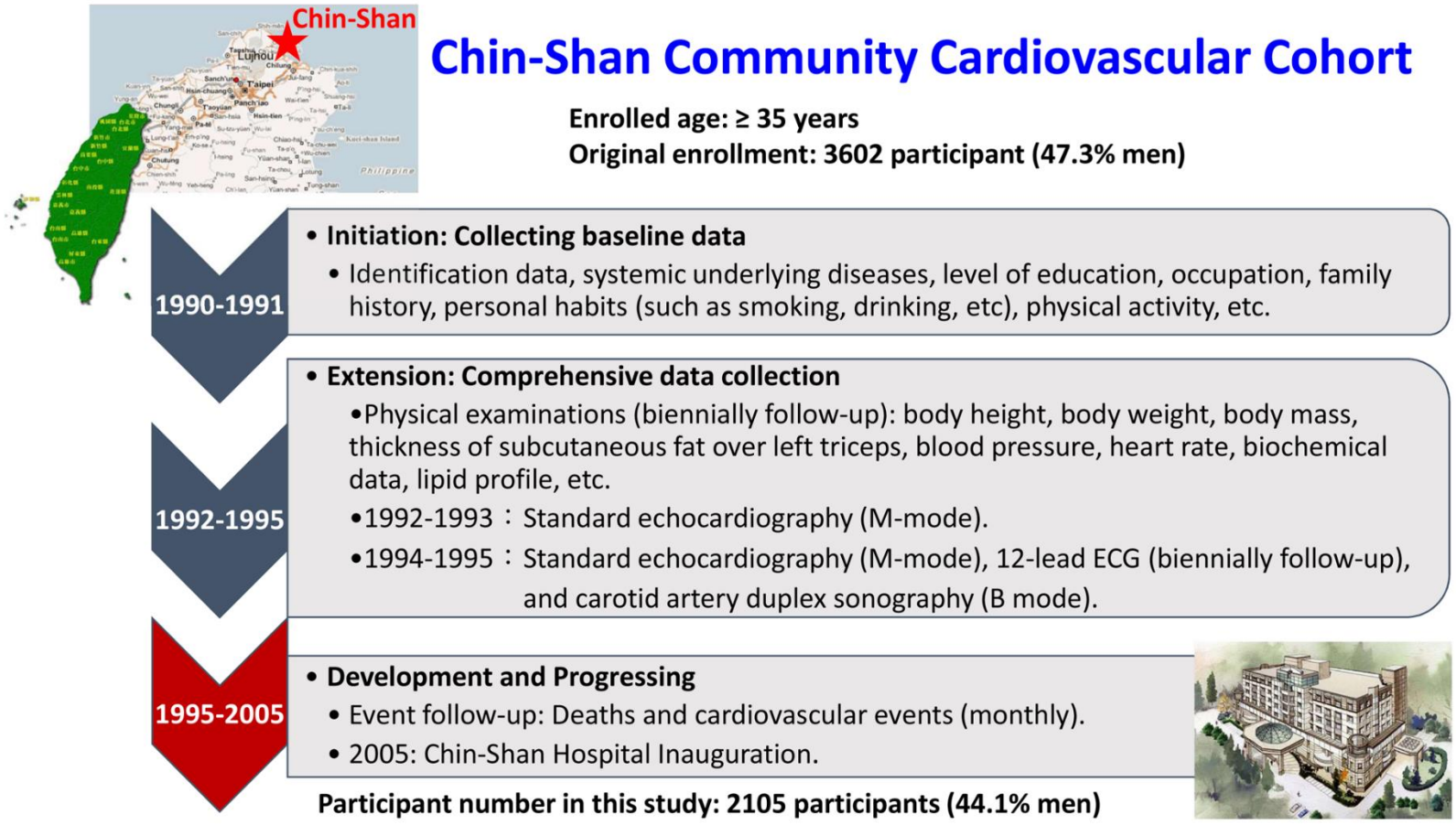

Figure 1-1: Data Collection Scheme-Project 1.

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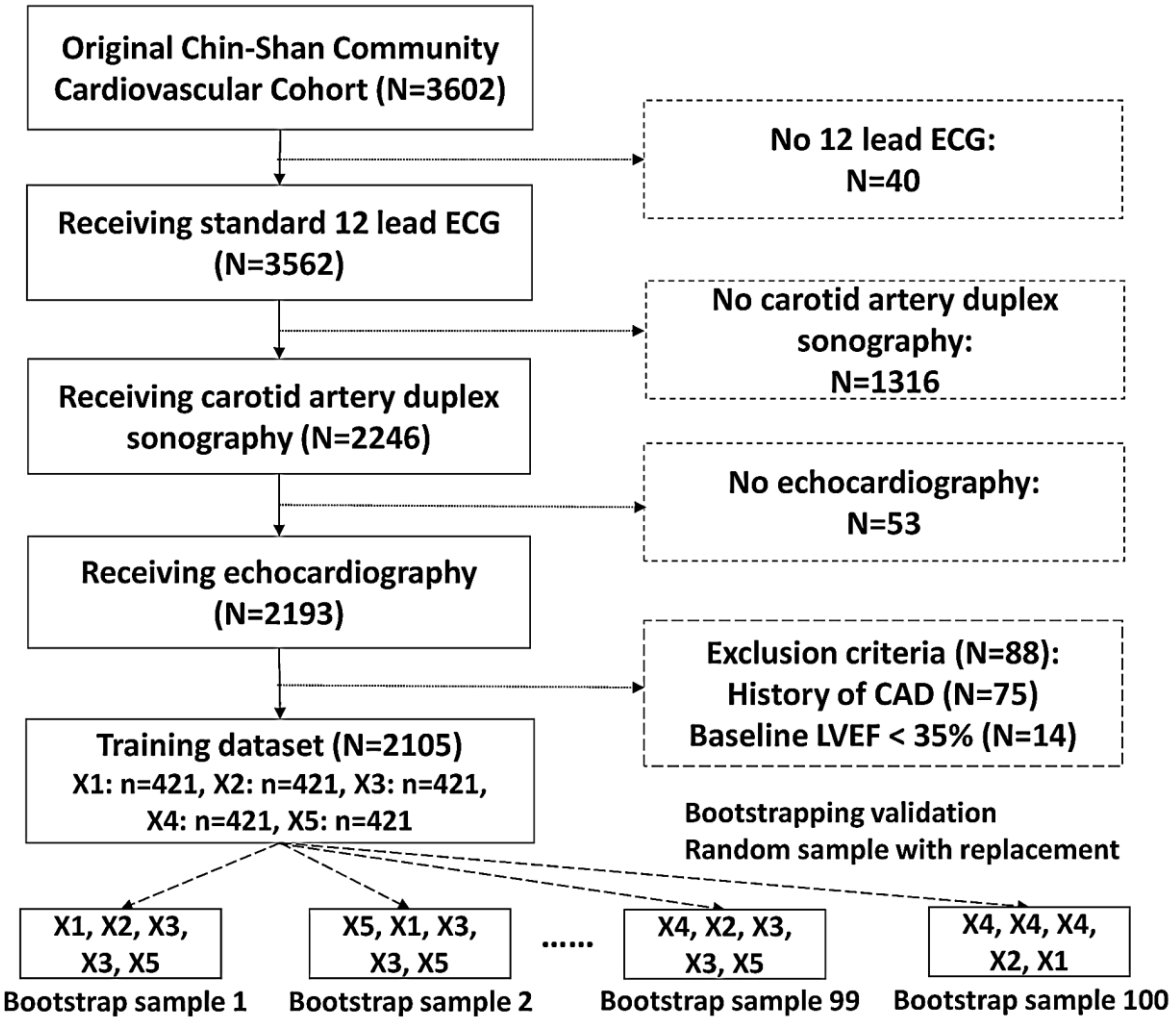

Figure 1-2: Study flow chart-Project 1.

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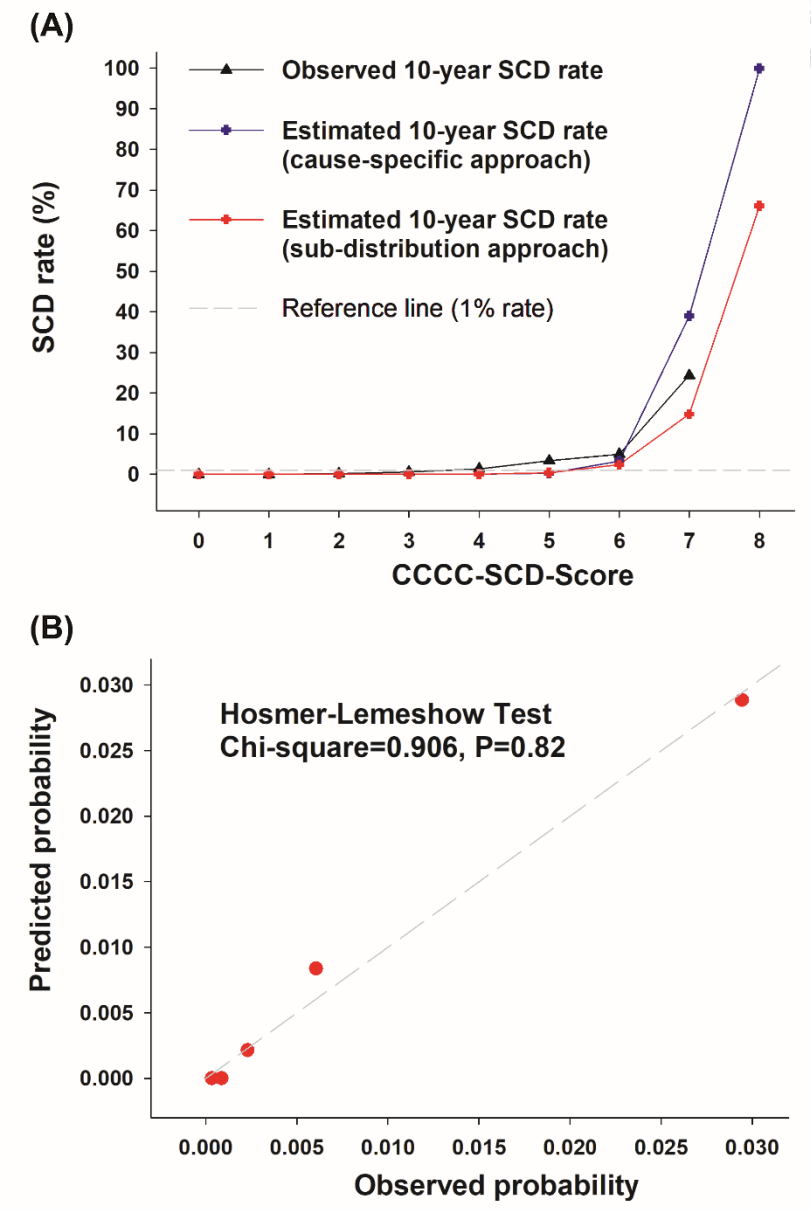

Figure 1-3: (A) Risk function based on various scores and (B) prediction accuracy based on the Hosmer-Lemeshow chi-squared test (x-axis: observed probability of SCD; y-axis: predicted probability of SCD).

SCD: sudden cardiac death.

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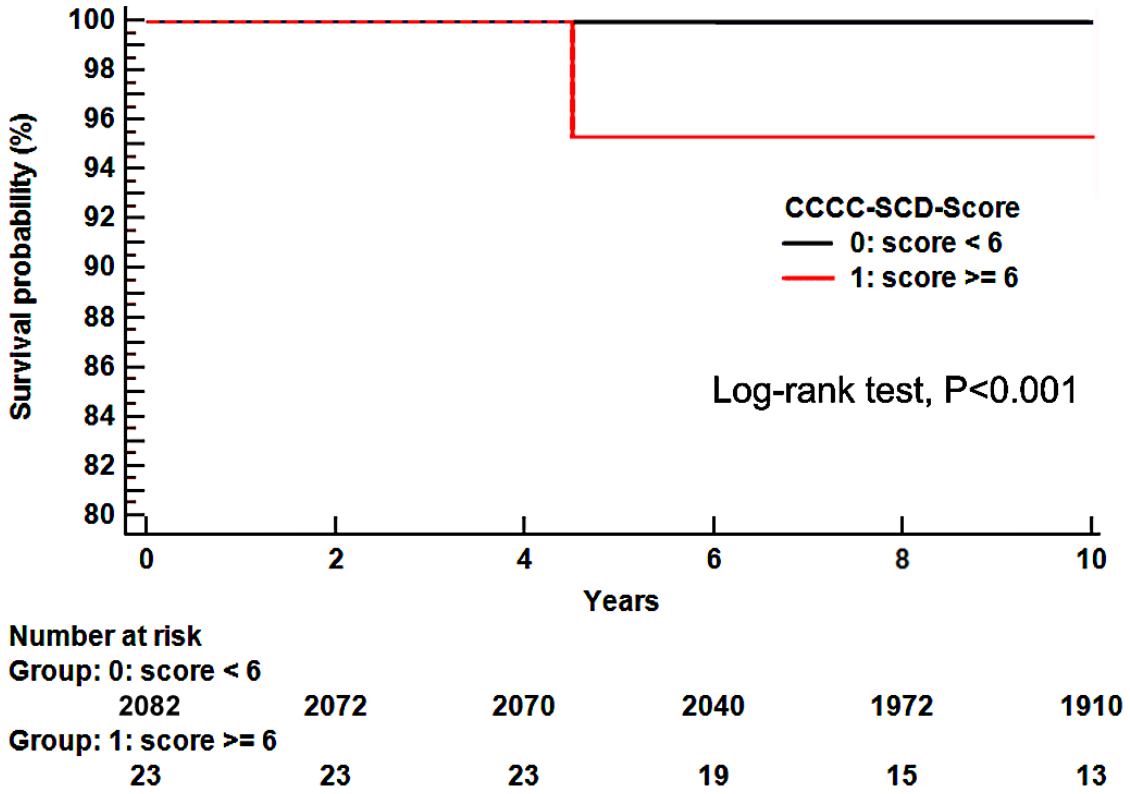

Figure 1-4: Kaplan–Meier survival plots based on the status of the CCCC-SCD-Score in the training dataset.

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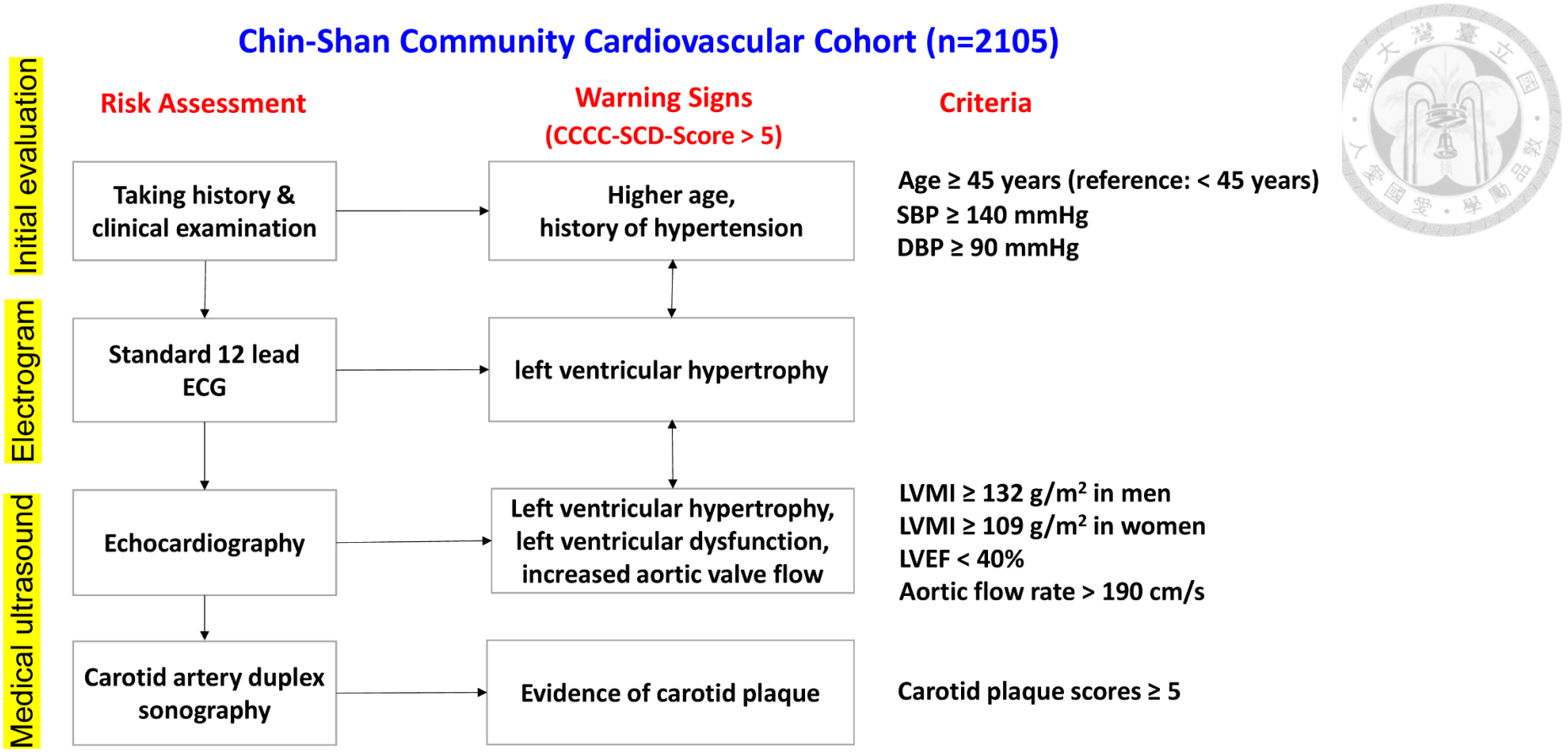

Figure 1-5: Summary for applying electrogram and medical ultrasound to detect the warning signs of sudden cardiac deaths based on the Chin-Shan Community Cardiovascular Cohort.

DBP: diastolic blood pressure; ECG: electrogram; LVMI: left ventricular mass index; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure.

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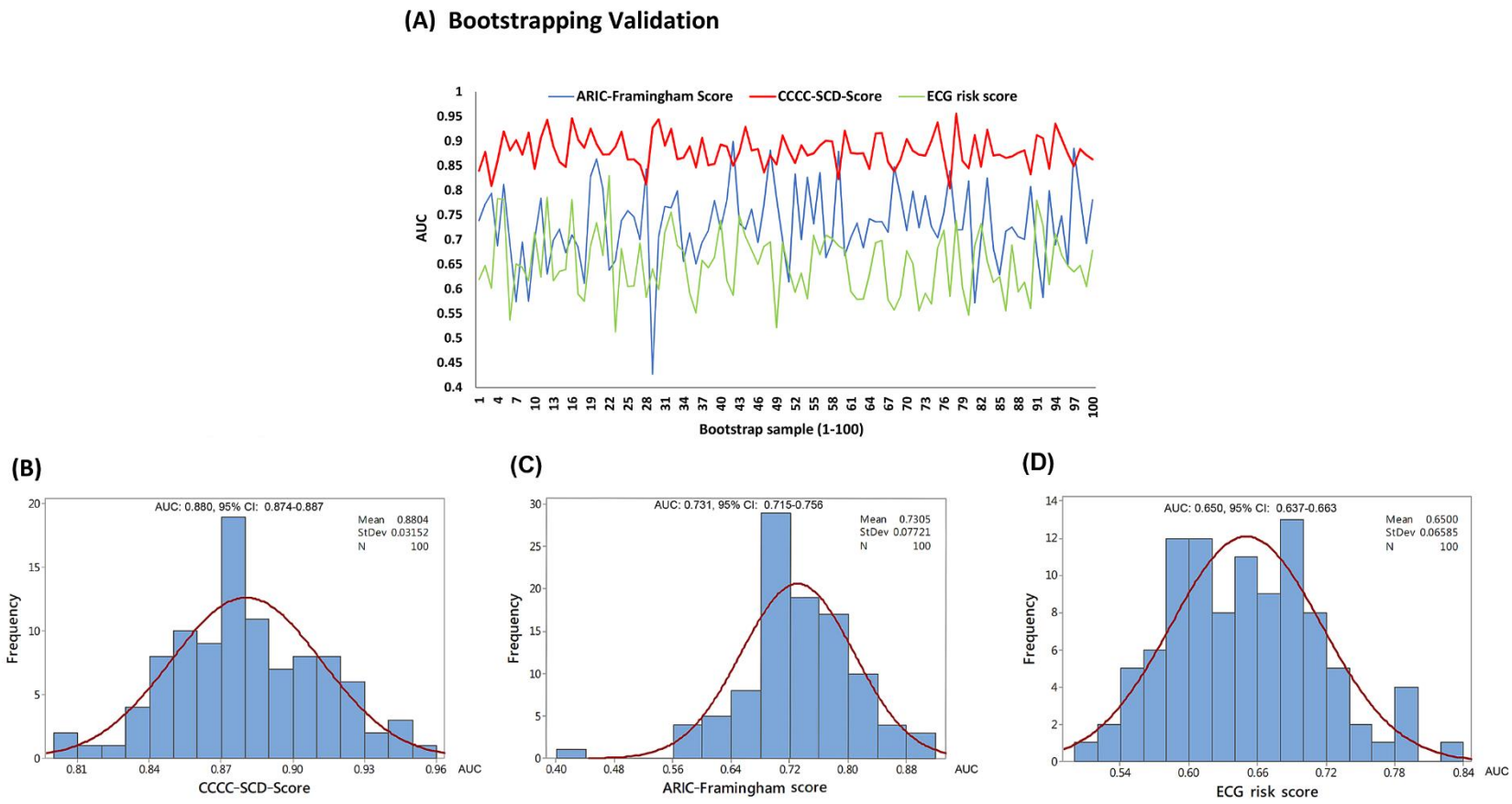

Figure 1-6: Discrimination performance based on the area under the receiver operating characteristic (ROC) curves (AUCs) for the various SCD prediction scores: (A) Distribution of the AUCs based on the bootstrapping validation (the training dataset was repeatedly resampled 100 times), and histogram of the AUCs based on the frequency (number) of bootstrap sample sets for: (B) CCCC-SCD-Score, (C) ARIC-Framingham score, and (D) ECG risk score.

AUC: area under the curve; CI: confidence interval; N: number; N: number; StDev: standard deviation.

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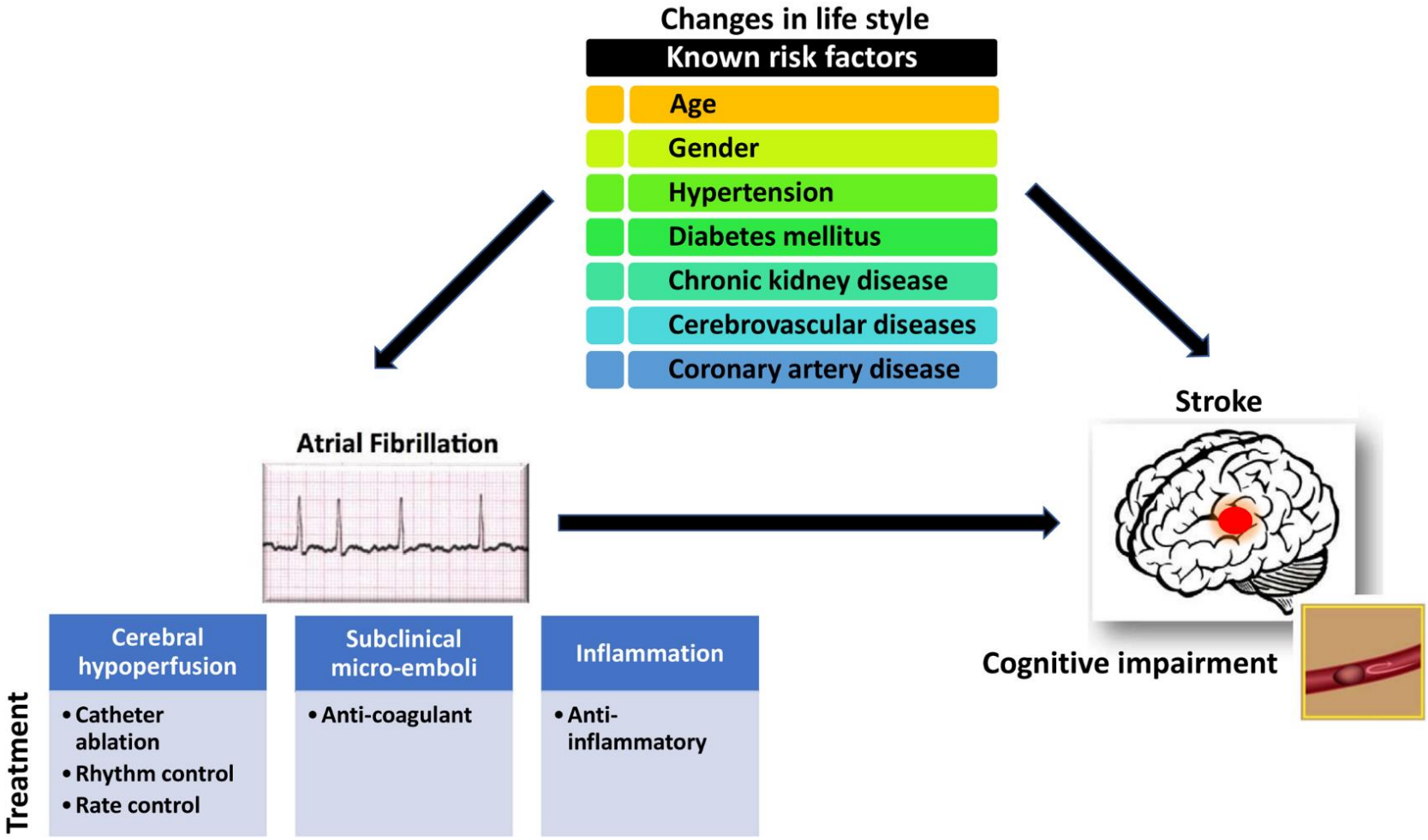

Figure 2-1: Biological mechanism of stroke due to atrial fibrillation.

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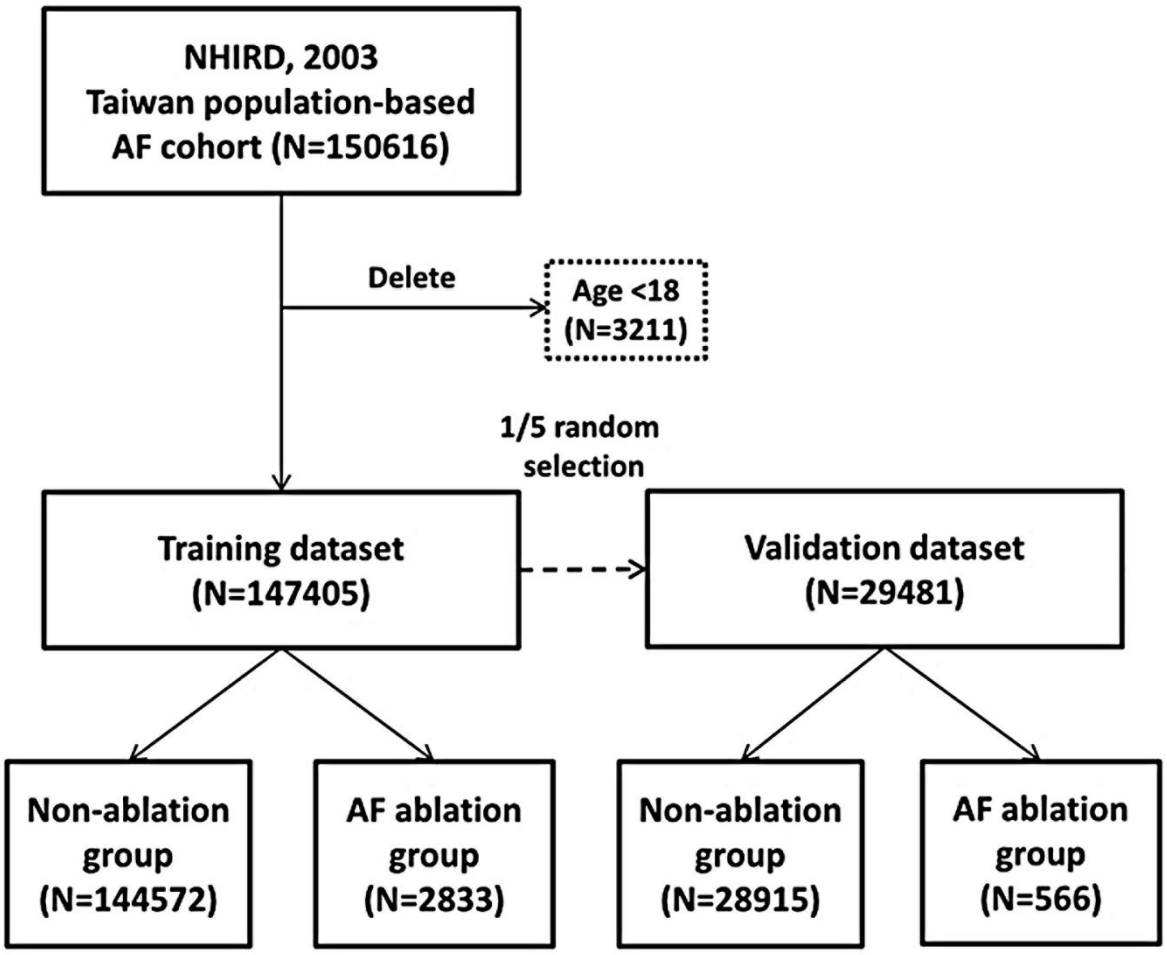

Figure 2-2: Study flow chart-Project 2.

AF: atrial fibrillation; NHIRD: Taiwan National Health Insurance database; TVGH: Taipei Veterans General Hospital.

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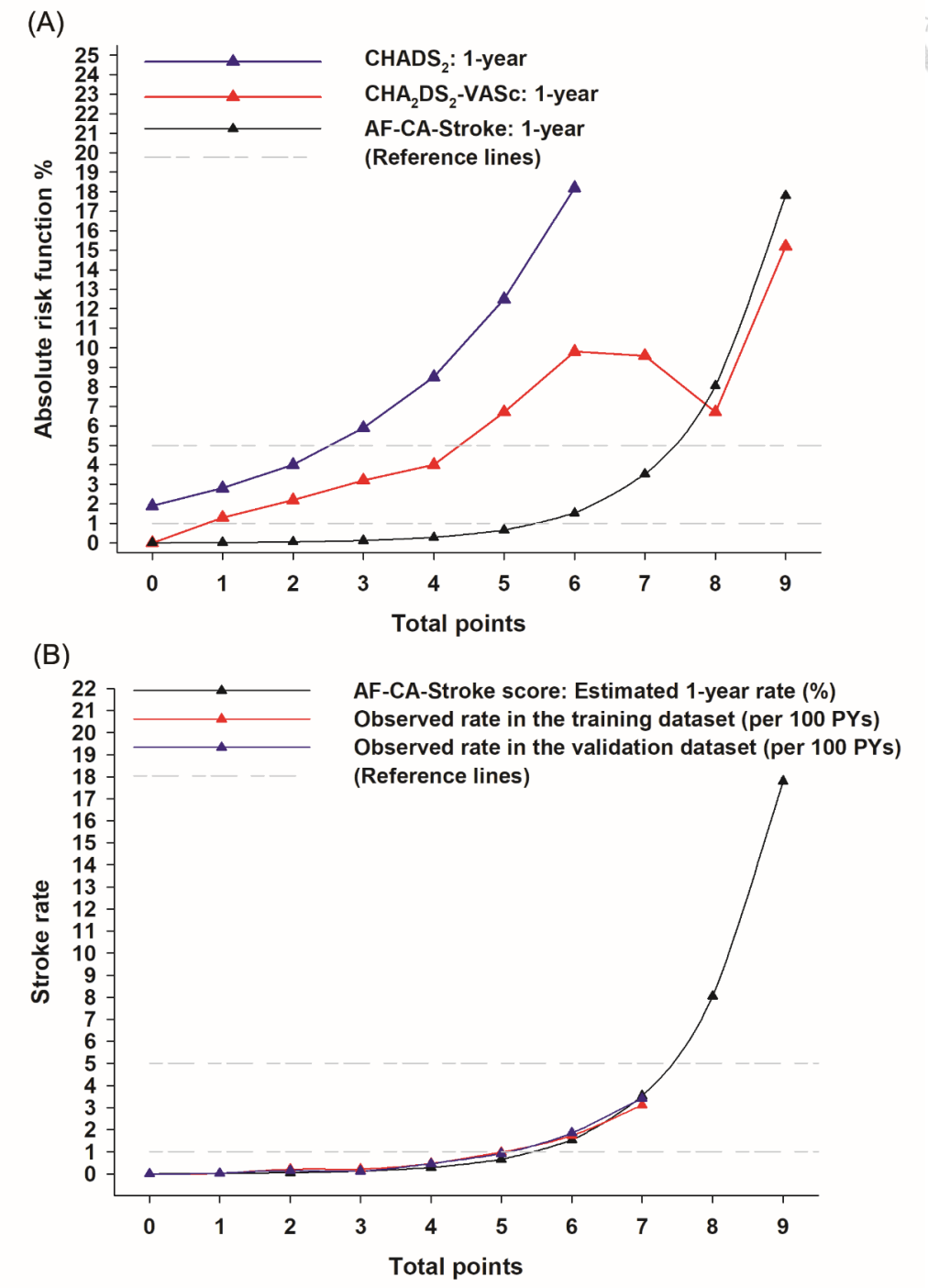

Figure 2-3: Risk functions of: (A) the comparisons of estimated 1-year risks among various scoring systems depending on the total points, (B) comparisons between estimated 1-year rate of AF-CA-Stroke score and observed stroke rates (per 100 person-years [PYs]) based on the AF-CA-Stroke score in the training dataset and validation dataset.

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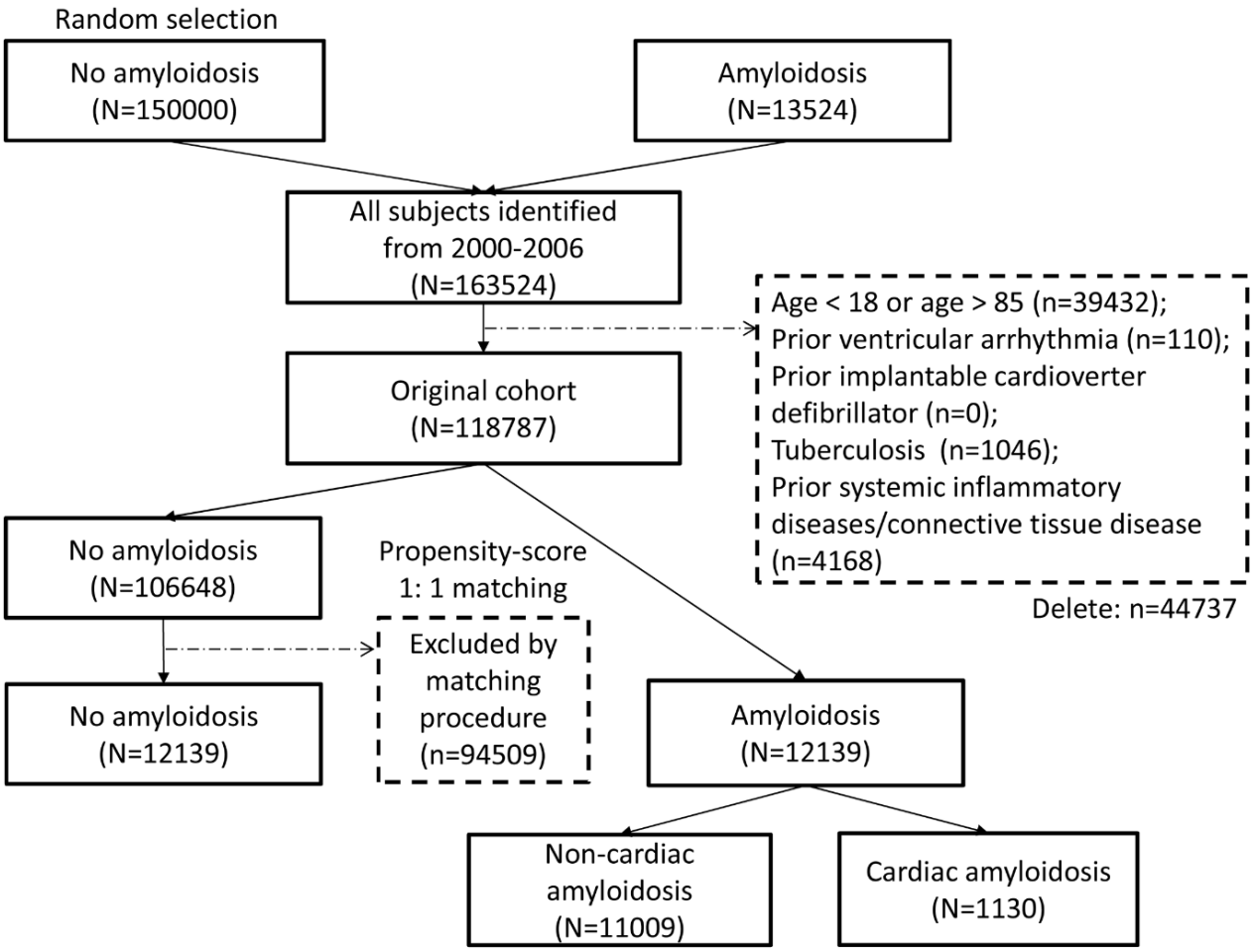

Figure 3-1: Study flow chart-Project 3.

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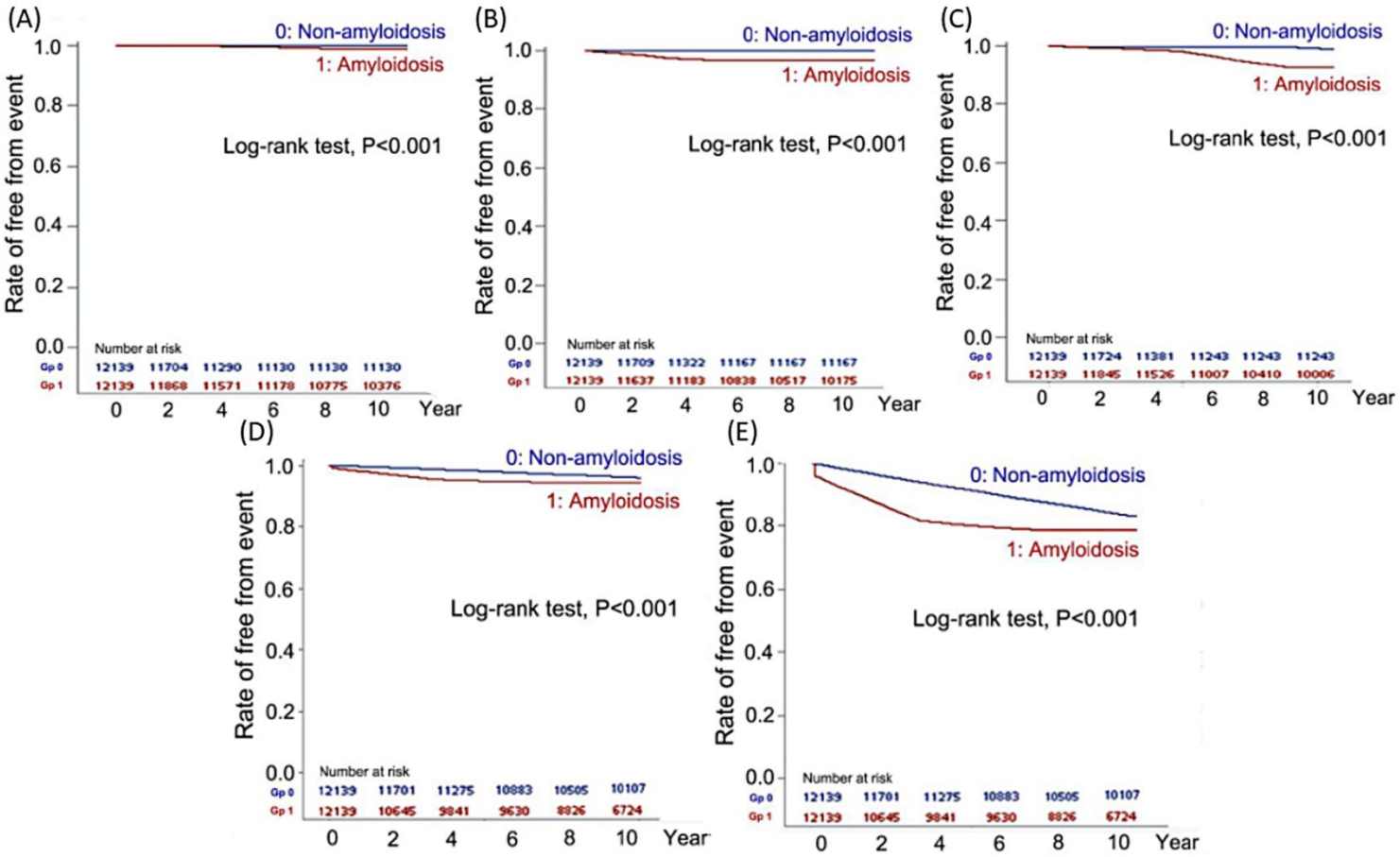

Figure 3-2: Kaplan-Meier event-free survival curves for new-onset events of (A) ventricular tachycardia (VT), (B) atrial fibrillation (AF), (C) heart failure (HF) related admission, (D) cardiovascular death, and (E) all-cause death. A significantly higher risk of new-onset VT, AF, HF related admission, cardiovascular death, and all-cause death in patients with amyloidosis compared to the control group. The risk of new-onset VT for the two groups was initially comparable for up to 7.5 years and then separated during the later period (A).

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Tables

Table 1-1: Studies of cardiac imaging in predicting sudden cardiac deaths

Study (author, year)	Population	Follow-up duration	Outcome	Factors	Event number	Age (years ± SD)	Gender (%)
Coronary Heart Disease (CHD) Study cohort, 1996-1972 Mini-Finland Health Survey, 1997-1980 (Holkeri A, 2020)	General population (Finland)	9.3±2.0 years (1980-2011)	Death, SCD	ECG risk score (12-lead ECG): heart rate > 80 bpm*, PP > 220 ms*, QRS > 110 ms*, left ventricular hypertrophy*, T-wave inversion*, prolonged QTc, frontal QRS-T angle > 90 degrees, ST depression	Total: 6830 Total death: 986 (14.4%) SCD: 123 (12.5% of death)	30–59 years (51.2±13.9 years)	45.5% men
Fingesture study, 1998-2017 (Holmström L, 2020)	Consecutive sudden cardiac death victims (Northern Finland and Lapland)	Not available	Myocardial fibrosis in SCD victims	ECG abnormalities: QRS > 110 ms*, LBBB*, intraventricular conduction delay (IVCD)*, fragmented QRS*, pathological Q waves, T wave inversion*, positive T wave in lead aVR (aVRT)*, any ECG abnormality	Total: 5869 Ischemic SCD: 4392 (75%) (689 with prior ECG) Non-ischemic SCD: 1477 (25%) (411 with prior ECG)	Total: 66±13 years; Ischemic SCD: 66±13 years; Non-ischemic SCD: 1477 (25%)	75% men Ischemic SCD: 80% men Non-ischemic SCD: 76% men

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Atherosclerosis Risk in Communities (ARIC) Study, 1993-1996 Cardiovascular Health Study (CHS), 1989-1990 (Konety SH, 2016)	ARIC: 100% African-American CHS: men and women ≥ 65 years United States communities	ARIC: 7.3 years (1993-2001) CHS: 13.1 years (1989-2006)	SCD	Echography: Mitral annular calcification*, reduced LVEF*, LV mass index*, mitral E to A < 0.7*, mitral E to A > 1.5*. Incident coronary heart disease (CHD) and heart failure as time-dependent covariates. Adjusting for Framingham risk score (FRS) variables, CHD, and renal function.	ARIC: 2383 CHS: 5366 SCD in ARIC: 44 (1.85%, 2.59 per 1000 PYs) SCD in CHS: 275 (5.12%, 4.39 per 1000 PYs)	ARIC: 45-65 years (72.9±5.6 years) CHS: ≥ 65 years (72.9±5.6 years)	ARIC: 36% men CHS: 42% men

*Significant risk factor.

ECG: electrogram; LBBB: left bundle branch block; LV: left ventricular; LVEF: left ventricular ejection fraction; SCD: sudden cardiac death.

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Table 1-2: Study of carotid artery duplex in predicting sudden cardiac deaths

Study (author, year)	Population	Follow-up duration	Outcome	Factors	Event number	Age (years ± SD)	Gender (%)
Atherosclerosis Risk in Communities (ARIC) Study, 1987-1989 Cardiovascular Health Study (CHS), 1989-1990, 1992-1993 (black) (Suzuki T, 2020)	ARIC: 100% African-American (45-65 years) CHS: men and women ≥ 65 years	ARIC: median of 23.5 years CHS: median of 13.1 years	SCD	<ARIC> CIMT (mean): First Quartile (reference): Forth Quartile HR (95% CI): 1.64 (1.15–2.63) Presence of plaque: 1.37 (1.13–1.67) <CHS> CIMT (maximum): First Quartile (reference): Forth Quartile HR (95% CI): 1.75 (1.22–2.51) Presence of plaque: 1.32 (1.04–1.68)	ARIC: 15307 CHS: 5555 SCD in ARIC: 569 (3.72%): 1.81 per 1000 PYs SCD in CHS: 302 (5.44%): 4.64 per 1000 PYs	<ARIC> 45-65 years No SCD: 54.1±5.8 years SCD: 56.2±5.6 years <CHS> ≥ 65 years No SCD: 72.8±5.5 years SCD: 73.4±5.7 years	ARIC: 36% men CHS: 42% men

CIMT: carotid intima-media thickness; PY: person-years; SCD: sudden cardiac death.

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Table 1-3: Prediction models of sudden cardiac death for general population

Study (author, year)	Model	Risk factors	Risk	Follow-up year, event	Population	Age	Gender
Coronary Heart Disease (CHD) Study cohort, 1996-1972 Mini-Finland Health Survey, 1997-1980 (Holkeri A, 2020)	Electrocardiographic (ECG) risk score (Risk in 10 years follow-up)	Heart rate > 80 bpm*, PP > 220 ms*, QRS > 110 ms*, left ventricular hypertrophy*, T-wave inversion*, prolonged QTc, frontal QRS-T angle > 90 degrees, ST depression (*: 1 score)	Ref: Score=0; Scores ≥3 (HR: 10.8, 95% CI: 3.23-36.25)	9.3±2.0 years (1980-2011) Total death: 986 (14.4%) SCD: 123 (12.5% of death)	General population (Finland); N=6830	30–59 years (51.2±13.9 years)	45.5% men
Atherosclerosis Risk in Communities (ARIC) Study (1987-1989), Framingham Study (1948) (Bogle BM, 2018)	ARIC-Framingham score (Simple Community-Based Risk-Prediction Score) (Risk in 10 years	(0.067*age) + (-1.262*male) + (0.008*cholesterol) + (0.444*lipid-lowing medication use) + (0.307*anti-hypertensive medication use) + (0.025*SBP) + (-	Mean 10-year risk >1% In white: Scores ≥8; In black: Scores ≥6	10-year SCD: 145 in ARIC, and 64 in Framingham	General population (USA); ARIC: N=11335; Framinghm:	45-65 years (mean: 54.4 years)	47.6% men

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	follow-up)	0.024*DBP) + (0.617*current smoker) + (0.787*diabetes mellites) + (0.74*body mass index)			N=5626		
The derivation cohort (Barcelona cohort and Ruti cohort, a multidisciplinary HF Unit, 2006-2010) (Lupón J, 2018)	ST2-SCD score (risk in 5 years follow-up) (bio-clinical approach)	Dichotomous variables: ST2 (interleukin-1 receptor-like 1)>45, LVEF <45%, HF duration >3 years, eGFR <55, age ≥ 60 years, and male sex	Score=0-1 (low); Score 2-3 (median) Score ≥4 (high)	10 years. Total death: 312; SCD: 40 (5.4% in total cohort; 12.8 of total death)	Patients with heart failure (Spain); N=893	Barcelona cohort: 68.4±12.4 years; Ruti cohort: 66.4±13.6 years	70% men

CI: confidence interval; HR: hazard ratio; SCD: sudden cardia death.

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Table 1-4: Baseline characteristics of the Chin-Shan Community Cardiovascular Cohort study

Characteristics	Total (N=2105)
Age, years	53.9±11.7
Men	928 (44.1%)
Body mass index, kg/m2	23.6±3.37
Hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg)	580 (27.6%)
Antihypertensive medication use	224 (10.6%)
Diabetes mellitus	685 (45.2%)
Hypoglycemic medication use	61 (2.90%)
Stroke	99 (4.70%)
Chronic kidney disease	186 (8.84%)
Smoking history	688 (32.7%)
Drinking history	590 (28.1%)
Regular exercise	668 (32.7%)
Body mass index (kg/m^2)	23.6±3.37
Fasting glucose, mg/dL	109.4±30.0
Total cholesterol, mg/dL	198.7±44.8
Triglyceride, mg/dL	125.1±91.8
Low-density lipoprotein, mg/dL	134.8±48.8
High-density lipoprotein, mg/dL	46.1±14.2

DBP: diastolic blood pressure; SBP: systolic blood pressure.

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Table 1-5: Competing-risk models in predicting risk of sudden cardiac death using conventional risk factors

Characteristics	Cause-specific hazard				Sub-distribution hazard			
	Uni-variable analysis		Multi-variable analysis		Uni-variable analysis		Multi-variable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years	1.13 (1.08-1.19)	<0.001	1.12 (1.06-1.17)	<0.001	1.11 (1.06-1.15)	<0.001	1.09 (1.04-1.15)	<0.001
Women	0.51 (0.16-1.61)	0.25			0.55 (0.18-1.73)	0.31		
Body mass index, kg/m^2	1.07 (0.91-1.25)	0.42			1.07 (0.94-1.21)	0.31		
Hypertension	6.20 (1.87-20.6)	0.003	3.64 (1.06-12.5)	0.040	5.27 (1.59-17.5)	0.007	3.50 (1.01-10.9)	0.048
Antihypertensive medication use	3.00 (0.62-14.4)	0.17			2.67 (0.72-9.90)	0.14		
Diabetes mellitus	2.07 (0.66-6.53)	0.21			1.77 (0.56-5.60)	0.33		
Hypoglycemic medication use	2.32 (0.30-18.0)	0.42			2.17 (0.28-17.0)	0.37		
Stroke	3.25 (0.42-25.4)	0.26			1.89 (0.25-14.6)	0.54		
Chronic kidney disease (eGFR < 60 ml/min/1.73m^2)	1.06 (0.14-8.24)	0.95			0.94 (0.13-7.00)	0.95		
Smoking history	3.42 (1.09-10.8)	0.036	2.95 (0.93-9.38)	0.07	3.13 (1.00-9.76)	0.049	2.69 (0.85-8.51)	0.09
Drinking history	1.41 (0.42-4.67)	0.58			1.35 (0.41-4.45)	0.63		
Regular exercise	2.64 (0.66-10.6)	0.17			1.72 (0.48-6.22)	0.41		
Body mass index (kg/m^2)	1.05 (0.87-1.26)	0.60			1.07 (0.94-1.21)	0.31		
Fasting glucose, mg/dL	1.003 (0.984-1.023)	0.74			1.006 (0.998-1.015)	0.16		
Total cholesterol, mg/dL	0.999 (0.984-1.015)	0.93			0.997 (0.984-1.011)	0.71		
Triglyceride, mg/dL	1.000 (0.994-1.006)	0.97			1.000 (0.995-1.004)	0.98		
Low-density lipoprotein, mg/dL	1.001 (1.014-1.010)	0.92			1.001 (0.991-1.012)	0.81		
High-density lipoprotein, mg/dL	0.994 (0.951-1.073)	0.79			0.997 (0.965-1.030)	0.84		

A P-value ≤ 0.1 in the uni-variable analysis was selected into multi-variable analysis for adjustment.

CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio.

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Table 1-6: Baseline characteristics of the electrograms

Characteristics	Total (N=2105)
Abnormal T wave	38 (1.81%)
Left ventricular hypertrophy	152 (7.22%)
QT prolongation	93 (4.42%)
Any AV block	47 (2.23%)
Any delayed conduction	210 (9.98%)
Any RBBB	44 (2.09%)
Any LBBB	3 (0.14%)
Any BBB	47 (2.23%)
Low voltage QRS	11 (0.52%)

AV: atrioventricular block; BBB: bundle branch block; RBBB: right bundle branch block; LBBB: left Bundle Branch block.

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Table 1-7: Competing-risk models in predicting risk of sudden cardiac death using the electrograms

Characteristics	Cause-specific hazard		Sub-distribution hazard	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Left ventricular hypertrophy	6.68 (1.82-25.5)	0.004	6.04 (1.47-24.9)	0.013
QT prolongation	0.65 (0.05-9.11)	0.75	1.25 (0.17-9.34)	0.83
Any AV block	3.26 (0.39-27.3)	0.28	2.78 (0.38-20.4)	0.31
Any delayed conduction	1.41 (0.29-6.97)	0.67	1.53 (0.41-5.69)	0.53

Model was adjusted for age group (< 45, 45-54, 55-64, 65-74, ≥ 75 years), gender, diabetes mellitus, hypertension, and smoking status.

AV: atrioventricular block CI: confidence interval; HR: hazard ratio.

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Table 1-8: Baseline characteristics of medical ultrasound imaging

Characteristics	Total (N=2105)
Carotid artery duplex sonography	
Intima-media thickness, mm	0.73±0.23
Carotid plaque scoring	0.49±1.80
Cardiac echocardiography	
Aortic root diameter, mm	30.5±4.31
Aortic flow, cm/s	113.2±21.7
Aortic valve diameter, mm	18.8±4.32
Left atrium diameter, mm	33.0±5.58
Posterior wall of the left ventricle, mm	10.1±2.23
Left ventricular mass index, g/m^2	121.4±42.8
Left ventricular ejection fraction, %	69.5±9.53

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Table 1-9: Competing-risk models in predicting risk of sudden cardiac death using medical ultrasound imaging

Characteristics	Cause-specific hazard		Sub-distribution hazard	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Carotid artery duplex sonography				
Intima-media thickness, mm	3.14 (0.27-36.9)	0.36	1.30 (0.36-4.67)	0.69
Carotid plaque scoring ≥ 5	4.86 (1.01-23.3)	0.048	5.76 (1.15-28.7)	0.033
Cardiac echocardiography				
Aortic root diameter, mm	1.02 (0.88-1.18)	0.78	1.03 (0.87-1.23)	0.71
Aortic flow rate > 190 cm/s	32.9 (4.12-263.7)	0.001	72.1 (12.4-418.8)	<0.001
Aortic valve diameter, mm	0.998 (0.91-1.10)	0.97	0.990 (0.87-1.13)	0.88
Left atrium diameter, mm	1.05 (0.96-1.16)	0.30	1.05 (0.98-1.12)	0.16
LV systolic dysfunction (LVEF < 40%)	16.2 (1.75-150.0)	0.014	23.6 (2.35-237.5)	0.007
LVH: LVMI ≥ 132 g/m^2 in men, LVMI ≥ 109 g/m^2 in women	4.57 (1.09-19.2)	0.038	5.92 (1.37-25.7)	0.018

Model was adjusted for age group (< 45, 45-54, 55-64, 65-74, ≥ 75 years), gender, diabetes mellitus, hypertension, and smoking status.

CI: confidence interval; EF: ejection fraction; HR: hazard ratio; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index.

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Table 1-10: Clinical point-based scoring system

Clinical risk factors	Distribution of the population, N=2105 (mean or proportion)	W_{i-j}-W_{i-ref}	Cause-specific approach			Sub-distribution approach			Negative binomial model		
			Estimated coefficient ($Beta_{risk\ factor}$)	$Beta_{risk\ factor}$ * (W_{i-j}-W_{i-ref})	Risk points	Estimated coefficient ($Beta_{risk\ factor}$)	$Beta_{risk\ factor}$ * (W_{i-j}-W_{i-ref})	Risk points	Estimated coefficient ($Beta_{risk\ factor}$)	$Beta_{risk\ factor}$ * (W_{i-j}-W_{i-ref})	Risk points
Age, +1 year	53.9±11.7		$Beta_{age-1}$= 0.251	$Beta_{age-10}$= 2.510		$Beta_{age-1}$= 0.191	$Beta_{age-10}$= 1.910		$Beta_{age-1}$= 0.304	$Beta_{age-10}$= 3.044	
<45 (reference)	26.1%	0		0.000	0		0.000	0		0.000	0
45-54	27.0%	10		2.510	1		1.910	1		3.044	1
55-64	27.2%	20		5.020	2		3.820	2		6.088	2
65-74	15.4%	30		7.530	3		5.730	3		9.133	3
≥75	4.28%	40		10.04	4		7.640	4		12.18	4
Hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg)	27.6%	1	1.606	1.606	1	1.105	1.105	1	1.929	1.929	1
LV systolic dysfunction (LVEF < 40%)	0.52%	1	3.595	3.595	1	1.966	1.966	1	2.964	2.964	1
LVH (ECG or echocardiography)	7.41%	1	1.655	1.655	1	1.734	1.734	1	4.123	4.123	1
Aortic flow > 190 cm/s	0.52%	1	3.177	3.177	1	2.786	2.786	1	4.006	4.006	1
Carotid plaque scores ≥ 5	3.28%	1	1.916	1.916	1	1.867	1.867	1	3.125	3.125	1

(W_{i-j}-W_{i-ref}) represents the difference between each value of risk factor and its reference value; Risk points=$Beta_{risk\ factor}$*(W_{i-j}-W_{i-ref}) / $Beta_{age-10}$. DBP: diastolic blood pressure; ECG: electrogram; LV: left ventricular; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; SBP: systolic blood pressure.

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Table 1-11: Estimated and observed 10-year risk function based on the Chin-Shan Community Cardiovascular Cohort

Scores	Total proportion (%)	Observed 10-year rate (%)	Cause-specific approach	Sub-distribution approach	Negative binomial model
			Estimated 10-year rate (%)	Estimated 10-year rate (%)	Estimated 10-year rate (%)
0	22.95	0.000	0.000	0.000	0.000
1	22.66	0.000	0.000	0.000	0.000
2	22.13	0.137	0.000	0.001	0.000
3	17.01	0.581	0.002	0.008	0.000
4	10.12	1.353	0.020	0.052	0.007
5	3.610	3.312	0.241	0.351	0.143
6	0.950	4.949	2.924	2.346	2.967
7	0.570	24.36	30.59	14.81	46.87
8	na	na	98.88	66.12	99.99
9	na	na	100.0	99.93	100.0

na: not available.

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Table 1-12: Predictive performance among various models

Step	Risk assessment	AUC	95% CI of AUC	P-value 1	P-value 2
1-0	**Taking history & clinical examination:** Age groups, and history of hypertension	0.842	0.772-0.912	Reference	0.11
2-0	**12-lead ECG:** Patterns of LVH	0.694	0.539-0.848	0.040	0.72
2-1	**Step 1-0 plus Step 2-0**	0.864	0.778-0.951	0.38	0.12
3-0	**Echocardiography data:** LV mass index, LVEF, and aortic flow rate	0.645	0.458-0.833	0.025	0.85
3-1	**Step 1-0 plus Step 3-0**	0.871	0.798-0.965	0.14	0.052
4-0	**Carotid artery duplex:** Carotid plaque score	0.561	0.461-0.620	<0.001	0.23
4-1	**Step 1-0 plus Step 4-0**	0.833	0.770-0.915	0.86	0.10
5-0	**Step 1-0 plus Step 2-0 plus Step 3-0**	0.908	0.834-0.983	0.035	0.027
6-0	**Step 1-0 plus Step 2-0 plus Step 3-0 plus Step 4-0**	0.908	0.834-0.983	0.035	0.027
7-0	**CCCC-SCD-Score**	0.888	0.807-0.969	0.039	0.031
8-0	**ARIC-Framingham score**	0.662	0.469-0.914	0.027	Reference
9-0	**ECG risk score**	0.666	0.498-0.835	0.013	0.85

ARIC: Atherosclerosis Risk in Communities Study; AUC: area under the curve of receiver operating characteristic curve; CI: confidence interval; ECG: electrogram; LV: left ventricular; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy.

P-value 1: each model was compared with reference of Step 1-0.

P-value 2: each model was compared with reference of Step 8-0.

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Table 2-1: Baseline characteristics of the training and validation datasets

Variables	Training dataset (N=147405)	Validation dataset (N=29481)
Age	72.3±12.0	72.2±12.0
Women	67155 (45.6%)	13395 (45.4%)
AF ablation	2833 (1.92%)	566 (1.92%)
$CHADS_2$	1.61±1.00	1.61±1.00
CHA_2DS_2-VASc	1.73±1.20	1.71±1.19
Diabetes mellitus	10163 (6.89%)	1957 (6.64%)
Hypertension	30196 (20.5%)	6164 (20.9%)
Congestive heart failure	32587 (22.1%)	6509 (22.1%)
Chronic kidney disease	2215 (1.50%)	426 (1.44%)
Prior stroke	24865 (16.9%)	4980 (16.9%)
Chronic obstructive pulmonary disease	12597 (8.55%)	2568 (8.71%)
Valvular heart diseases	6642 (4.51%)	1322 (4.48%)
Hyperlipidemia	2234 (1.52%)	452 (1.53%)
Prior CAD	6555 (4.45%)	1308 (4.44%)
Vascular diseases	28731 (19.5%)	5698 (19.33%)
Thyroid diseases	1684 (1.14%)	313 (1.06%)

AF: atrial fibrillation; CAD: coronary artery disease.

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Table 2-2: Baseline characteristics of the training dataset

Variables	Training cohort (N=147405)		
	AF-no ablation (N=144572)	AF ablation (N=2833)	P-value
Age	72.6±11.7	54.5±14.7	<0.001
Women	66257 (45.8%)	898 (31.7%)	<0.001
$CHADS_2$	1.63±1.00	0.62±0.79	<0.001
CHA_2DS_2-VASc	1.73±1.19	0.85±0.98	<0.001
Diabetes mellitus	10034 (6.94%)	129 (4.55%)	<0.001
Hypertension	29625 (20.5%)	571 (20.2%)	0.66
Congestive heart failure	32430 (22.4%)	157 (5.54%)	<0.001
Chronic kidney disease	2209 (1.53%)	6 (0.21%)	<0.001
Prior stroke	24767 (17.1%)	98 (3.46%)	<0.001
Chronic obstructive pulmonary disease	12564 (8.69%)	33 (1.16%)	<0.001
Valvular heart diseases	6504 (4.50%)	138 (4.87%)	0.34
Hyperlipidemia	2104 (1.46%)	130 (4.59%)	<0.001
Prior CAD	6512 (4.50%)	43 (1.52%)	<0.001
Vascular diseases	28480 (19.7%)	251 (8.86%)	<0.001
Thyroid diseases	1647 (1.14%)	37 (1.31%)	0.41

AF: atrial fibrillation; CAD: coronary artery disease.

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Table 2-3: Basic characteristics and estimated effect in the training dataset

Risk factors	Mean or proportion (%)	Hazard ratio (95% confidence interval)	P-value
Included in the novel system			
Age, +1 year	73.2 years	1.088 (1.085-1.092)	<0.001
AF, no catheter ablation	98.1%	1.83 (1.24-2.69)	0.002
Prior history of stroke	16.5%	2.11 (1.98-2.24)	<0.001
Chronic kidney disease	1.5%	1.63 (1.32-2.01)	<0.001
Prior CAD or vascular diseases	19.5%	1.62 (1.53-1.72)	<0.001
Excluded from the novel system			
Diabetes mellitus	6.8%	1.28 (1.16-1.40)	<0.001
Congestive heart failure	22.1%	1.17 (1.09-1.25)	<0.001
Valvular heart diseases	4.5%	1.21 (1.05-1.39)	0.007
Chronic obstructive pulmonary disease	8.5%	1.10 (0.99-1.21)	0.07
Hypertension	20.5%	0.86 (0.80-0.91)	0.12
Women	45.6%	0.89 (0.84-0.94)	<0.001
Hyperlipidemia	1.5%	0.87 (0.69-1.10)	0.26
Thyroid diseases	1.2%	0.39 (0.20-0.63)	<0.001

AF: atrial fibrillation; CAD: coronary artery disease.

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Table 2-4: Clinical point-based scoring system

Clinical risk factors	Estimated coefficient ($Beta_{risk\ factor}$)	W_{i-j}-W_{i-ref}	$Beta_{risk\ factor}$ * (W_{i-j}-W_{i-ref})	Risk points
Age, +1 year	$Beta_{age-1}$=0.085			$Beta_{age-10}$=0.850
<35 (reference)		0.00	0.000	0
35-44		12.5	1.060	1
45-54		22.5	1.907	2
55-64		32.5	2.755	3
65-74		42.5	3.602	4
≥75		52.5	4.450	5
AF, no catheter ablation	0.604	1	0.604	1
Prior history of stroke	0.745	1	0.745	1
Chronic kidney disease	0.488	1	0.488	1
Prior history of CAD or vascular diseases	0.482	1	0.482	1

(W_{i-j}-W_{i-ref}) represents the difference between each value of risk factor and its reference value;

Risk points=$Beta_{risk\ factor}$*(W_{i-j}-W_{i-ref}) / $Beta_{age-10}$.

AF: atrial fibrillation; CAD: coronary artery disease.

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Table 2-5: Total points and absolute risk functions for various scoring systems

AF-CA-Stroke				$CHADS_2$		CHA_2DS_2-VASc	
Total points	**1-year estimated risk (%)**	**Observed rate (per 100 PYs) in the training dataset**	**Observed rate (per 100 PYs) in the validation dataset**	**Total points**	**1-year estimated risk (%)**	**Total points**	**1-year estimated risk (%)**
1	0.02%	0.02%	0.03%	1*	2.80%	1	1.30%
2	0.05%	0.21%	0.15%	2	4.00%	2	2.20%
3	0.12%	0.22%	0.12%	3	5.90%	3*	3.20%
4	0.28%	0.47%	0.46%	4	8.50%	4	4.00%
5	0.66%	0.98%	0.92%	5	12.5%	5	6.70%
6*	1.53%	1.73%	1.85%	6	18.2%	6	9.80%
7	3.53%	3.12%	3.43%	na	Na	7	9.60%
8	8.05%	na	na	na	Na	8	6.70%
9	17.8%	na	na	na	Na	9	15.2%

*Best cut-of-value predicting incident stroke event by calculating the Youden index of the area under receive operating characteristic curve: Sensitivity + Specificity -1.

na: not available; PYs: person-years.

$CHADS_2$: congestive heart failure (1 point), hypertension (1 point), age≥75 years (1 point), diabetes mellitus (1 point), stroke (2 points);

CHA_2DS_2-VASc: congestive heart failure (1 point), hypertension (1 point), age≥65 years (1 point), age≥75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular diseases (1 point), women (1 point);

AF-CA-Stroke: refer to **Table 2-4**.

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Table 2-6: Summary of the category-free net reclassification improvement

Models	Applying in the training database		Applying in the validation dataset	
	Category-free NRI	P-value for NRI	Category-free NRI	P-value for NRI
$CHADS_2$	-	Reference	-	Reference
CHA_2DS_2-VASc	0.23	<0.001	0.29	<0.001
R_2CHADS_2	0.16	<0.001	0.18	<0.001
$R_2CHA_2DS_2$-VASc	0.24	<0.001	0.30	<0.001
AF-CA-Stroke	0.26	<0.001	0.32	<0.001

NRI: net reclassification improvement.

$CHADS_2$: congestive heart failure (1 point), hypertension (1 point), age≥75 years (1 point), diabetes mellitus (1 point), stroke (2 points);

CHA_2DS_2-VASc: congestive heart failure (1 point), hypertension (1 point), age≥65 years (1 point), age≥75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular diseases (1 point), women (1 point);

R_2CHADS_2: chronic kidney disease (2 points), congestive heart failure (1 point), hypertension (1 point), age≥75 years (1 point), diabetes mellitus (1 point), stroke (2 points);

$R_2CHA_2DS_2$-VASc: chronic kidney disease (2 points), congestive heart failure (1 point), hypertension (1 point), age≥65 years (1 point), age≥75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular diseases (1 point), women (1 point).

AF-CA-Stroke: refer to **Table 2-4**.

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Table 2-7: Comparisons for the area under curve of the operating characteristic curve by applying the novel scoring system

Models	Applying in the training database		Applying in the validation dataset	
	AUC (95% confidence interval)	P-value of pair-wise Comparison for AUC	AUC (95% confidence interval)	P-value of pair-wise Comparison for AUC
$CHADS_2$	0.577 (0.570-0.584)	Reference	0.590 (0.574-0.607)	Reference
CHA_2DS_2-VASc	0.602 (0.595-0.609)	<0.001	0.615 (0.599-0.631)	<0.001
R_2CHADS_2	0.578 (0.571-0.585)	0.64	0.593 (0.576-0.609)	0.36
$R_2CHA_2DS_2$-VASc	0.603 (0.596-0.610)	<0.001	0.617 (0.601-0.632)	<0.001
AF-CA-Stroke	0.637 (0.631-0.644)	<0.001	0.658 (0.644-0.675)	<0.001

AUC: area under curve of the operating characteristic curve (ROC).

$CHADS_2$: congestive heart failure (1 point), hypertension (1 point), age≥75 years (1 point), diabetes mellitus (1 point), stroke (2 points);

CHA_2DS_2-VASc: congestive heart failure (1 point), hypertension (1 point), age≥65 years (1 point), age≥75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular diseases (1 point), women (1 point);

R_2CHADS_2: chronic kidney disease (2 points), congestive heart failure (1 point), hypertension (1 point), age≥75 years (1 point), diabetes mellitus (1 point), stroke (2 points);

$R_2CHA_2DS_2$-VASc: chronic kidney disease (2 points), congestive heart failure (1 point), hypertension (1 point), age≥65 years (1 point), age≥75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular diseases (1 point), women (1 point).

AF-CA-Stroke: refer to **Table 2-4**.

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Table 2-8: Baseline characteristics of the validation dataset

Variables	Validation Cohort (N=29481)		
	AF-no ablation (N=28915)	AF ablation (N=566)	P-value
Age	72.6±11.6	55.0±14.6	<0.001
Women	13224 (45.7%)	171 (30.2%)	<0.001
$CHADS_2$	1.63±1.00	0.60±0.78	<0.001
CHA_2DS_2-VASc	1.73±1.19	0.83±0.97	<0.001
Diabetes mellitus	1933 (6.69%)	24 (4.24%)	0.021
Hypertension	6058 (21.0%)	106 (18.7%)	0.20
Congestive heart failure	6479 (22.4%)	30 (5.30%)	<0.001
Chronic kidney disease	423 (1.46%)	3 (0.53%)	0.07
Prior stroke	4962 (17.2%)	18 (3.18%)	<0.001
Chronic obstructive pulmonary disease	2558 (8.85%)	10 (1.77%)	<0.001
Valvular heart diseases	1287 (4.45%)	35 (6.18%)	0.049
Hyperlipidemia	433 (1.50%)	19 (3.36%)	<0.001
Prior CAD	1297 (4.49%)	11 (1.94%)	0.004
Vascular diseases	5641 (19.5%)	57 (10.1%)	<0.001
Thyroid diseases	303 (1.05%)	10 (1.77%)	0.10

AF: atrial fibrillation; CAD: coronary artery disease.

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Table 2-9: Stroke rates based on various scoring system in the training dataset

	$CHADS_2$		CHA_2DS_2-VASc	
Incidence rate:	Low risk (0)	High risk (> 0)	Low risk (0-1)	High risk (> 1)
per 1000 PYs (95% CI)	(N=16016, 10.9%)	(N=131389, 89.1%)	(N=68661, 46.6%)	(N=78744, 53.4%)
	1.54 (1.30-1.77)	9.19 (8.94-9.43)	5.81 (5.55-6.07)	9.92 (9.60-10.2)

	AF-CA-Stroke				**AF-CA-Stroke:**			
Incidence rate:	Low risk (0-5)	High risk (> 5)	Low risk (0-5)	High risk (> 5)	Low risk (0-5)	High risk (> 5)	Low risk (0-5)	High risk (> 5)
per 1000 PYs (95% CI)	16016 (100%)	0 (0.00%)	102028 (77.7%)	29361 (22.3%)	63899 (93.1%)	4762 (6.94%)	54145 (68.8%)	24599 (31.2%)
	1.54 (1.30-1.77)	0 (0-0)	7.07 (6.84-7.31)	18.4 (17.6-19.2)	5.39 (5.13-5.65)	13.1 (11.4-14.8)	6.79 (6.48-7.09)	19.4 (18.5-20.3)

CI: confidence interval; N: number; PYs: person-years.

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Table 2-10: Stroke rates based on ablation status and various scoring system in the training dataset

	AF ablation=0 (N=144572, 98.1%))				AF ablation=1 (N=2833, 1.92%)			
CHA2DS2-VASc	**CHA2DS2-VASc**				**CHA2DS2-VASc**			
	Low risk (0-1)		High risk (> 1)		Low risk (0-1)		High risk (> 1)	
Incidence rate:	(N=66451, 46.0%)		(N=78121, 54.0%))		(N=2210, 78.0%)		(N=623, 22.0%)	
per 1000 PYs (95% CI)	6.06 (5.78-6.33)		9.99 (9.67-10.3)		0.72 (0.30-1.15)		3.74 (1.85-5.64)	
	Low risk (0-5)	High risk (> 5)	Low risk (0-5)	High risk (> 5)	Low risk (0-5)	High risk (> 5)	Low risk (0-5)	High risk (> 5)
	(N=61867,	(N=4584,	(N=53682,	(N=24439,	(N=2032,	(N=178,	(N=463,	(N=160,
AF-CA-Stroke	93.1%)	6.90%)	79.2%)	20.8%)	91.9%)	8.05%)	74.3%)	25.7%)
	5.63 (5.36-5.90)	13.6 (11.9-15.4)	6.84 (6.53-7.15)	19.5 (18.6-20.4)	0.42 (0.08-0.76)	4.92 (0.61-9.24)	1.96 (0.39-3.52)	9.55 (3.31-15.8)
Incidence rate:	**AF-CA-Stroke**				**AF-CA-Stroke:**			
per 1000 PYs (95% CI)	Low risk (0-5)		High risk (> 5)		Low risk (0-5)		High risk (> 5)	
	(N=115549, 79.9%)		(N=29023, 20.1%)		(N=2495, 88.1%)		(N=338, 11.9%)	
	6.21 (6.01-6.42)		18.6 (17.8-19.4)		0.69 (0.30-1.09)		7.15 (3.41-10.9)	

AF: atrial fibrillation; CI: confidence interval; N: number; PYs: person-years.

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Table 3-1: The summary of prior reports investing the incidence of amyloidosis

Study (author, year)	Population	Study year	Study data source	Type of amyloidosis	Total N	Incidence	Age
Simms RW, 1994	Olmstead country, Minnesota, United States	1950-1989	Literature review of epidemiological study	Primary secondary (AL)	Total N= 2225	Men: 1.41 per 100000 PYs; Women: 0.57 per 100000 PYs; Total: 0.89 per 100000 PYs	All ages (age-adjusted rate)
Swedish Hospital Discharge and Outpatients Registers (Hemminki K, 2012)	Sweden	2001-2008	Hospital-based cohort stydu	All amyloidosis: ICD-10-CM code: E85	Total N= 949	0.83 per 100000 PYs	All ages
National Health Service commissioned the National Amyloidosis Centre (NAC) (Pinney JH, 2013)	England	2000-2008	Epidemiological study: Death due to amyloidosis	Systemic amyloidosis	Total N=2543	0.8 per 100000 PYs	All ages
Wisniowski B, 2019	Australia	1999-2013	Laboratory information systems from Queensland public	Amyloidosis	Total N=447	Men: 1.51 per 100000 PYs; Women: 0.74 per 100000 PYs	≥ 20 years.

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			and private sector pathology laboratories				
Gilstrap LG, 2019	United States	2000-2014	The Medicare Provider and Analysis Review (MedPAR) files from the Centers for Medicare & Medicaid Services (CMS)	Cardiac amyloidosis	Total N=121122	17 per 100000 PYs	≥ 65 years
Danish national registries (Westin O, 2021)	Danish	1998-2017	Nationwide study	Cardiac amyloidosis	Total N=619	0.61 per 100000 PYs	All ages

PYs: person-years.

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Table 3-2: Baseline characteristics of the study population

Variables	Original cohort			Propensity-score matched cohort		
	No amyloidosis (N=106648)	Amyloidosis (N=12139)	*p*-value	No amyloidosis (N=12139)	Amyloidosis (N=12139)	*p*-value
Age (years)	49.8±17.6	52.1±16.1	<0.001	52.1±16.1	52.1±16.1	>0.99
Male gender (n, %)	45509 (42.7%)	5971 (49.2%)	<0.001	5971 (49.2%)	5971 (49.2%)	>0.99
Cardiac amyloidosis (diagnosis during follow-up; n, %)	0 (0.00%)	1130 (9.31%)	<0.001	0 (0.00%)	1130 (9.31%)	<0.001
Underlying diseases (n, %)						
Hypertension	48951 (45.9%)	5024 (41.4%)	<0.001	5024 (41.4%)	5024 (41.4%)	>0.99
Diabetes mellitus	24037 (22.5%)	2348 (19.3%)	<0.001	2348 (19.3%)	2348 (19.3%)	>0.99
Atrial fibrillation	1098 (1.03%)	2 (0.02%)	<0.001	123 (1.01%)	2 (0.02%)	<0.001
Conduction disturbance	174 (0.16%)	0 (0.00%)	<0.001	18 (0.15%)	0 (0.00%)	<0.001
Cardiomyopathy	253 (0.24%)	4 (0.03%)	<0.001	27 (0.22%)	4 (0.03%)	<0.001
Coronary artery disease	1576 (1.48%)	0 (0.00%)	<0.001	161 (1.33%)	0 (0.00%)	<0.001
Stroke/TIA	10948 (10.3%)	13 (0.11%)	<0.001	1208 (10.0%)	13 (0.11%)	<0.001
Congestive heart failure	4052 (3.80%)	18 (0.15%)	<0.001	431 (3.6%)	18 (0.15%)	<0.001
Valvular heart disease	1084 (1.02%)	3 (0.02%)	<0.001	93 (0.77%)	3 (0.02%)	<0.001
Chronic kidney disease	2429 (2.28%)	59 (0.49%)	<0.001	272 (2.24%)	59 (0.49%)	<0.001
Hyperlipidemia	21786 (20.4%)	28 (0.23%)	<0.001	2311 (19.0%)	28 (0.23%)	<0.001
Hyperuricemia	12510 (11.7%)	19 (0.16%)	<0.001	1439 (11.9%)	19 (0.16%)	<0.001
Chronic liver disease	16907 (15.9%)	48 (0.40%)	<0.001	1970 (16.2%)	48 (0.40%)	<0.001
COPD	20227 (19.0%)	26 (0.21%)	<0.001	2479 (20.4%)	26 (0.21%)	<0.001
Thyroid disease	2118 (1.99%)	7 (0.06%)	<0.001	243 (2.00%)	7 (0.06%)	<0.001
Cancer	6034 (5.66%)	47 (0.39%)	<0.001	776 (6.39%)	47 (0.39%)	<0.001
Medication uses (n, %)						
ACEi	31220 (29.3%)	3380 (9.77%)	0.001	3198 (26.3%)	3380 (27.8%)	0.009
ARB	28081 (26.3%)	3220 (10.3%)	0.64	2811 (23.2%)	3220 (26.5%)	<0.001
CCB	18984 (17.8%)	2068 (17.0%)	0.037	1894 (15.6%)	2068 (17.0%)	0.003
Beta-blockers	54449 (51.1%)	5274 (47.2%)	<0.001	6065 (50.0%)	5274 (47.2%)	<0.001
AADs	7496 (7.03%)	883 (7.27%)	0.32	838 (6.90%)	883 (7.27%)	0.26
AAD: Ia	573 (0.54%)	86 (0.71%)	0.016	60 (0.49%)	86 (0.71%)	0.031
AAD: Ib	3630 (3.40%)	395 (3.25%)	0.39	407 (3.35%)	395 (3.25%)	0.67
AAD: Ic	1236 (1.16%)	182 (1.50%)	0.001	132 (1.09%)	182 (1.50%)	0.005
AAD: III	2854 (2.68%)	366 (3.02%)	0.029	319 (2.63%)	366 (3.02%)	0.07
Anti-platelet	40155 (37.7%)	4462 (36.8%)	0.054	4395 (36.2%)	4462 (36.8%)	0.37
Warfarin	2302 (2.16%)	309 (2.55%)	0.006	239 (1.97%)	309 (2.55%)	0.002

AAD: antiarrhythmic agents; ACEi: angiotensin- converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium channel blocker; COPD indicates chronic obstructive pulmonary disease; TIA, transient ischemic attack.

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Table 3-3: Baseline characteristics for patients with cardiac amyloidosis and non-cardiac amyloidosis

Variables	Patients with amyloidosis (Total N=12139)		
	Non-cardiac (N=11009)	Cardiac (N=1130)	*p*-value
Age (years)	50.3±15.5	69.1±10.2	<0.001
Male gender (n, %)	5140 (46.7%)	831 (73.5%)	<0.001
Underlying diseases (n, %)			
Hypertension	4057 (36.9%)	967 (85.6%)	<0.001
Diabetes mellitus	1883 (17.1%)	465 (41.2%)	<0.001
Atrial fibrillation	0 (0.00%)	2 (0.18%)	0.009
Conduction disturbance	0 (0.00%)	0 (0.00%)	Na
Cardiomyopathy	0 (0.00%)	4 (0.35%)	<0.001
Coronary artery disease	0 (0.00%)	0 (0.00%)	Na
Stroke/TIA	8 (0.07%)	5 (0.44%)	0.005
Congestive heart failure	0 (0.00%)	18 (1.59%)	<0.001
Valvular heart disease	2 (0.02%)	1 (0.09%)	0.25
Chronic kidney disease	38 (0.35%)	21 (1.86%)	<0.001
Hyperlipidemia	23 (0.21%)	5 (0.44%)	0.18
Hyperuricemia	15 (0.14%)	4 (0.35%)	0.09
Chronic liver disease	42 (0.38%)	6 (0.53%)	0.45
COPD	17 (0.15%)	9 (0.80%)	<0.001
Thyroid disease	5 (0.05%)	2 (0.18%)	0.50
Cancer	40 (0.36%)	7 (0.62%)	0.20
Medication uses (n, %)			
ACEi	2643 (24.0%)	737 (65.2%	<0.001
ARB	2490 (22.6%)	730 (64.6%)	<0.001
CCB	1548 (14.1%)	520 (46.0%)	<0.001
Beta-blockers	4926 (44.7%)	798 (70.6%)	<0.001
AADs	547 (4.97%)	336 (29.7%)	<0.001
AAD: Ia	53 (0.48%)	33 (2.92%)	<0.001
AAD: Ib	293 (2.66%)	102 (9.03%)	<0.001
AAD: Ic	103 (0.94%)	79 (6.99%)	<0.001
AAD: III	155 (1.41%)	211 (18.7%)	<0.001
Anti-platelet	3573 (32.5%)	889 (78.7%)	<0.001
Warfarin	148 (1.33%)	161 (14.2%)	<0.001

AAD: antiarrhythmic agents; ACEi: angiotensin- converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium channel blocker; COPD indicates chronic obstructive pulmonary disease; Na: not available; TIA, transient ischemic attack.

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Table 3-4: Cumulative event rate, incidence rate, and crude risk of cardiovascular events in patients with and without amyloidosis

Outcomes	Variables	Total numbers	PYs	Cumulative event rate (%)	*p*-value	Incidence rate (per 10000 PYs, 95% CI)	Crude HR (95% CI)	*p*-value
Ventricular tachycardia	No amyloidosis	12139	287575	97 (0.80%)	0.014	3.37 (2.70-7.12)	1 (reference)	-
	With amyloidosis	12139	156334	134 (1.10%)		8.57 (7.12-10.0)	6.91 (4.20-11.4)	<0.001
Atrial fibrillation	No amyloidosis	12139	286990	316 (2.60%)	<0.001	11.0 (9.80-12.2)	1 (reference)	
	With amyloidosis	12139	152596	460 (3.79%)		30.2 (27.4-32.9)	5.01 (3.75-6.69)	<0.001
Heart failure-related admission	No amyloidosis	12139	286988	608 (5.01%)	<0.001	21.2 (19.5-22.9)	1 (reference)	-
	With amyloidosis	12139	153399	826 (6.80%)		53.9 (50.2-57.5)	6.19 (5.12-7.50)	<0.001
Cardiovascular death	No amyloidosis	12139	143935	447 (3.93%)	<0.001	33.1 (30.2-36.1)	1 (reference)	-
	With amyloidosis	12139	112615	597 (4.92%)		53.0 (48.8-57.3)	5.32 (4.57-6.18)	<0.001
All-cause death	No amyloidosis	12139	143935	2224 (18.3%)	<0.001	154.5 (148.1-160.9)	1 (reference)	-
	With amyloidosis	12139	112615	2589 (21.3%)		229.9 (221.0-238.8)	4.39 (4.09-4.70)	<0.001

CI: confidence interval; HR: hazard ratio; PYs: person-years.

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Table 3-5: Cumulative event rate, incidence rate, and crude risk of cardiovascular events in amyloidosis patients with or without cardiac type

Outcomes	Variables	Total numbers	PYs	Cumulative event rate (%)	*p*-value	Incidence rate (per 10000 PYs, 95% CI)	Crude HR (95% CI)	*p*-value
Ventricular tachycardia	Non-cardiac	11009	145434	10 (0.09%)	<0.001	0.69 (0.26-1.11)	1 (reference)	-
	Cardiac	1130	10900	124 (11.0%)		113.8 (93.7-133.8)	53.9 (19.9-146.4)	<0.001
Cardiovascular death	Non-cardiac	11009	107344	336 (3.05%)	<0.001	31.3 (28.0-34.6)	1 (reference)	-
	Cardiac	1130	5271	209 (18.5%)		495.2 (435.1-555.2)	1.75 (1.49-2.06)	<0.001
All-cause death	Non-cardiac	11009	107344	1781 (16.2%)	<0.001	165.9 (158.2-173.6)	1 (reference)	-
	Cardiac	1130	5271	808 (71.5%)		1532.9 (1427.2-1638.6)	1.02 (0.94-1.11)	0.60

CI: confidence interval; HR: hazard ratio; PYs: person-years.

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Table 3-6: Adjusted hazard ratio for long-term outcomes in patients with amyloidosis

Outcomes	Model	Hazard ratio*	95% confidence interval		*p*-value
Ventricular tachycardia	1	6.90	4.19	11.4	<0.001
	2	7.90	4.49	13.9	<0.001
Atrial fibrillation	1	5.26	3.92	7.05	<0.001
	2	6.21	4.38	8.78	<0.001
Heart failure-related admission	1	6.54	5.38	7.93	<0.001
	2	54.7	37.1	80.7	<0.001
Cardiovascular death	1	5.43	4.67	6.31	<0.001
	2	5.09	4.23	6.12	<0.001
All-cause death	1	4.40	4.11	4.72	<0.001
	2	5.11	4.69	5.57	<0.001

*Hazard ratios were analyzed for amyloidosis patients versus controls.

Model 1: adjusted for age and sex;

Model 2: Model 1+hypertension, diabetes mellitus, congestive heart failure, hyperlipidemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, thyroid disease, prior coronary artery disease, prior stroke, cancer.

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Table 3-7: Adjusted hazard ratio for long-term outcomes in patients with cardiac amyloidosis.

Outcomes	Model	Hazard ratio*	95% confidence interval		*p*-value
Ventricular tachycardia	1	61.2	22.4	167.0	<0.001
	2	153.3	54.3	432.7	<0.001
Cardiovascular death	1	1.63	1.39	1.93	<0.001
	2	1.34	1.02	1.78	0.04
All-cause death	1	1.00	0.92	1.09	0.99
	2	1.03	0.88	1.20	0.75

*Hazard ratios were analyzed for amyloidosis patients versus controls.

Model 1: adjusted for age and sex;

Model 2: Model 1+hypertension, diabetes mellitus, congestive heart failure, hyperlipidemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, thyroid disease, prior coronary artery disease, prior stroke, cancer.

doi:10.6342/NTU202201040

Table 3-8: Characteristics of amyloidosis patients with and without ventricular tachycardia

Variables	Without VT (N=12005)	With VT (N=134)	*P* value	Univariable		Multivariable*	
				Hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Age (years old)	51.9±16.0	66.4±12.2	<0.001	1.003 (0.99-1.02)	0.77		
Male (n, %)	5875 (48.9%)	96 (71.6%)	<0.001	1.05 (0.67-1.65)	0.82		
Pacemaker	140 (1.17%)	(9.70%)	<0.001	2.60 (1.39-4.85)	0.003	1.46 (0.76-2.81)	0.25
Underlying diseases							
Atrial fibrillation	430 (3.58%)	30 (22.4%)	<0.001	2.17 (1.40-3.38)	0.001	1.27 (0.77-2.81)	0.35
History of heart failure	15 (0.12%)	3 (2.24%)	0.012	4.68 (1.16-18.9)	0.031	1.86 (1.22-2.85)	0.004
Hypertension	4918 (41.0%)	106 (79.1%)	<0.001	1.65 (1.01-2.68)	0.044	0.81 (0.36-1.80)	0.60
Diabetes mellitus	2285 (19.0%)	63 (47.0%)	<0.001	1.86 (1.27-2.72)	0.001	1.61 (1.08-2.41)	0.021
Stroke	13 (0.10%)	0 (0.00%)	>0.99	Na	Na		
Chronic kidney disease	53 (0.44%)	6 (4.48%)	<0.001	2.46 (0.78-7.45)	0.12		
Chronic liver disease	45 (0.37%)	3 (2.24%)	0.016	4.34 (1.38-13.7)	0.012	7.33 (2.24-24.0)	0.001
COPD	24 (0.20%)	2 (1.49%)	0.033	2.67 (0.66-10.8)	0.17		
Thyroid disease	7 (0.06%)	0 (0.00%)	>0.99	Na	Na		
Hyperlipidemia	28 (0.23%)	0 (0.00%)	>0.99	Na	Na		
Cancer	47 (0.39%)	0 (0.00%)	>0.99	Na	Na		
Medication uses							
ACEi	3294 (27.4%)	86 (64.2%)	<0.001	1.76 (1.18-2.64)	0.006	1.47 (0.83-2.61)	0.19
ARB	3143 (26.2%)	77 (57.5%)	<0.001	1.43 (0.96-2.09)	0.08	0.91 (0.55-1.49)	0.70
CCB	2007 (16.7%)	61 (45.5%)	<0.001	1.59 (1.09-2.33)	0.017	1.12 (0.72-1.73)	0.61
Beta-blockers	5635 (46.9%)	89 (66.4%)	<0.001	0.83 (0.57-1.23)	0.35		
AADs	838 (6.98%)	45 (33.6%)	<0.001	2.30 (1.53-3.45)	<0.001	1.60 (1.02-2.51)	0.043
Anti-platelet	4365 (36.4%)	97 (72.4%)	<0.001	1.45 (0.95-2.24)	0.09	0.97 (0.60-1.58)	0.91
Warfarin	288 (2.40%)	21 (15.7%)	<0.001	2.49 (1.48-4.17)	<0.001	1.55 (0.88-2.72)	0.13

*Adjusted for variables with $p < 0.10$ in the univariable analysis.

AAD: antiarrhythmic agents; ACEi: angiotensin- converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium channel blocker; CI: confidence interval; COPD indicates chronic obstructive pulmonary disease; Na: not available; TIA, transient ischemic attack; VT: ventricular tachycardia.

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Table 3-9: Characteristics of amyloidosis patients with and without cardiovascular death

Variables	Without CV death (N=11524)	With CV death (N=597)	*P* value	Univariable		Multivariable*	
				Hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Age (years old)	51.1±15.7	70.7±9.42	<0.001	1.03 (1.02-1.04)	<0.001	1.02 (1.01-1.03)	<0.001
Male (n, %)	5498 (47.6%)	473 (79.2%)	<0.001	1.26 (1.03-1.53)	<0.001	1.06 (0.86-1.31)	0.56
Type: Cardiac amyloidosis	869 (7.53%)	261 (43.7%)	<0.001	1.75 (1.49-2.06)	<0.001	1.30 (0.91-1.86)	0.15
Pacemaker	111 (0.96%)	42 (7.04%)	<0.001	2.04 (1.49-2.80)	<0.001	1.36 (0.98-1.89)	0.07
Underlying diseases							
Ventricular tachycardia related admission	93 (0.81%)	41 (6.87%)	<0.001	1.93 (1.40-2.65)	<0.001	1.50 (1.07-2.12)	0.026
Atrial fibrillation	348 (3.02%)	112 (18.8%)	<0.001	1.63 (1.33-2.01)	<0.001	1.01 (0.77-1.34)	0.92
Heart failure related admission	626 (5.42%)	200 (33.5%)	<0.001	1.63 (1.38-1.94)	<0.001	1.03 (0.74-1.42)	0.88
Hypertension	4548 (39.4%)	476 (79.7%)	<0.001	1.56 (1.28-1.90)	<0.001	1.08 (0.78-1.49)	0.63
Diabetes mellitus	2134 (18.5%)	214 (35.8%)	<0.001	0.92 (0.78-1.09)	0.35		
Stroke/TIA	10 (0.09%)	3 (0.50%)	0.023	1.57 (0.50-4.88)	0.44		
Chronic kidney disease	46 (0.40%)	13 (2.18%)	<0.001	2.23 (1.29-3.88)	0.004	2.41 (1.36-4.26)	0.003
Chronic liver disease	45 (0.39%)	3 (0.50%)	0.51	0.63 (0.20-1.96)	0.43		
COPD	20 (0.17%)	6 (1.00%)	0.001	1.32 (0.59-2.95)	0.50		
Thyroid disease	7 (0.06%)	0 (0.00%)	>0.99	Na	Na		
Hyperlipidemia	25 (0.22%)	3 (0.50%)	0.16	1.46 (0.47-4.54)	0.51		
Cancer	44 (0.38%)	3 (0.50%)	0.50	0.51 (0.16-1.58)	0.24		
Medication uses							
ACEi	3010 (26.1%)	370 (62.0%)	<0.001	1.42 (1.21-1.68)	<0.001	1.05 (0.84-1.31)	0.66
ARB	2880 (25.0%)	340 (57.0%)	<0.001	1.27 (1.08-1.50)	0.004	0.93 (0.76-1.13)	0.45

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CCB	1838 (15.9%)	230 (38.5%)	<0.001	1.41 (1.20-1.67)	<0.001	1.08 (0.90-1.31)	0.41
Beta-blockers	5347 (46.3%)	377 (63.1%)	<0.001	0.98 (0.83-1.16)	0.81		
AADs	747 (6.47%)	136 (22.8%)	<0.001	1.63 (1.35-1.98)	<0.001	1.25 (1.02-1.55)	0.033
Anti-platelet	4013 (34.8%)	449 (75.2%)	<0.001	1.71 (1.42-2.06)	<0.001	1.33 (1.08-1.64)	0.007
Warfarin	251 (2.17%)	58 (9.72%)	<0.001	1.36 (1.03-1.79)	0.029	0.93 (0.69-1.26)	0.64

*Adjusted for variables with $p < 0.10$ in the univariable analysis.

AAD: antiarrhythmic agents; ACEi: angiotensin- converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium channel blocker; CI: confidence interval; COPD indicates chronic obstructive pulmonary disease; CV: cardiovascular; Na: not available; TIA, transient ischemic attack.

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Appendices

Appendix 1

發文方式：紙本遞送

檔　號：
保存年限：

國立臺灣大學醫學院附設醫院　函

地址：10002台北市中山南路7號
承辦人：顏鈺芳
電話：02-23123456分機63596
傳真：02-2395-1950
電子信箱：ntuhrec@ntuh.gov.tw

受文者：內科部簡國龍醫師
發文日期：中華民國99年3月18日
發文字號：校附醫倫字第0993700862號
速別：普通件
密等及解密條件或保密期限：普通
附件：如文

主旨：有關　台端所主持之「N-3脂肪酸　，生物標記因子，臨床次疾病與心血管疾病發生之社區世代研究設計/Fatty Acids as Biomarkers, Subclincial Diseases and the Risk of Cardiovascular Disease: a Community-based Cohort Study」（本院案號：201003001R）純學術臨床試驗案，符合快速審查條件及研究倫理規範，通過本院研究倫理委員會審查，同意核備，並提C研究倫理委員會第3次會議報備追認，請　查照。

說明：

一、本臨床試驗核准之有效期限為1年，計畫主持人應於到期前的1個月提出持續審查申請表，本案需經持續審查，方可繼續執行。

二、本會同意之臨床試驗計畫書之版本日期為：2010,3-11. Version。

三、臨床試驗執行期間，請確實依據「藥品優良臨床試驗準則」之相關規定辦理；為符合「藥品優良臨床試驗準則」結案查核作業，請計畫主持醫師保存所有文件備查。

四、依據國際醫學雜誌編輯委員會(The International Committee of Medical Journal Editors, ICMJE)之投稿規定，臨床試驗研究計畫投稿者，需於招募第一位受試者參與

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試驗前，將通過研究倫理委員會審核之臨床試驗計畫資料登錄於臨床試驗公開網站，完成登錄作業後，國際醫學雜誌編輯委員會(ICMJE)才會接受研究結果之發表。WHO對臨床試驗研究計畫之定義為任何對受試者或特定族群進行一個或多個與健康有關的介入措施(如藥物、外科處置、器材、行為治療、飲食介入及照護過程改變)以評估對健康的效益之計畫，非屬上述臨床試驗計畫，請計畫主持人自行決定是否登錄。

五、本院已向美國國家衛生研究院(National Institutes of Health, NIH) ClinicalTrials. gov 網站- Protocol Registration System (PRS https:// register. clinicaltrials.gov/)申請本院專用帳號，供本院計畫主持人(PI) 登錄所主持之臨床試驗研究計畫，登入網頁之帳號及密碼如下列：

(一)Organization：NTaiwanUH

(二)User Name：NTUH

(三)Password：NTUH99

六、隨函檢附臨床研究重要訊息通知單，請依計畫需要辦理相關事宜。

正本：內科部簡國龍醫師
副本：研究倫理委員會

院長陳明豐

doi:10.6342/NTU202201040

Appendix 2

國立台灣大學醫學院附設醫院C研究倫理委員會

Research Ethics Committee C
National Taiwan University Hospital
7, Chung-Shan South Road, Taipei, Taiwan 100, R.O.C
Phone: 2312-3456 Fax: 23951950

免審證明

許可日期：2013 年 5 月 28 日

倫委會案號：201305044W

計畫名稱：台灣地區非傳染性疾病之個別危險因素之醫療資源利用情形及死亡相關風險之比較分析。

部門/計畫主持人：內科部 簡國龍醫師

文件版本日期：【*計畫書：Version-1, 20130424*】

上述計畫業經本院C研究倫理委員會審查，符合政府相關法律規範之免審範圍，本委員會的運作符合優良臨床試驗準則及政府相關法律規章，計畫主持人須依本院規定通報非預期問題。

主任委員 何弘能

Certificate of Exempt Review

Date of certificate: May 28, 2013

NTUH-REC No.:201305044W

Title of protocol : Adult Mortality and Medical Utilization Attributable to Preventable Risk Factors for Non-Communicable Diseases in Taiwan.

Department/ Principle Investigator : Department of Internal Medicine / Dr. Kuo-Liong Chien

Version date of documents : 【*Protocol: Version-1, 20130424*】

The protocol has been reviewed by the Research Ethics Committee C of the National Taiwan University Hospital and comply the categories of exempt in accordance with the governmental laws and regulations. The committee is organized under, and operates in accordance with, the Good Clinical Practice guidelines and governmental laws and regulations.

The investigator is required to report Unanticipated Problems in accordance with the NTUH requirements.

Hong-Nerng Ho, M.D.
Chairman
Research Ethics Committee C

doi:10.6342/NTU202201040

Appendix 3

臺 北 榮 民 總 醫 院
TAIPEI VETERANS GENERAL HOSPITAL
201 SHIH-PAI ROAD. SEC.2
TAIPEI, TAIWAN 11217
REPUBLIC OF CHINA
TEL:(886)-2-2871-2121

Clinical Trial/Research Approval Letter

Sep. 17, 2021

IRB-TPEVGH No.: 2021-09-014BC
Protocol No: NHIRD-CV-110
Protocol Title: Applying the National Health Insurance Research Databases to Explore the Long-term Outcomes in Patients with Cardiovascular Diseases under Various Treatment Strategies and Risk Factors
Department/Principal Investigator: Division of Cardiology, Department of Medicine / Yenn-Jiang Lin, M.D.
Version date of documents:

1. Protocol: Version 3, 2021/09/14
2. Chinese Synopsis: Version 3, 2021/09/14
3. Informed Consent Form: waived
4. DSMP: waived

According to the written operating procedures, GCP, and the applicable regulatory requirements, this study project is reviewed by the Institutional Review Board (2) of Taipei Veterans General Hospital, and approved on Sep 17, 2021. This approval is valid for 1 year till Sep 16, 2022.
The board is organized under, and operates according to International Conference on Harmonisation (ICH) / WHO Good Clinical Practice (GCP) and the applicable laws and regulations.
The principal investigator is required to report Serious Adverse Events and Unanticipated Problems in accordance with the governmental laws and regulations and TPEVGH requirements.
The principal investigator is required to submit the application for extension before the expiration date of 6 weeks to 3 months (at least 6 weeks). (If indicated by the regulations and laws, this project should be taken after the approval of Ministry of Health and Welfare, R.O.C.)

臺北榮民總醫院 人體試驗委員會 Institutional Review Board Taipei Veterans General Hospital

Hsu Ma, M.D.
Chairman
Institutional Review Board
Taipei Veterans General Hospital
Taiwan, R.O.C.

doi:10.6342/NTU202201040

Programming

Coding 1-1: Calculating Person-years

/*μ 之 95% CI = X ± 1.96 * (σ / √n)

PY= (d/ n) *1000 (Per 1000 persons → person-years) ;

d = number of events upon which the rate is based ;

n = denominator of the rate (area population for crude birth and death rates, live births for infant death rates) ;

Lower Limit = (1000 / n) (d - (1.96 x square root of d)) ;

Upper Limit = (1000 / n) (d + (1.96 x square root of d)) ;*/

```
/*Per 1000 person-years; 95% confidence interval*/
proc univariate data=data.Scd_2021_ecg_echo_f
(keep=case n age_gr sex CCCC_SCD_Score_new CCCC_SCD_Score_r death scd scd_cate_new death_py) noprint;
var n death scd death_py ; *class CCCC_SCD_Score_new ; * imt_4p aof_4p imt_78 aof_130 scd_cate_new ;
output out=py sum= n death scd death_py; run;
data py; set py;
L1= death- (sqrt(death)*1.96);
L2=scd - (sqrt(scd)*1.96);
U1= death+ ( sqrt(death)*1.96);
U2=scd + ( sqrt(scd)*1.96);
A= 1000/death_py;

SCD_rate=scd / death_py* 1000;
SCD_L95CI= A*L2;
SCD_U95CI= A*U2;

death_rate=death / death_py* 1000;
death_L95CI= A*L1;
death_U95CI= A*U1;

if SCD_L95CI <0 then SCD_L95CI=0; else if SCD_L95CI >=0 then SCD_L95CI=SCD_L95CI;
if death_L95CI <0 then death_L95CI=0; else if death_L95CI >=0 then death_L95CI=death_L95CI;
run;
proc print data=py; run;
```


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Coding 1-2: Regression Models

```
/* SCD: 0=alive or non-SCD; 1=SCD;
SCD_death (Competing event of interest): Alive=0; SCD=1; Non-SCD death=2*/

/*Traditional Cox proportional hazards model*/
proc phreg data=data.Scd_2021_ecg_echo_f;
class
sex (ref=first) age_gr (ref=first) ef40 (ref=first) htn (ref=first)
Carotid_plaque5 (ref=first) lvh_ecg_echo (ref=first) aof_190 (ref=first)
/ param=ref; *Disease (order=internal ref=first);
model death_py*SCD(0)=age htn lvh_ecg_echo Carotid_plaque5 aof_190    EF40/ RISKLIMITS;
run;

/*Competing risk-1: Cause specific hazard-CSH*/
proc phreg data=data.Scd_2021_ecg_echo_f;
class
sex (ref=first) age_gr (ref=first) ef40 (ref=first) htn (ref=first)
Carotid_plaque5 (ref=first) lvh_ecg_echo (ref=first) aof_190 (ref=first)
/ param=ref; *Disease (order=internal ref=first);
model death_py*scd_death (0,2)=age htn lvh_ecg_echo Carotid_plaque5 aof_190    EF40/ RISKLIMITS;
run;

/*Competing risk-2: Sub-distribution hazard-SDH*/
proc phreg data=data.Scd_2021_ecg_echo_f;
class
sex (ref=first) age_gr (ref=first) ef40 (ref=first) htn (ref=first)
Carotid_plaque5 (ref=first) lvh_ecg_echo (ref=first) aof_190 (ref=first)
/ param=ref; *Disease (order=internal ref=first);
model death_py*scd_death(0)= age htn lvh_ecg_echo Carotid_plaque5 aof_190    EF40/ RISKLIMITS eventcode=1;
run;
```


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```
/*Grouping for follow-up period*/
data Scd_2021_ecg_echo_f; set data.Scd_2021_ecg_echo_f;
fu_year_gp=.;
if  0 <=  death_py <6 then fu_year_gp =1;
else if 6<=  death_py <11 then fu_year_gp =2;
else if 11<=  death_py <16 then fu_year_gp =3;
else fu_year_gp =4;
log_py= log (death_py);
run;

/*Negative Binomial Regression: more variation than expected under a Poisson model E(Y) = VAR(Y)*/
proc genmod data = py_scd_gp ;
class
age_gr (ref=first) ef40 (ref=first) htn (ref=first)
Carotid_plaque5 (ref=first) lvh_ecg_echo (ref=first) aof_190 (ref=first)  fu_year_gp (ref=first)
/ param=ref; *Disease (order=internal ref=first);
model scd  = age_gr  htn  ef40  lvh_ecg_echo  aof_190  Carotid_plaque5  fu_year_gp /
type3 dist=negbin link=log offset=log_py;
run;
```


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Coding 1-3: Bootstrapping

```
%%MATLAB
    % title={'case', 'death', 'SCD', 'death_py', 'CCCC_SCD_Score_new', 'ARIC_Framingham_Score', 'ECG_risk_score'};
    %
    % Len=size(data,1)/5;
    %
    % Randtable=[randi([1,Len],Len,100); randi([1+Len,Len*2],Len,100); randi([1+2*Len,Len*3],Len,100);
    randi([1+3*Len,Len*4],Len,100); randi([1+4*Len,Len*5],Len,100);];
    load('data.mat')

    %%
    for ii=1:100
        resamdata.CCCC_SCD_Score_new(:,ii)=data(Randtable(:,ii),5);
        resamdata.ARIC_Framingham_Score(:,ii)=data(Randtable(:,ii),6);
        resamdata.ECG_risk_score(:,ii)=data(Randtable(:,ii),7);
        resamdata.SCD(:,ii)=data(Randtable(:,ii),3);
        resamdata.CaseNo(:,ii)=data(Randtable(:,ii),1);
    end
    %%
    for ii=1:100

     [X,Y,T,AUC] = perfcurve(data(:,3),data(:,5),1);

   [~,~,~, CCCC_SCD_Score_new.AUC(ii,1)] = perfcurve( resamdata.SCD(:,ii),
            resamdata.CCCC_SCD_Score_new(:,ii), 1);
   [~,~,~,    ARIC_Framingham_Score.AUC(ii,1)] = perfcurve( resamdata.SCD(:,ii),
            resamdata.ARIC_Framingham_Score(:,ii), 1);
   [~,~,~, ECG_risk_score.AUC(ii,1)] = perfcurve( resamdata.SCD(:,ii),
            resamdata.ECG_risk_score(:,ii), 1);
  End
```


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Coding 1-4: ROC Comparisons

```
/*ROC comparisons*/;
ods graphics on;
proc logistic data=data.Scd_2021_ecg_echo_f    plots(only)=(roc)    ;
model SCD (event='1')=CCCC_SCD_Score_new      ARIC_Framingham_Score    ECG_risk_score    /nofit;      /*Delete “nofit”:
an integrated model*/
roc 'CCCC-SCD-Score'    CCCC_SCD_Score_new;
roc 'ARIC-Framingham score'    ARIC_Framingham_Score;
roc 'Electrocardiographic risk score' ECG_risk_score;
roccontrast    reference('ARIC-Framingham score')/ estimate e;
run;
ods graphics off;
```


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Coding 1-5: Sample Size & Power for Study 1

```
# Required N: Power and Sample Size Calculations in Survival Data
# Workshop on Computational Biostatistics and Survival Analysis Shariq Mohammed
# https://shariq-mohammed.github.io/files/cbsa2019/2-power-and-sample-size.html
# We will calculate power and event number in survival analysis using R.

# Install and call the R package
install.packages("powerSurvEpi")
library(powerSurvEpi)

# Log-Mean Method
expLogMeanDeaths = function(Delta, alpha, pwr){
   z.alpha = qnorm(alpha, lower.tail=F)
   z.beta = qnorm(1-pwr, lower.tail=F)
   num = (z.alpha + z.beta)^2
   denom = (log(Delta))^2
   dd = num/denom
   dd
}

# Suppose that we are designing study where we plan a 5% level (one-sided) test, and we need 99% power
to detect a hazard ratio of 3.5.

# Required N: Log-mean based approach
expLogMeanDeaths (Delta = 3.5, alpha = 0.05, pwr = 0.99)

# We can find the required number of SCD as follows: N=10
# That is, we would need ≈10 SCD events according to the log mean method.
```


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```
# Required N: Likelihood-Ratio Based Approach
expLikeRatio = function(d, alpha, pwr){
   num = qchisq(alpha, df=(2*d), lower.tail=F)
   denom = qchisq(pwr, df=(2*d), lower.tail=F)
   Delta = num/denom
   Delta
}
expLRdeaths = function(Delta, alpha, pwr){
   LR = function(d, alpha, pwr, Delta){
      expLikeRatio(d, alpha, pwr) - Delta
   }
   # Find the root for the function LR(d)
   result = uniroot(f = LR, lower = 1, upper = 1000,
                            alpha = alpha, pwr = pwr, Delta = Delta)
   result$root
}
```

Suppose that we are designing study where we plan a 5% level (one-sided) test, and we need 99% power to detect a hazard ratio of 3.5.

```
# Required N: Likelihood ratio based approach
expLRdeaths (Delta = 3.5, alpha = 0.05, pwr = 0.99)
```

We can find the required number of SCD as follows: N=11
That is, we would need ≈11 SCD events according to the likelihood ratio method.

doi:10.6342/NTU202201040

```
# Power Calculation in the Analysis of Survival Data
# Example 14.42 in Rosner B. Fundamentals of Biostatistics.
# (6-th edition). (2006) page 809
#k numeric: ratio of participants in group E (experimental group) compared to group C (control group).
#m: integer. expected total number of events over both groups.
#RR: numeric. postulated hazard ratio.
#alpha: numeric. type I error rate.

powerCT.default0(k = 0.01,
m = 13,
RR = 15,
alpha = 0.05)
        # Power = 99.2%
```


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#Power Calculation for Cox Proportional Hazards Regression with Nonbinary Covariates for Epidemiological Studies

#n: integer. total number of subjects.
#theta: numeric. postulated hazard ratio.
#sigma2: numeric. variance of the covariate of interest.
#psi: numeric. proportion of subjects died of the disease of interest.
#rho2: numeric. square of the multiple correlation coefficient between the covariate of interest and other covariates.
#alpha: numeric. type I error rate.

example in the EXAMPLE section (page 557) of Hsieh and Lavori (2000).
Hsieh and Lavori (2000) assumed one-sided test, while this implementation assumed two-sided test.
Hence alpha=0.1 here (two-sided test) will correspond to alpha=0.05 of one-sided test in Hsieh and Lavori's (2000) example.

```
powerEpiCont.default(n = 2105,
theta = 15,
sigma2 = 0.762^2,
psi = 0.01,
rho2 = (1-exp(161.3/2105))^2,
alpha = 0.05)
        # Power > 99.9%
```


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Coding 2-1: ROC & Category-free NRI

```
/*ROC comparisons*/
ods graphics on;
proc logistic data= test.Study_AF_92_101_random      plots=roc;
model stroke_admi (event='1')=    Score_1 Score_1_r Score_2    CHADS2    CHA2DS2VASc      R2CHADS2
R2CHA2DS2VASc        CHADS2_abl CHA2DS2VASc_abl    R2CHADS2_abl    R2CHA2DS2VASc_abl
/nofit;      /*Delete “nofit”: an integrated model*/ roc ' Score 1'    Score_1;
roc ' Score 2'    Score_2;
roc ' CHADS2'    CHADS2;
roc ' CHA2DS2VASc'    CHA2DS2VASc;
roc ' R2CHADS2'    R2CHADS2;
roc ' R2CHA2DS2VASc'    R2CHA2DS2VASc;
roc ' CHADS2_abl'    CHADS2_abl;
roc ' CHA2DS2VASc_abl'    CHA2DS2VASc_abl;
roc ' R2CHADS2_abl'    R2CHADS2_abl;
roc ' R2CHA2DS2VASc_abl'    R2CHA2DS2VASc_abl;
roccontrast    reference(' CHA2DS2VASc')/ estimate e;
run;
ods graphics off;


/*Category-free NRI*/
proc logistic data=test.Study_AF_92_101_r;
*class lvh;
model    stroke_admi =      Score_1;
output out=test1 p=prob1 xbeta=xbeta1;
run;quit;

proc logistic data=test1;
*class lvh;
model    stroke_admi =      Score_2;
output out=test2 p=prob2 xbeta=xbeta2;
run;quit;
```


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```
proc logistic data=test2;
*class lvh;
model    stroke_admi =    CHADS2 ;
output out=test3 p=prob3 xbeta=xbeta3;
run;quit;

proc logistic data=test3;
*class lvh;
model    stroke_admi =     CHA2DS2VASc    ;
output out=test4 p=prob4 xbeta=xbeta4;
run;quit;

proc logistic data=test4;
*class lvh;
model    stroke_admi =     R2CHADS2    ;
output out=test5 p=prob5 xbeta=xbeta5;
run;quit;

proc logistic data=test5;
*class lvh;
model    stroke_admi =     R2CHA2DS2VASc       ;
output out=test6 p=prob6 xbeta=xbeta6;
run;quit;

data test.Study_AF_92_101_r; set test6;
M_score_1 =    prob3-prob1;
if M_score_1 >=0 then G_score1=1; else G_score1=0;
M_score_2 =    prob3-prob2;
if M_score_2 >=0 then G_score2=1; else G_score2=0;
M_CHA2DS2VASc = prob3 - prob4;
if M_CHA2DS2VASc >=0 then G_CHA2DS2VASc=1; else    G_CHA2DS2VASc=0;
M_R2CHADS2 = prob3 - prob5;
if M_R2CHADS2 >=0 then G_R2CHADS2=1; else      G_R2CHADS2=0;
M_R2CHA2DS2VASc = prob3 - prob6;
if M_R2CHA2DS2VASc >=0 then G_R2CHA2DS2VASc=1; else      G_R2CHA2DS2VASc=0; run;
```


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/*Category-free NRI can be simply calculate via the following formula*/

/* PM+ > PM: Probability increased in the new model

PM+ < PM: Probability decreased in the new model

	PM+ < PM	PM+ > PM
Stroke_admi: 0	SL	SH
Stroke_admi: 1	DL	DH

Favors model M+

DH = 276

SL = 12176

Favors model M

DL = 229

SL = 7631

Category-free NRI = (DH – DL) / (DH + DL) + (SL – SH) / (SL + SH) = 0.360

*/

proc freq data=test.Study_AF_92_101_r;

table stroke_admi*G_score1/ EXACT CHISQ;

run;

proc freq data=test.Study_AF_92_101_r;

table stroke_admi*G_CHA2DS2VASc/ EXACT CHISQ;

run;

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Coding 2-2: Sample Size & Power for Study 2

```
install.packages("powerSurvEpi")
library(powerSurvEpi)

# Power Calculation in the Analysis of Survival Data
# Example 14.42 in Rosner B. Fundamentals of Biostatistics.
# (6-th edition). (2006) page 809
#k numeric: ratio of participants in group E (experimental group) compared to group C (control group).
#m: integer. expected total number of events over both groups.
#RR: numeric. postulated hazard ratio.
#alpha: numeric. type I error rate.

powerCT.default0(k = 0.2,
m = 5583,
RR = 5,
alpha = 0.05)
        # Power > 99.9%
```


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Coding 3-1: Propensity-score Matching Technique

```
/*************************************************************************************************/
/*     PROGRAM NAME  ：propensity score matching test.sas
/*     PURPOSE       ：
/*     NOTES         ：
/*     AUTHOR        ：
/*     CREATED DATE  ：2012.11.06
/*     UPDATED DATE  ：
        /*************************************************************************
**********/
/*STEP 1: (1)Estimating the propensity score
                (2)Creating Kernel Density Plot of Propensity Score*/

proc sort data=data.AF; by descending gp_new; run;
title j=center height=12 pt font=Arial Bold Italic "PS-logistic regression model fitting";

proc logistic data=data.AF;
       class   sex        dm    htn     dm    copd   /* (ref=first)*/;
       model gp_new= age     dm    htn     dm    copd   / lackfit;
/*requests Hosmer and Lemeshow goodness-of-fit test*/
        output out=out_ps prob=ps xbeta=logit_ps;/*create new data set: out_ps*/
run;   /*new variable: ps:propensity score   logit_ps: logit of propensity score*/

title2 "Kernel Density Plot of Propensity Score";
data gp;
        set out_ps(keep=gp_new   ps);/*將原本PS值的變項，依照組別給予不同的欄位名稱*/
              if gp_new="1" then PEI=ps;
               else OP=ps;
run;

proc sgplot data=gp;
       density PEI /scale=percent /*若以個數呈現: Count*/
                        type=kernel
                        legendlabel='PEI'   /*組別的名稱*/
                        LINEATTRS=(COLOR=red); /*線條顏色*/
```


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```
        density OP    /scale=percent
                      type=kernel
                      legendlabel='OP'
                      LINEATTRS=(color=blue);/*利用不同組別(不同變項)各畫一條但在同一張圖上*/
        xaxis label='Estimated probability' max=1 min=0 ;/*X軸名稱與最大最小值等的設定*/
        yaxis max=30;
        keylegend / noborder location=inside position=topright;/*設定組別標籤的格式*/
run;

/*STEP 2: (1)Compute standard deviation of the logit of the propensity score
                (2)Create calipers of width 0.15 standard deviations of the logit of PS*/
proc means std data=out_ps;
        var logit_ps;
         output out=stddata (keep=std) std=std;
run;

data stddata;
          set stddata;
           std=0.15*std;/*calipers of width 0.1-0.2 standard deviations of the logit of PS*/
run;

data _null_;/*Create Macro variable that contain the width of caliper for matching*/
        set stddata;
         call symput('stdcal',std);
run;

/*STEP 3: (1)Match subjects based on the calipers*/
proc sort data=out_ps;by gp_new;run;

data out_ps;
        set out_ps;
                id=_N_;
run;

%INC "D:\work\Project 56-PS matching\PS matching\Macro_propensity score matching_greedy matching.sas";
```


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```
/*Import the PS-macro: Macro_propensity score matching_greedy matching.sas*/
/*%gmatch(data=*dataset*,*the name of the SAS data set*
        group=*treatment*, *the variable identifying treated or untreated subject *
        id=*participants id*, **
        mvars=*variables for matching*,
        wts=1,*weights corresponding to each matching variable*
        dist=1,*the type of distance to calculate 1:weighted sum [default] *
        dmaxk=*maximum allowable difference*,
        ncontls=*numbers of control each case*,
        seedca=15022012,
        seedco=16022012,
        out=output dataset,
        print=F);*/
%gmatch(data=out_ps,group=gp_new,id=id,mvars=logit_ps,wts=1,dist=1,dmaxk=&stdcal,ncontls=1,
      seedca=15022012,seedco=16022012,out=matchpairs,print=F);

/*Create a data set containing the matched control and case group*/
data Matchpairs;
    set Matchpairs;
        pair_id=__IDCA;/*set pair id number-used case id number*/
run;

/*created case_match and control_match dataset for linking and selecting participants from baseline data source*/
data case_match;
    set matchpairs;
        pair_id=__IDCA;
        case_id=__IDCA;/*link by*/
        logit_ps=__CA1;
    keep pair_id case_id logit_ps;
run;

data control_match;
    set matchpairs;
        pair_id=__IDCA;
        control_id=__IDCO;/*link by*/
```


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```
            logit_ps=__CO1;
        keep pair_id control_id logit_ps;
run;

proc sort data=control_match;by control_id;run;
proc sort data=case_match nodupkey;by case_id;run;/*1:N matching should delete duplicate cases*/

data case;set out_ps;if gp_new=1;case_id=id;run;
data control;set out_ps;if gp_new=0;control_id=id;run;

proc sort data=case;by case_id;run;
proc sort data=control;by control_id;run;

data control_match_1;
      merge control_match(in=ap) control(in=bp);
                by control_id;
                 if ap=1;
run;

data case_match_1;
       merge case_match(in=ap) case(in=bp);
                 by case_id;
                   if ap=1 and bp=1;
run;

/*Final data set-long form*/
data data.AF_PS ;set control_match_1 case_match_1;run;
proc sort data= data.AF_PS ;by pair_id;run;
```


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```
/*SAS macro: Macro_propensity score matching_greedy matching*/
/*-------------------------------------------------------------------*
  | The documentation and code below is supplied by HSR CodeXchange.
  |
  *-------------------------------------------------------------------*/


 /*-------------------------------------------------------------------*
  | MACRO NAME    : gmatch
  | SHORT DESC    : Match 1 or more controls to cases using the
  |                 GREEDY algorithm
  *-------------------------------------------------------------------*
  | CREATED BY    : Kosanke, Jon                    (04/07/2004 16:32)
  |               : Bergstralh, Erik
  *-------------------------------------------------------------------*
  | PURPOSE
  |
  | GMATCH Macro to match 1 or more controls for each of N cases
  | using the GREEDY algorithm--REPLACES GREEDY option of MATCH macro.
  | Changes:
  | --cases and controls in same dataset
  | --not mandatory to randomly pre-ort cases and controls, but recommended
  | --options to transform X's and to choose distance metric
  | --input parameters consistent with %DIST macro for optimal matching
  |
  | *******
  |
  | Macro name: %gmatch
  |
  | Authors: Jon Kosanke and Erik Bergstralh
  |
  | Date: July 23, 2003
  |       October 31, 2003...tweaked print/means based on "time" var
  |
  | Macro function:
  |
  | Matching using the GREEDY algorithm
  |
  | The purpose of this macro is to match 1 or more controls(from a total
  | of M) for each of N cases.    The controls may be matched to the cases by
```


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| one or more factors(X's). The control selected for a particular
| case(i) will be the control(j) closest to the case in terms of Dij.
| Dij can be defined in multiple ways. Common choices are the Euclidean
| distance and the weighted sum of the absolute differences between the
| case and control matching factors. I.e.,
|
| Dij= SQRT [SUM { W.k*(X.ik-X.jk)**2}], or
|
| Dij= SUM { W.k*ABS(X.ik-X.jk) },
|
| where the sum is over the number
| of matching factors X(with index
| k) and W.k = the weight assigned
| to matching factor k and X.ik =
| the value of variable X(k) for
| subject i.
|
| The control(j) selected for a case(i) is the one with the smallest Dij
| (subject to constraints DMAX and DMAXK, defined below). In the case of
| ties, the first one encountered will be used. The higher the user-defined
| weight, the more likely it is that the case and control will be matched
| on the factor. Assign large weights (relative to the other weights) to
| obtain exact matches for two-level factors such as gender. An option to
| using weights might be to standarize the X's in some fashion. The macro
| has options to standardize all X's to mean 0 and variance 1 and to use
| ranks.
|
| The matching algorithm used is the GREEDY method. Using the greedy method,
| once a match is made it is never broken. This may result in inefficiencies
| if a previously matched control would be a better match for the current
| case than those controls currently available. (An alternative method is to
| do optimal matching using the VMATCH & DIST macros. This method guarantees
| the best possible matched set in terms of minimizing the total Dij.)
| The GREEDY method generally produces very good matches, especially if the
| control pool is large relative to the number of cases. When multiple
| controls/case are desired, the algorithm first matches 1 control to all
| cases and then proceeds to select second controls.
|
|
| The gmatch macro checks for missing values of matching variables and the

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```
| time variable(if specified) and deletes those observations from the input
| dataset.
|
| Call statement:
|
|
| %gmatch(data=,group=,id=,
|          mvars=,wts=,dmaxk=,dmax=,transf,
|          time=, dist=,
|          ncontls=,seedca=,seedco=,
|          out=,outnmca=,outnmco=,print=);
|
| Parameter definitions(R=required parameter):
|
|
|  R      data   SAS data set containing cases and potential controls. Must
|                contain the ID, GROUP, and the matching variables.
|
|  R      group SAS variable defining cases. Group=1 if case, 0 if control.
|
|  R       id    SAS CHARACTER ID variable for the cases and controls.
|
|
|  R    mvars   List of numeric matching variables common to both case and
|                control data sets.   For example, mvars=male age birthyr.
|
|  R      wts   List of non-negative weights corresponding to each matching
|                variable.   For example wts=10 2 1 corresponding to male, age
|                and birthyr as in the above example.
|
|       dmaxk   List of non-negative values corresponding to each matching
|                variable.   These numbers are the largest possible absolute
|                differences compatible with a valid match.   Cases will
|                NOT be matched to a control if ANY of the INDIVIDUAL
|                matching factor   differences are >DMAXK.   This optional
|                parameter allows one to form matches of the type male+/-0,
|                age+/-2, birth year+/-5 by specifying DMAXK=0 2 5.
|
|       dmax    Largest value of Dij considered to be a valid match.   If
|                you want to match exactly on a two-level factor(such as
```


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gender coded as 0 or 1) then assign DMAX to be less than the weight for the factor. In the example above, one could use wt=10 for male and dmax=9. Leave DMAX blank if any Dij is a valid match. One would typically NOT use both DMAXK and DMAX. The only advantage to using both, would be to further restrict potential matches that meet the DMAXK criteria.

dist Indicates type of distance to calculate.

1=weighted sum(over matching vars) of absolute case-control differences(default)

2=weighted Euclidean distance

time Time variable used for risk set matching. Matches are only valid if the control time > case time. May need to

transf Indicates whether all matching vars are to be transformed (using the combined case+control data) prior to computing distances. 0=no(default),
1=standardize to mean 0 and variance 1,
2=use ranks of matching variables.

ncontls Indicates the number of controls to match to each case. The default is 1. With multiple controls per case, the algorithm will first match every case to one control and then again match each case to a second control, etc. Controls selected on the first pass will be stronger matches than those selected in later rounds. The output data set contains a variable (cont_n) which indicates on which round the control was selected.

seedca Seed value used to randomly sort the cases prior to matching. This positive integer will be used as input to the RANUNI function. The greedy matching algorithm is order dependent which, among other things means that cases matched first will be on average more similar to their controls than those matched last(as the number of control choices will be limited). If the matching order is related to confounding factors (possibly age or

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| calendar time) then biases may result. Therefore it is
| generally considered good practice when using the GREEDY
| method to randomly sort both the cases and controls
| before beginning the matching process.
|
| seedco Seed value used to randomly sort the controls prior to
| matching using the GREEDY method. This seed value must
| also be a positive integer.
|
|
| print= Option to print data for matched cases. Use PRINT=y to
| print data and PRINT=n or blank to not print. Default is y.
|
| out=name of SAS data set containing the results of the matching
| process. Unmatched cases are not included. See outnm
| below. The default name is __out. This data set will have
| the following layout:
|

Case_id	Cont_id	Cont_n	Dij	Delta_caco MVARS_ca MVARS_co
1	67	1	5.2	(Differences & actual
1	78	2	6.1	values for matching factors
2	52	1	2.9	for cases & controls)
2	92	2	3.1	
.	.	.	.	
.	.	.	.	

|
| outnmca=name of SAS data set containing NON-matched cases.
| Default name is __nmca .
|
| outnmco=name of SAS data set containing NON-matched controls.
| Default name is __nmco .
|
|
| References: Bergstralh, EJ and Kosanke JL(1995). Computerized
| matching of controls. Section of Biostatistics
| Technical Report 56. Mayo Foundation.
|
|
| Example: 1-1 matching by male(exact), age(+-2) and year(+-5).
| The wt for male is not relevant, as only exact matches

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```
|                on male will be considered.    The weight for age(2) is
|                double that for year(1).
|
|
|          %gmatch(data=all, group=ca_co,id=clinic,
|                     mvars=male age_od yr_od,
|                     wts=2 2 1, dmaxk=0 2 5,out=mtch,
|                     seedca=87877,seedco=987973);
|
*-------------------------------------------------------------------*
| OPERATING SYSTEM COMPATIBILITY
|
| UNIX SAS v8     :     YES
| UNIX SAS v9     :
| MVS SAS v8      :
| MVS SAS v9      :
| PC SAS v8       :
| PC SAS v9       :
*-------------------------------------------------------------------*
| EXAMPLES |
| Another example is located at the bottom of the code.
*-------------------------------------------------------------------*
| Copyright 2004 Mayo Clinic College of Medicine.
|
| This program is free software; you can redistribute it and/or
| modify it under the terms of the GNU General Public License as
| published by the Free Software Foundation; either version 2 of
| the License, or (at your option) any later version.
|
| This program is distributed in the hope that it will be useful,
| but WITHOUT ANY WARRANTY; without even the implied warranty of
| MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE. See the GNU
| General Public License for more details.
*-------------------------------------------------------------------*/

%MACRO GMATCH(DATA=,GROUP=,ID=,
              MVARS=,WTS=,DMAXK=,DMAX=,DIST=1,
              NCONTLS=1, TIME=,TRANSF=0,
              SEEDCA=,SEEDCO=,PRINT=y,
              OUT=__OUT,OUTNMCA=__NMCA,OUTNMCO=__NMCO);
```


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```
%LET BAD=0;

%IF %LENGTH(&DATA)=0 %THEN %DO;
    %PUT ERROR: NO DATASET SUPPLIED;
    %LET BAD=1;
%END;

%IF %LENGTH(&ID)=0 %THEN %DO;
    %PUT ERROR: NO ID VARIABLE SUPPLIED;
    %LET BAD=1;
%END;

%IF %LENGTH(&GROUP)=0 %THEN %DO;
    %PUT ERROR: NO CASE(1)/CONTROL(0) GROUP VARIABLE SUPPLIED;
    %LET BAD=1;
%END;

%IF %LENGTH(&MVARS)=0 %THEN %DO;
    %PUT ERROR: NO MATCHING VARIABLES SUPPLIED;
    %LET BAD=1;
%END;

%IF %LENGTH(&WTS)=0 %THEN %DO;
    %PUT ERROR: NO WEIGHTS SUPPLIED;
    %LET BAD=1;
%END;

%LET NVAR=0;
%DO %UNTIL(%SCAN(&MVARS,&NVAR+1,' ')= );
    %LET NVAR=%EVAL(&NVAR+1);
%END;
%LET NWTS=0;
%DO %UNTIL(%QSCAN(&WTS,&NWTS+1,' ')= );
    %LET NWTS=%EVAL(&NWTS+1);
%END;
%IF &NVAR^= &NWTS %THEN %DO;
    %PUT ERROR: #VARS MUST EQUAL #WTS;
    %LET BAD=1;
%END;
```


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```
%LET NK=0;
 %IF %QUOTE(&DMAXK)^=    %THEN %DO %UNTIL(%QSCAN(&DMAXK,&NK+1,' ')= );
     %LET NK=%EVAL(&NK+1);
 %END;
 %IF &NK>&NVAR %THEN %LET NK=&NVAR;
 %DO I=1 %TO &NVAR;
     %LET V&I=%SCAN(&MVARS,&I,' ');
 %END;

%IF &NWTS>0 %THEN %DO;
        DATA _NULL_;
        %DO I=1 %TO &NWTS;
            %LET W&I=%SCAN(&WTS,&I,' ');
            IF &&W&I<0 THEN DO;
                PUT 'ERROR: WEIGHTS MUST BE NON-NEGATIVE';
                CALL SYMPUT('BAD','1');
            END;
        %END;
        RUN;
 %END;

%IF &NK>0 %THEN %DO;
        DATA _NULL_;
        %DO I=1 %TO &NK;
            %LET K&I=%SCAN(&DMAXK,&I,' ');
            IF &&K&I<0 THEN DO;
                PUT 'ERROR: DMAXK VALUES MUST BE NON-NEGATIVE';
                CALL SYMPUT('BAD','1');
            END;
        %END;
        RUN;
 %END;

  %MACRO MAX1;
    %IF &DMAX^= %THEN %DO;
       & __D<=&DMAX
    %END;
    %DO I=1 %TO &NK;
       & ABS(__CA&I-__CO&I)<=&&K&I
```


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```
   %END;
 %MEND MAX1;

%macro greedy;
 %GLOBAL BAD2;

   data __CHECK; set &DATA;
        __id=&id;
        if __id="" then delete;
        %DO I=1 %TO &NVAR;
              IF %scan(&mvars,&i)=. THEN DELETE;
         %END;
         %IF &TIME^= %THEN %DO;
              IF &TIME=. THEN DELETE;
         %END;
    run;

   *** transform data if requested/separate cases & controls;
   %if &transf=1 %then %do;
   proc standard data=__check m=0 s=1 out=_stdzd; var &mvars;
   data _caco;
     set _stdzd;
   %end;

   %if &transf=2 %then %do;
   proc rank data=__check out=_ranks; var &mvars;
   data _caco;
     set _ranks;
   %end;

   %if &transf=0 %then %do;
   data _caco;
     set __check;
   %end;


   DATA __CASE; SET _caco;
        if &group=1;
   DATA __CASE; SET __CASE END=EOF;
    KEEP __IDCA __CA1-__CA&NVAR __R &mvars
```


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```
    %if &time^= %then %do;
          __catime
    %end;
     ;
    __IDCA=&ID;
    %if &time^= %then %do;
        __catime=&time;
    %end;
    %DO I=1 %TO &NVAR;
        __CA&I=&&V&I;
    %END;
    %if &seedca^= %then %do;
    SEED=&SEEDCA;
    __R=RANUNI( SEED    );
    %end;
    %else %do;
    __R=1;
    %end;

    IF EOF THEN CALL SYMPUT('NCA',_N_);
PROC SORT; BY __R __IDCA;

DATA __CONT; SET _caco;
    if &group=0;
DATA __CONT; SET __CONT END=EOF;
  KEEP __IDCO __CO1-__CO&NVAR __R &mvars
   %if &time^= %then %do;
        __cotime
   %end;
   ;
    __IDCO=&ID;
    %if &time^= %then %do;
        __cotime=&time;
    %end;
    %DO I=1 %TO &NVAR;
        __CO&I=&&V&I;
    %END;
    %if &seedco^= %then %do;
    SEED=&SEEDCo;
    __R=RANUNI( SEED    );
```


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```
    %end;
    %else %do;
    __R=1;
    %end;

    IF EOF THEN CALL SYMPUT('NCO',_N_);
RUN;
%LET BAD2=0;
%IF &NCO < %EVAL(&NCA*&NCONTLS) %THEN %DO;
    %PUT ERROR: NOT ENOUGH CONTROLS TO MAKE REQUESTED MATCHES;
    %LET BAD2=1;
%END;

%IF &BAD2=0 %THEN %DO;
    PROC SORT; BY __R __IDCO;
    DATA __MATCH;
     KEEP __IDCA __CA1-__CA&NVAR __DIJ __MATCH __CONT_N
     %if &time^= %then %do;
         __catime __cotime
     %end;
     ;
     ARRAY __USED(&NCO) $ 1 _TEMPORARY_;
        DO __I=1 TO &NCO;
            __USED(__I)='0';
        END;
        DO __I=1 TO &NCONTLS;
            DO __J=1 TO &NCA;
                SET __CASE POINT=__J;
                __SMALL=.;
                __MATCH=.;
                DO __K=1 TO &NCO;
                    IF __USED(__K)='0' THEN DO;
                        SET __CONT POINT=__K;

                      %if &dist=2 %then %do;
                       **wtd euclidian dist;
                        __D= sqrt(
                        %do k=1 %to &nvar;
                        %scan(&wts,&k)*(__ca&k - __co&k)**2
                        %if &k<&nvar %then + ;
```


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```
                %end;
                 );
               %end;
               %else %do;
                **wtd sum absolute diff;
                 __D=
                %do k=1 %to &nvar;
                %scan(&wts,&k)*abs(__ca&k - __co&k )
                %if &k<&nvar %then + ;
                %end;
                   ;
               %end;

                IF __d^=. & (__SMALL=. | __D<__SMALL) %MAX1
                %if &time^= %then %do;
                    & __cotime > __catime
                %end;
                THEN DO;
                    __SMALL=__D;
                    __MATCH=__K;
                    __DIJ=__D;
                    __CONT_N=__I;
                END;
            END;
        END;
        IF __MATCH^=. THEN DO;
            __USED(__MATCH)='1';
            OUTPUT;
        END;
    END;
  END;
  STOP;
DATA &OUT;
 SET __MATCH;
 SET __CONT POINT=__MATCH;
 KEEP __IDCA __IDCO __CONT_N __DIJ __CA1-__CA&NVAR
      __CO1-__CO&NVAR __d1-__d&nvar __absd1-__absd&nvar   __WT1-__WT&NVAR
          __catime __cotime __dtime;

 %if &time= %then %do;
```


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```
        __cotime=.; __catime=.;
    %end;
    LABEL
                __catime="&time/CASE"
                __cotime="&time/CONTROL"
                __dtime="&time/ABS. DIFF"
            __CONT_N='CONTROL/NUMBER'
            __DIJ='DISTANCE/D_IJ'
           %DO I=1 %TO &NVAR;
            __CA&I="&&V&I/CASE"
            __CO&I="&&V&I/CONTROL"
            __absd&I="&&V&I/ABS. DIFF "
            __d&I="&&V&I/DIFF "
            __WT&I="&&V&I/WEIGHT"
          %END;
            ;
        %DO I=1 %TO &NVAR;
            __d&i= (__CA&I-__CO&I);          **raw diff;
            __absd&I=abs(__CA&I-__CO&I); **abs diff;
            __WT&I=&&W&I;
        %END;
            __dtime=__cotime-__catime;

   PROC SORT DATA=&OUT; BY __IDCA __CONT_N;
   proc sort data=__case; by __IDCA;
   data &outnmca; merge __case
         &out(in=__inout where=(__cont_n=1)); by __idca;
         if __inout=0; **non-matches;

   proc sort data=__cont; by __IDCO;
   proc sort data=&out; by __IDCO;
   data &outnmco; merge __cont
         &out(in=__inout); by __idco;
         if __inout=0; **non-matched controls;
   proc sort data=&out; by __IDCA; **re-sort by case id;

%if %upcase(&print)=Y %then %do;
   PROC PRINT data=&out LABEL SPLIT='/';
    VAR __IDCA __IDCO __CONT_N
```


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```
  __DIJ
 %DO I=1 %TO &NVAR;
  __absd&I
 %END;
 %if &time^= %then %do;
  __dtime
 %end;
 %DO I=1 %TO &NVAR;
  __CA&I __CO&I
 %END;
 %if &time^= %then %do;
  __catime __cotime
 %end;
  ;
 sum __dij;

title9'Data listing for matched cases and controls';
footnote"Greedy matching(gmatch) macro: data=&data group=&group id=&id       ";
footnote2"      mvars=&mvars    wts=&wts dmaxk=&dmaxk dmax=&dmax ncontls=&ncontls";
 footnote3"     transf=&transf dist=&dist time=&time seedca=&seedca    seedco=&seedco";
footnote4"      out=&out      outnmca=&outnmca    outnmco=&outnmco";
run;
title9'Summary data for matched cases and controls--one obs/control';
 %if &sysver ge 8 %then %do;
proc means data=&out    maxdec=3 fw=8
   n mean median min p10 p25 p75 p90 max sum;
%end;
%else %do;
proc means data=&out maxdec=3
 n mean min max sum;
%end;
class __cont_n;
 var __dij

      %do I=1 %TO &NVAR;
           __absd&I
      %end;
      %if &time^= %then %do;
           __dtime
      %end;
```


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```
        %do I=1 %TO &NVAR;
             __ca&I
        %end;
        %if &time^= %then %do;
             __catime
        %end;
        %do I=1 %TO &NVAR;
             __co&I
        %end;
        %if &time^= %then %do;
             __cotime
        %end;
            ;
run;
*** estimate matching var means within matched sets for controls;
proc means data=&out    n mean noprint; by __idca;
  var __dij
%do i=1 %to &nvar;
     __co&i
%end;
         __cotime
     ;
output out=_mcont n=n_co mean=__dijm
%do i=1 %to &nvar;
   __com&i
%end;
       __tcom
   ;
data _onecase; set &out; by __idca; if first.__idca;
data __camcon; merge _onecase _mcont; by __idca;

keep __idca n_co __dijm
       __dtime __catime    __tcom
  %do i=1 %to &nvar;
    __ca&i __com&i    __actd&i __absd&i
  %end;
;



%do i=1 %to &nvar;
```


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```
    __absd&i=abs(__ca&i - __com&i);
    __actd&i=(__ca&i - __com&i);
  %end;
    __dtime=__tcom-__catime
     ;

 label
  n_co="No./CONTROLS"
  __dijm="Average/Dij"
  __dtime="&time/Mean Time DIFF"
  __tcom="&time/Mean CONT TIME"

 %do i=1 %to &nvar; %let vvar=%scan(&mvars,&i);
    __absd&i="&vvar/Mean ABS. DIFF"
    __com&i="&vvar/Mean CONTROL"
 %end;
    ;
title9'Summary data for matched cases and controls--one obs/case(using average control value)';
%if &sysver ge 8 %then %do;
proc means data=__camcon maxdec=3 fw=8
   n mean median min p10 p25 p75 p90 max sum;
%end;
%else %do;
proc means data=__camcon maxdec=3
   n mean min max sum;
%end;
var n_co __dijm
%do i=1 %to &nvar;
 __absd&i
%end;
%if &time^= %then %do;
 __dtime
%end;
%do i=1 %to &nvar;
__ca&i
%end;
%if &time^= %then %do;
 __catime
%end;
%do i=1 %to &nvar;
```


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```
        __com&i
        %end;
        %if &time^= %then %do;
        __tcom
        %end;
              ;
     %end; **end of print=y loop**;
    %END;    **end of bad2=0 loop**;
    run;
    title9; footnote;
    run;

    %mend greedy;

    %IF &BAD=0 %THEN %DO;
            %GREEDY
    %END;
%MEND GMATCH;

    /*    **test data;
DATA FAKEREG;
          DO I = 1 TO 3000;
                    *id = _n_;
                     id=i;
                    SEX = MOD(I, 2);
                    IF mod(I, 21) THEN CASE = 0; ELSE CASE = 1;
                    *AGE = (INT(RANUNI(12378937)*10000)/100);
                     age= int(ranuni(123789837)*100);
                    DROP i ;
                    OUTPUT;
          END;

RUN;
data fakereg;set fakereg; timex=5; if case=0 then timex=6;

%gmatch(data=fakereg,group=case, id=id,
          mvars=age sex,wts=2 1,dmaxk= 5 0, transf=0,
          time=timex, dist=1, ncontls=2,seedca=234098,seedco=0489,
          out=regccout,outnmco=matched,print=Y);
               run;       */
```


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Coding 3-2: Conditional Cox Proportional Hazards Model

```
/*Conditional (matched) Cox proportional hazards model*/
PROC PHREG DATA=Test.Amyloidosis ;
class sex (ref=first) agegp (ref=first)
htn (ref=first) af_afl (ref=first) acs (ref=first) stroke (ref=first)
hyperlipidemia (ref=first) copd (ref=first) statin (ref=first) insulin (ref=first) oha (ref=first) ace_arb (ref=first) ccb
(ref=first) beta_b (ref=first)
aad (ref=first) noac (ref=first) anti_platelet (ref=first) warfarin (ref=first) ;
MODEL fu_vt_year * VT (0)= Amyloidosis age sex htn dm acs copd /
RISKLIMITS ties=exact rl;
/*How to handle ties in the failure time*/
/*切記一定要存在!!discrete或exact皆可以*/;
id pair_id; /* pair_id: paired ID based on a matched study (e.g. PS-matching)*/
RUN;
```


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Coding 3-3: Sample Size & Power for Study 3

```
# Sample Size Calculation for Conditional Logistic Regression with Binary Covariate

#N: integer. Number of sets. Each set contains nD cases and nH controls.
#power: numeric. Power of the test for if the exposure variable is associated with the risk of diseases
#OR: numeric. Odds ratio = exp(θ), where θ is the regression coefficient of the
#exposure: variable.
#pE: numeric. Population prevalence of exposure.
#nD: integer. Number of cases per set.
#nH: integer. Number of controls per set.
#R2: numeric. Coefficient of determination of the exposure variable and other covariates
#alpha: numeric. family-wise type I error rate.
#nTests: integer. Number of tests.

# Estimate power: Amyloidosis
power = powerConLogistic.bin(
N = 12139*2,
power = NULL,
OR = 6.5,
pE = 6/100000,
nD = 12139,
nH = 12139,
R2 = 0.01,
alpha = 0.05,
nTests = 1)
print(power)
      # > 0.99
```


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Publications

<First author>

1. Yun-Yu Chen, Fa-Po Chung, Yenn-Jiang Lin, Ta-Chen Su, Wei-Tien Chang*, Kuo-Liong Chien. Epidemiological Characteristics and Meteorological Factors of Sudden Death among General Population of Ethnic Chinese in Taiwan: An Eighteen-Year Follow-Up Report in A Community. Acta Cardiol Sin. 2022 (SCI, accepted) (Project 1).
2. Yun-Yu Chen, Yenn-Jiang Lin*, Kuo-Liong Chien*, Tze-Fan Chao, Li-Wei Lo, Shih-Lin Chang, Fa-Po Chung, Chin-Yu Lin, Ting-Yung Chang, Ling Kuo, Yu-Cheng Hsieh Cheng-Hung Li, Shih-Ann Chen. Novel Model-Based Point Scoring System for Predicting Stroke Risk in Atrial Fibrillation Patients: Results from a Nationwide Cohort Study with Validation. Int J Cardiol Heart Vasc. 2021;34:100787 (ESCI) (Project 2).
3. Yun-Yu Chen, Ming-Jen Kuo, Fa-Po Chung, Yenn-Jiang Lin*, Kuo-Liong Chien, Yu-Cheng Hsieh, Shih-Lin Chang, Li-Wei Lo, Yu-Feng Hu, Tze-Fan Chao, Jo-Nan Liao, Ting-Yung Chang, Chin-Yu Lin, Ling Kuo, Ta-Chuan Tuan, Cheng-I Wu, Chih-Min Liu, Shin-Huei Liu, Cheng-Hung Li, Shih-Ann Chen. Risks of Ventricular Tachyarrhythmia and Mortality in Patients with Amyloidosis– A Long-term Cohort Study. Acta Cardiol Sin. 2022 (SCI, accepted) (Project 3).

<Co-first author>

1. Dony Yugo, Yun-Yu Chen, Yenn-Jiang Lin*, Kuo-Liong Chien, Shih-Lin Chang, Li-Wei Lo, Yu-Feng Hu, Tze-Fan Chao, Fa-Po Chung, Jo-Nan Liao, Ting-Yung Chang, Chin-Yu Lin, Ta-Chuan Tuan, Ling Kuo, Cheng-I Wu, Chih-Min Liu, Shin-Huei Liu, Cheng-Hung Li, Yu-Cheng Hsieh, Shih-Ann Chen. Long-term Mortality and Cardiovascular Outcomes in Patients with Atrial Flutter after Catheter Ablation. Europace. 2021;euab308 (SCI).
2. Guan-Yi Li, Yun-Yu Chen, Fa-Po Chung*, Kuo-Liong Chien, Chiao-Po Hsu*, Yenn-Jiang Lin. Long-term Outcomes of Bioprosthetic or Mechanical Valve Replacement in End-stage Renal Disease: A Nationwide Population-based Retrospective Study. Front Cardiovasc Med. 2021;8:745370 (SCI).
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<Second author>

1. Guan-Yi Li, Yun-Yu Chen, Kuo-Liong Chien, Yenn-Jiang Lin, Tzu-Ting Kuo*, Fa-Po Chung*. Clinical Significance of Ventricular Tachyarrhythmias in Patients Undergoing Valve Replacement: A Nationwide Population-based Study. Front Cardiovasc Med. 2021;8:676897 (SCI).
2. Yu-Cheng Hsieh, Yun-Yu Chen, Kuo-Liong Chien, Fa-Po Chung, Li-Wei Lo, Shih-Lin Chang, Tze-Fan Chao, Yu-Feng Hu, Chin-Yu Lin, Ta-Chuan Tuan, Jo-Nan Liao, Yenn-Jiang Lin*, Shih-Ann Chen. Catheter Ablation of Atrial Fibrillation Reduces the Risk of Dementia and Hospitalization during a Very Long-term Follow-up. Int J Cardio. 2020;304:75-81 (SCI).

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Decision Letter (ACS-2022-0069.R2)

From: klwang2@vghtpe.gov.tw

To: klchien@ntu.edu.tw

CC: acs@tsoc.org.tw

Subject: Acta Cardiologica Sinica - Decision on Manuscript ID ACS-2022-0069.R2

Body: 02-Jun-2022

Dear Prof. Chien:

It is a pleasure to accept your manuscript entitled "Epidemiological Characteristics and Meteorological Factors of Sudden Death among General Population of Ethnic Chinese in Taiwan: An Eighteen-Year Follow-Up Report in A Community" in its current form for publication in the Acta Cardiologica Sinica.

Thank you for your fine contribution. On behalf of the Editors of the Acta Cardiologica Sinica, we look forward to your continued contributions to the Journal. You will receive galley proofs of your article in the near future.

Thank you for submitting this interesting paper to the ACTA CARDIOLOGICA SINICA.

Sincerely,
Dr. Kang-Ling Wang, Deputy Editor-in-Chief
Prof. Tzung-Dau Wang, Editor-in-Chief
Acta Cardiologica Sinica
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Novel model-based point scoring system for predicting stroke risk in atrial fibrillation patients: Results from a nationwide cohort study with validation

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ABSTRACT

Background: The stroke risk scoring system for atrial fibrillation (AF) patients can vary considerably based on patients' status while receiving ablation. This study aimed to demonstrate a novel scoring system for stroke risk stratification based on the status of catheter ablation.
Methods: First, 787 patients with AF undergoing ablation were matched according to age, sex, and underlying diseases with the same number of patients not undergoing ablation using the propensity-score (PS)-matched cohort. Multivariate Cox model-derived coefficients were used to construct a simple point-based clinical model using the PS-matched cohort. Thereafter, the novel model (AF-CA-Stroke score) was validated in a nationwide AF cohort.
Results: The AF-CA-Stroke score was calculated based on age (point = 5), ablation status (point = 4), prior history of stroke (point = 4), chronic kidney disease (point = 2), diabetes mellitus (point = 1), and congestive heart failure (point = 1). Risk function to predict the 1-, 5-, 10-year absolute stroke risks was reported. The estimated area under the receive operating characteristic curve of the AF-CA-Stroke score in the PS-matched cohort was 0.845 (95% confidence interval: 0.824–0.865) to predict long-term stroke. A validation study showed that discrimination abilities in the AF-CA-Stroke scores were significantly higher than those in the $CHADS_2/CHA_2DS_2$-VASc scores. The best cut-off value of the AF-CA-Stroke score to predict future strokes was ≥ 5.
Conclusions: This novel model-based point scoring system effectively identifies stroke risk using clinical factors and AF ablation status of patients with AF. Various age stratifications and AF ablation should be considered in AF management.

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia that increases the risk of stroke and mortality in adults [1,2]. The stroke risk in AF patients varies greatly (ranging from 1% to 15% per year), and dependents on several demographic and clinical factors [3]. Effective risk stratification of stroke is a cornerstone for AF management [4]. Pharmacologic therapies for AF management includes rate control, rhythm control, and thromboembolic prevention [5]. However, the long-term efficacy of rate control and rhythm control may be limited on reducing stroke risk based on the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study [6]. Catheter ablation has become an alternative therapy for AF. As compared with rhythm control therapy, catheter ablation was associated with reduced subsequent AF episodes [7]. A prior study using the Taiwan National Health Insurance database (NHIRD) demonstrated that AF catheter ablation was associated with lower stroke risk [8]. A recent

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meta-analysis (analyzing one randomized clinical trial - the Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation [CABANA] and other eight large matched population studies) exhibited reduced stroke risk in AF patients with catheter ablation than medical therapy [9].

Currently, the $CHADS_2$ and CHA_2DS_2-VASc scores as the conventional scoring systems are commonly used to identify stroke risk and determine antithrombotic therapies in patients with AF [10,11]. Prior studies suggested that AF patients with $CHADS_2$ score of "0" or CHA_2DS_2-VASc score of "0–1" could be used to stratify truly low stroke risk in AF patients undergoing catheter ablation [12–14]. However, the stroke risk scoring systems for AF patients can vary considerably based on the status while receiving the AF ablation and was not considered in conventional scoring systems. This study aimed to demonstrate a scoring system for stroke risk stratification using the conventional risk factors plus the status of catheter ablation, as compared with the conventional scoring systems.

2. Methods

2.1. Study design and study population

This study included a propensity-score (PS) matched cohort (Cohort 1) and a validation AF cohort (Cohort 2). Participants with prior AF ablation or aged < 18 years before the baseline were excluded from this study. This study was approved by the Institutional Review Board (IRB Number: 201305044W and 2017-09-013BCF) of the Taipei Veterans General Hospital (TVGH) in accordance with the Good Clinical Practice Guidelines.

2.2. Propensity-score matched Cohort (Cohort 1)

In Cohort 1, AF patients receiving catheter ablation for pulmonary vein isolation from 2003 to 2012 based on the TVGH AF ablation dataset were studied to construct a novel scoring system. TVGH AF ablation dataset recruited patients based on the consensus for performing AF catheter ablation, including: (1) AF types, AF history, and left atrial size; (2) the severity of underlying cardiovascular diseases; (3) history of pharmacologic therapies; and (4) the patients' will and the physicians' judgment [15].

Comparison cohort of the non-ablation group was derived by randomly selecting 10,000 patients with AF without ablation in 2003 from the NHIRD. In order to minimize the impact of higher stroke risk due to imbalanced distributions between patients with AF without/with ablation in Cohort 1, for AF patients undergoing ablation were age- sex-, underlying disease-matched to the same number of patients with AF without ablation (Fig. 1).

2.3. Validation AF Cohort (Cohort 2)

Cohort 2 was a nationwide cohort generating from the NHIRD in 2003. In Cohort 2, a total of 147,225 patients with AF aged over 17 years as the validation AF cohort were identified; among them, 1,897 drug refractory patients with AF with catheter ablation of pulmonary ablation were confirmed according to procedure code of AF catheter ablation (Cohort 2; Fig. 1). The newly constructed scoring system constructed in Cohort 1 was validated using Cohort 2.

2.4. Ascertainment of baseline Data

The NHIRD was provided by the Health and Welfare Data Science Center, Taipei, Taiwan. The NHIRD includes records of outpatient visits, hospital admissions, prescriptions, and disease diagnoses for > 99% of the 23 million population. All patient information was anonymized, and the requirement for written informed consent from patients was officially waived. All participants in the ablation group provided written informed consent. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding system was used for identifying

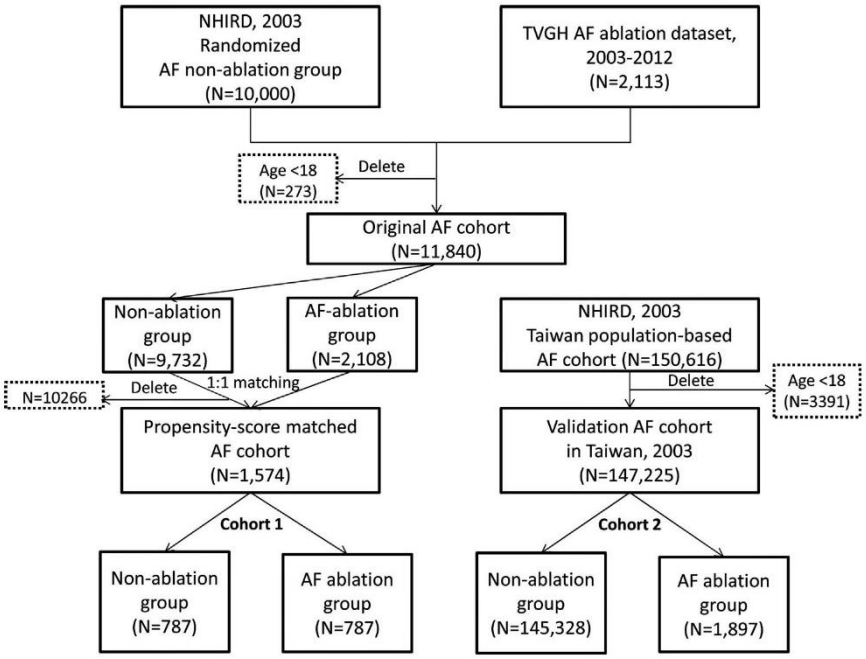

Fig. 1. Study flow chart (AF: atrial fibrillation; NHIRD: Taiwan National Health Insurance database; TVGH: Taipei Veterans General Hospital).

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Table 1
Basic characteristics and estimated coefficient.

Risk factors	Mean or proportion (%)	Hazard ratio (95% confidence interval)	P-value
Included in the novel system			
Age, +1 year	54.5 years	1.05 (1.04–1.07)	<0.001
AF, no catheter ablation	50%	4.64 (3.24–6.64)	<0.001
Prior history of stroke	6.0%	6.89 (5.07–9.36)	<0.001
Chronic kidney disease	0.9%	4.54 (2.14–9.65)	<0.001
Diabetes mellitus	7.4%	1.55 (1.01–2.36)	0.04
Congestive heart failure	6.4%	1.58 (1.01–2.47)	0.048
Excluded from the novel system			
Hypertension	36.8%	0.80 (0.60–1.06)	0.12
Prior acute coronary syndromes	2.5%	0.35 (0.09–1.41)	0.14
Vascular disease	2.7%	0.48 (0.15–1.51)	0.21
Hyperlipidemia	12.6%	0.76 (0.49–1.19)	0.23
Thyroid diseases	3.4%	0.69 (0.31–1.56)	0.38
Valvular diseases	4.1%	1.25 (0.68–2.29)	0.47
Chronic obstructive disease	3.0%	1.23 (0.61–2.49)	0.57
Female	30%	1.01 (0.77–1.32)	0.97

the disease diagnoses (details for ascertainment of baseline data, $CHADS_2$/ CHA_2DS_2-VASc scoring systems were summarized in the Data in Brief). The diagnoses were confirmed only if the patient had at least one incidence of hospitalization or at least three consecutive outpatient visits with the above listed diseases to improve the accuracy of coding (refer to the Data in Brief). The diagnostic accuracy of AF (ICD-9-CM: 427.31) using this definition in NHIRD has been validated previously [16]. For Cohort 2, the status of receiving AF ablation or not was based on: (1) an AF diagnosis of ICD-9-CM code: 427.31; (2) a procedural code of AF catheter ablation; and (3) a procedural code for *trans*-septal puncture [8]. Medications were identified using the codes based on the Anatomical Therapeutic Chemical (ATC) Classification System.

2.5. Follow-up strategy and outcome confirmation

This study evaluated the rates of stroke (ICD-9-CM: 430–438) using the NHIRD database. The accuracy of identifying ischemic stroke using the NHIRD was approximately 94% [17]. Participants were followed until the occurrence of first stroke event or at the end of 2015. Deaths were recorded to the Death Registry and followed until the end of 2016.

2.6. Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as proportion. For Cohort 1, the AF ablation group was 1:1 matched in the PS regarding age, sex, hypertension, chronic kidney disease, and chronic obstructive pulmonary disease with a 0.15 caliper width to patients with AF without ablation.

Cox proportional hazard models were used to evaluate stroke risk with hazard ratio (HR) with 95% confidence interval (CI). This study examined the incremental predictive values of adding these variables into the multivariate Cox model-derived coefficients to construct a simple point-based clinical model using Cohort 1. The final risk factors in the multivariate model were selected from the univariate model using a significance level of 0.1. The categorization point model was constructed according to clinical covariates in Cohort 1 by applying the methods of the Framingham study risk score functions [18,19] (see details in the Data in Brief). Finally, to adjust for the over-optimism in model fitting, the novel model (AF-CA-Stroke score) was validated using Cohort 2. The initial clinical model included age (years), sex, receiving AF ablation or not, congestive heart failure, hypertension, diabetes mellitus, prior stroke, vascular diseases, acute coronary diseases, chronic kidney disease, chronic obstructive pulmonary disease, valvular heart diseases, hyperlipidemia, and thyroid diseases. The "point" of stroke risk assessment of < 1% at 1 year was set to be "low risk", 1–5% at 1 year was set to be "moderate risk", and > 5% at 1 year was set to be "high risk".

We compared the performance of the novel AF-CA-Stroke score model with the $CHADS_2$/CHA_2DS_2-VASc scoring systems. The integrated discrimination abilities of area under receive operating characteristic curve (AUC), integrated discrimination improvement (IDI) and category-free net reclassification improvement (NRI) were assessed to compare among all models [20,21]. The best cut-of-value predicting the incident stroke events was calculated using the Youden index of the AUC (sensitivity + specificity −1). The Kaplan–Meier method was used to compare the stroke-free survival rate in different score groups. All statistical analyses were performed using the SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at two-tailed $P < 0.05$.

3. Results

3.1. Propensity-score matched Cohort (Cohort 1)

A total of 11,840 patients with AF were identified in the original cohort, including 2,108 patients in the TVGH AF ablation dataset

Table 2
Clinical point-based scoring system.

Clinical risk factors	Estimated coefficient ($Beta_{risk\ factor}$)	W_{i-j}-W_{i-ref}	$Beta_{risk\ factor}$ * (W_{i-j}-W_{i-ref})	Risk points
Age, +1 year	$Beta_{age-1}$ = 0.052			$Beta_{age-10}$ = 0.52
<35 (reference)		0	0	0
35–44		12.5	0.65	1
45–54		22.5	1.18	2
55–64		32.5	1.70	3
65–74		42.5	2.22	4
≥75		52.5	2.74	5
AF, no catheter ablation	1.90	1	1.90	4
Prior history of stroke	2.07	1	2.07	4
Chronic kidney disease	0.94	1	0.94	2
Diabetes mellitus	0.55	1	0.55	1
Congestive heart failure	0.49	1	0.49	1

(W_{i-j}-W_{i-ref}) represents the difference between each value of risk factor and its reference value;
Risk points = $Beta_{risk\ factor}$*(W_{i-j}-W_{i-ref})/$Beta_{age-10}$.

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and 9,732 patients without ablation (see Fig. 1 and **Table S1** in the Data in Brief). After PS-matching, a total of 1,574 patients were studied for constructing a model-based scoring system. The baseline characteristics of Cohort 1 (mean age: 54.5 years, 30% of them were women) are summarized in Table 1 and **Table S2** in the Data in Brief. This study identified 237 stroke events (25.5% in the non-ablation group and 4.6% in the AF ablation group) during a mean follow-up duration of 7.8 ± 3.4 years.

Significant risk factors in the multivariate Cox regression model are summarized in Table 1. The new "AF-CA-Stroke" score to estimate stroke risks in patients with AF was developed according to the survival function at 1, 5, 10 years. Depending on the 1-year increment of baseline beta coefficient change in age, up to 5 points were assigned for the following age groups: <35 years: 0, 35–44 years: 1, 45–54 years: 2, 55–64 years: 3, 65–74 years: 4, and ≥ 75 years: 5 points (Table 2). The AF-CA-Stroke scoring system includes other important clinical risk factors, such as ablation status (point = 4), prior history of stroke (point = 4), chronic kidney disease (point = 2), diabetes mellitus (point = 1), and congestive heart failure (point = 1) (Table 2). The absolute risk function that predicts the 1-, 5-, 10-year stroke rates by calculating the AF-CA-Stroke scores and 1-year stroke rates of the $CHADS_2$ and CHA_2DS_2-VASc scores are summarized in Fig. 2 **and** Table 3.

Because information regarding the AF subtypes, AF recurrences, methods of AF ablation were not available in the NHIRD study (AF types were available only in AF ablation group in Cohort 1). Hence, we used AF-related admissions as the surrogate of AF recurrences. The AF-related admission rates were 55.4% vs. 34.2% in the non-ablation vs. ablation groups in Cohort 1 (P < 0.001; **Table S2** in the Data in Brief). In the sub-analysis of this study using the TVGH AF ablation dataset in Cohort 1, when adjusting for multi-variate risk factors of age, sex, risk scores (including: various status of underlying diseases), and anti-coagulant uses (warfarin and non-vitamin K antagonist oral anticoagulants [NOAC]), AF-related admissions in AF ablation group did not significantly affect the incident stroke risk: HR = 5.39 (95% CI: 0.57–50.8), P = 0.14. In the ablation group, AF patients with persistent AF (15.2%; **Table S2** in the Data in Brief) were not associated with increased stroke risk in this study: HR = 1.47 (95% CI: 0.72–3.00), P = 0.29. In addition, the uses of warfarin (HR = 0.69, 95% CI: 0.13–3.64, P = 0.66) and NOAC (HR = 0.73, 95% CI: 0.15–3.66, P = 0.70) were not associated with increased future stroke risk.

3.2. Validation AF Cohort (Cohort 2)

In Cohort 2, a total of 1,897 (1.3%) patients with AF underwent catheter ablation (**Table S3** in the Data in Brief). A total of 46,863 stroke events were identified from the total of 147,225 patients with AF (32.1% in non-ablation group and 14.5% in AF ablation group) during a mean follow-up of 5.1 ± 3.2 years. Fig. 2**C** demonstrates the trends of stroke rates of estimated 1-year rates (%) and observed rates (per 100 person-years). The validation study showed that discrimination abilities of category-free NRI (NRI: 0.251, P < 0.001) were significantly higher and the absolute IDI (IDI: 0.01, P = 0.79) was similar in the AF-CA-Stroke score as compared with the CHA_2DS_2-VASc score system (**Table S4 and S6** in the Data in Brief). The discrimination ability of AF-CA-Stroke score in terms of AUCs for predicting the 1-, 5-, 10-year incident stroke risks was significantly higher than that of conventional score systems in both Cohorts 1 and 2 (all P < 0.001; Fig. 3). The estimated AUCs using the AF-CA-Stroke score was 0.845 (95% confidence interval [CI]: 0.824–0.865) in Cohort 1 and 0.649 (95% CI: 0.646–0.652) in Cohort 2 (Fig. 3 **and Table S4** in the Data in Brief). Youden indices indicated that the best cut-off-values predicting the incident stroke event were ≥ 5, ≥1, and ≥ 3 in the AF-CA-Stroke, $CHADS_2$, and CHA_2DS_2-VASc scoring systems, respectively (Table 3).

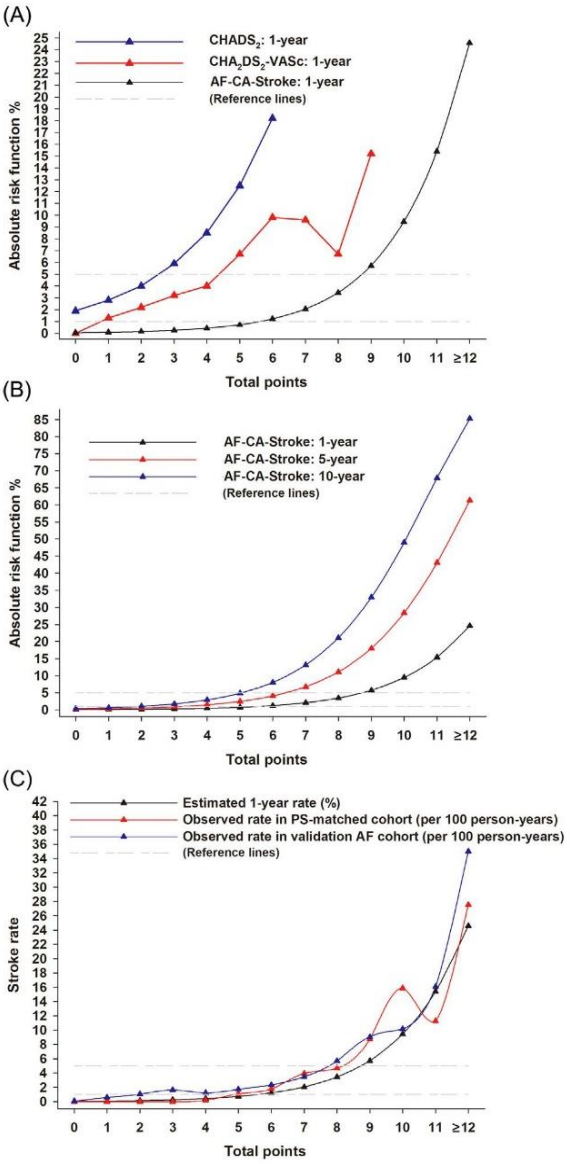

Fig. 2. Risk functions of: (A) the comparisons of estimated 1-year risks among various scoring systems depending on the total points, (B) estimated 1-, 5-, 10-year risks of the AF-CA-Stroke score, and (C) comparisons between estimated 1-year rate and observed stroke rate (per 100 person-years) of the AF-CA-Stroke score in Cohort 1 and Cohort 2.

3.3. Distributions among various scoring systems and incident stroke risks

Fig. 4 summarizes the score distributions and stroke events among various soring systems with and without ablation. The average AF-CA-Stroke scores in the ablation group were similar between Cohorts 1 and 2 (Fig. 4**A & 4D**). In the Cox proportional hazard model, subgroup analysis on various AF-CA-Stroke scores showed that scores of ≥ 5 had significantly higher risk of future stroke (P for trend < 0.001; **Figure S1** in the Data in Brief). Based

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on the risk assessment of stroke at 1 year, patients with total points of AF-CA-Stroke scores between 0 and 4 were identified as low stroke risk, 5–8 points as moderate stroke risk, and > 8 points as high stroke risk. **Figure S2** in the Data in Brief shows the results of survival analyses based on various score groups categorized by the AF-CA-Stroke scores. In addition, one increment of the AF-CA-Stroke score contributed to 37% increased stroke risk in patients with AF (HR: 1.37, 95% CI: 1.36–1.38; P < 0.001) (in the non-ablation group, HR: 1.38, 95% CI: 1.37–1.39; and in the AF-ablation group, HR: 1.64, 95% CI: 1.55–1.75).

Table 4 summarizes accurate stroke rates during the 1-, 5-, 10-year follow-up periods based on risk groups of scoring systems and ablation status in Cohorts 1 and 2. For all patients with AF, 0.1%, 0.2%, and 0.4% incident strokes occurred during 1-, 5-, 10-year follow-up periods in Cohort 1, and 1.9%, 5.0%, and 6.7% incident strokes occurred during 1-, 5-, 10-year follow-up periods in Cohort 2, respectively, as identified by AF-CA-Stroke scores of < 5 (low risk). In contrast, 1.9%, 6.0%, and 10% incident strokes occurred during 1-, 5-, 10-year follow-up periods in Cohort 1, and 5.9%, 14.4%, and 18.4% during 1-, 5-, 10-year follow-up periods in Cohort 2, respectively, based on CHA_2DS_2-VASc scores of < 2 (low risk).

In Cohort 2 (Fig. 4**D-4F**, Table 4), a total of 33.4% patients with AF ablation with CHA_2DS_2-VASc scores of ≥ 2 were identified. However, 18.1% of patients with AF ablation were identified as AF-CA-Stroke scores of ≥ 5. For the AF ablation group, 2.5%, 18.3%, and 66.7% of patients developed incident strokes within 1 year in the low-, moderate-, high-risk groups according to AF-CA-Stroke scores, respectively (Table 4). Conversely, 2.3%, 9.7%, and 64.3% of patients developed incident strokes within 1 year in the low-, moderate-, high-risk groups according to CHA_2DS_2-VASc scores, respectively.

4. Discussions

4.1. Primary findings

This study developed a novel model-based point scoring system (AF-CA-Stroke score) to predict incident stroke events in patients with AF based on six clinical variables using a matched AF cohort. Risk functions to predict the 1-, 5-, 10-year estimated stroke risks were reported. The accurate stroke trends in both PS-matched and AF validation cohorts were nearly matched to the 1-year estimated risk function according to AF-CA-Stroke scores were demonstrated. The AF-CA-Stroke score had significantly higher decimation abilities in predicting 1-year, 5-year, and 10-year incident stroke events than conventional score systems.

4.2. Effects of various age groups and comorbidities on stroke risks

Evidences revealed that the incidence of AF increased with aging, which also led to worse prognosis, incident stroke events, and higher mortality in patients with AF [22]. Most developed countries have accepted the age of 65 years as a definition of elderly. Ages 60 and 65 years are often used, despite its arbitrary nature. Currently, the $CHADS_2$ system includes age ≥ 75 years as 1 point [10], the CHA_2DS_2-VASc set age ≥ 65 years as 1 point and ≥ 75 years as 2 points in predicting future stroke risk in patients with AF [10]. However, to identify the risk of stroke in patients with AF, aging and incident comorbidities are generally a complex issue, and previous studies had difficulties in discussing this issue. A meta-analysis concluded that age as a criterion in patients with AF shall not be simply considered based on gender or age stratifications of ≥ 65/≥75 years [23]. Age and comorbidities mutually impact the stroke risks in patients with AF [4,24,25]. Taipei Group described that a younger age of > 50 years had an increased stroke risk even without comorbidity based on the NHIRD analysis in Taiwan, and stroke risks vary based on the status of comorbidities in various age groups [25,26]. In the current study, the model-based scoring system depending on the baseline beta coefficient changes in age was constructed, with up to 5 points being assigned to the age groups, and a total of > 12 points were established in our novel AF-CA-Stroke scoring system. This newly developed AF-CA-Stroke score can provide more flexibility in predicting long-term stroke risks in patients with AF in various age groups and conditions regardless of gender.

4.3. Managing stroke risks in patients with AF and the impact of catheter ablation

Several stroke prediction models have been developed and validated by previous studies [10,11,27–29]. For the management of stroke risks in patients with AF, both European and American guidelines recommend to use $CHADS_2$ and CHA_2DS_2-VASc scoring systems to determine an optimal strategy of stroke prevention [10,11]. Chao, TF, et al. demonstrated that AF patients in Asian with CHA_2DS_2-VASc score of 0 had a truly low stoke risk than $CHADS_2$

Table 3
Total points and absolute risk functions for various scoring systems.

AF-CA-Stroke				$CHADS_2$		CHA_2DS_2-VASc	
Total points	1-year estimated risk (%)	5-year estimated risk (%)	10-year estimated risk (%)	Total points	1-year estimated risk (%)	Total points	1-year estimated risk (%)
0	0.05%	0.18%	0.36%	**0**	1.90%	**0**	0.00%
1	0.09%	0.30%	0.61%	**1***	2.80%	**1**	1.30%
2	0.15%	0.51%	1.02%	**2**	4.00%	**2**	2.20%
3	0.26%	0.86%	1.72%	**3**	5.90%	**3***	3.20%
4	0.43%	1.44%	2.88%	**4**	8.50%	**4**	4.00%
5*	0.72%	2.42%	4.82%	**5**	12.5%	**5**	6.70%
6	1.22%	4.05%	7.99%	**6**	18.2%	**6**	9.80%
7	2.05%	6.73%	13.1%			**7**	9.60%
8	3.43%	11.1%	21.1%			**8**	6.70%
9	5.71%	18.0%	32.9%			**9**	15.2%
10	9.44%	28.4%	49.0%				
11	15.2%	43.1%	67.9%				
≥12	≥24.6%	≥61.3%	≥85.3%				

*Best cut-of-value predicting incident stroke event by calculating the Youden index of the area under receive operating characteristic curve: Sensitivity + Specificity −1.
$CHADS_2$: congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (1 point), diabetes mellitus (1 point), stroke (2 points);
CHA_2DS_2-VASc: congestive heart failure (1 point), hypertension (1 point), age ≥ 65 years (1 point), age ≥ 75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular diseases (1 point), female (1 point);
AF-CA-Stroke: refer to Table 2.

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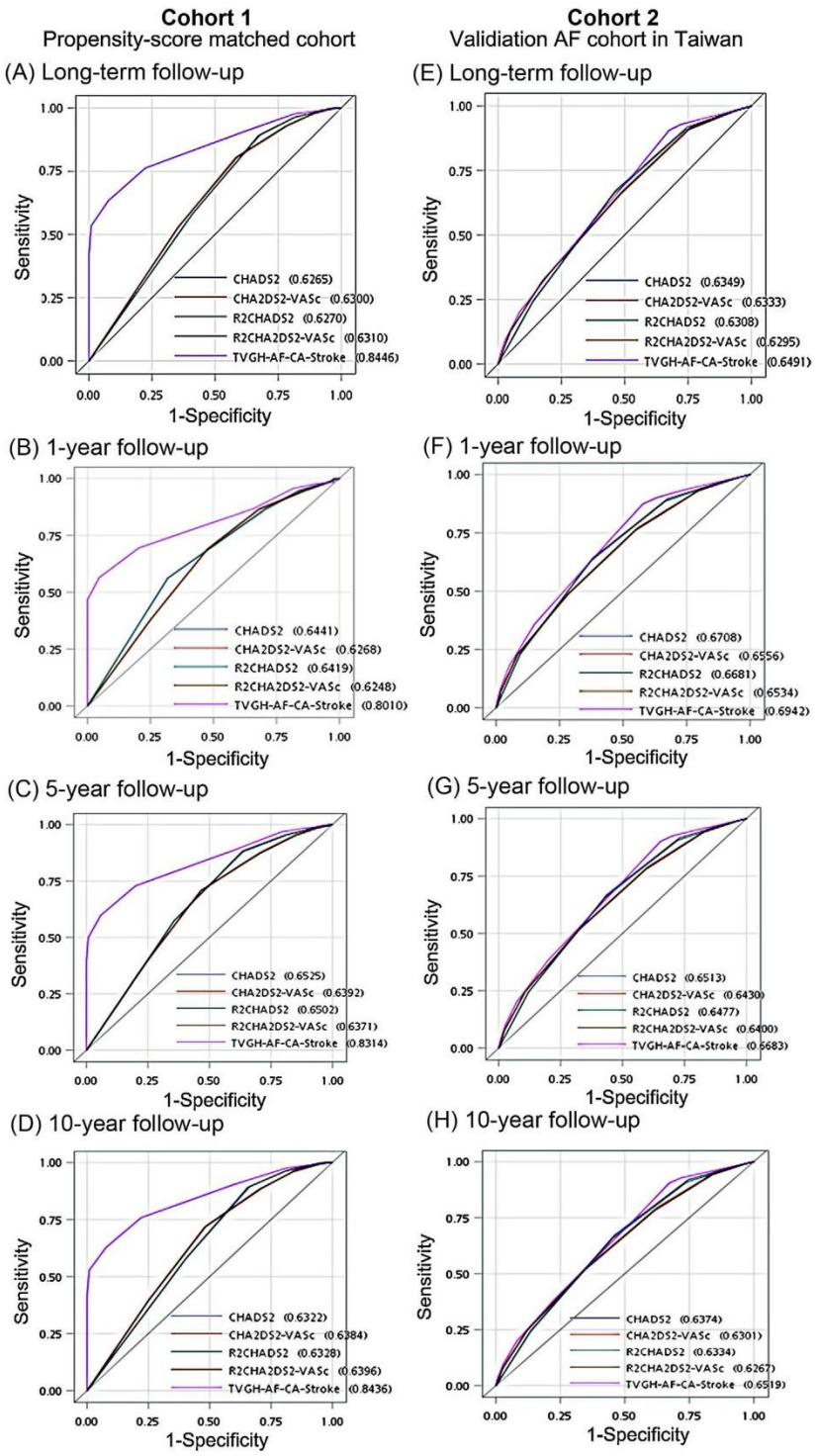

Fig. 3. Discrimination abilities of area under receive operating characteristic curves (ROC) for the propensity-score matched cohort (Cohort 1) during (A) long-term, (B) 1-year, (C) 5-year, and (D) 10-year follow-up ($P < 0.001$ when AF-CA-Stroke score compares with other all scores); and for the validation AF cohort (Cohort 2) during (E) long-term, (F) 1-year, (G) 5-year, and (H) 10-year follow-up ($P < 0.001$ when AF-CA-Stroke score compares with other all scores).

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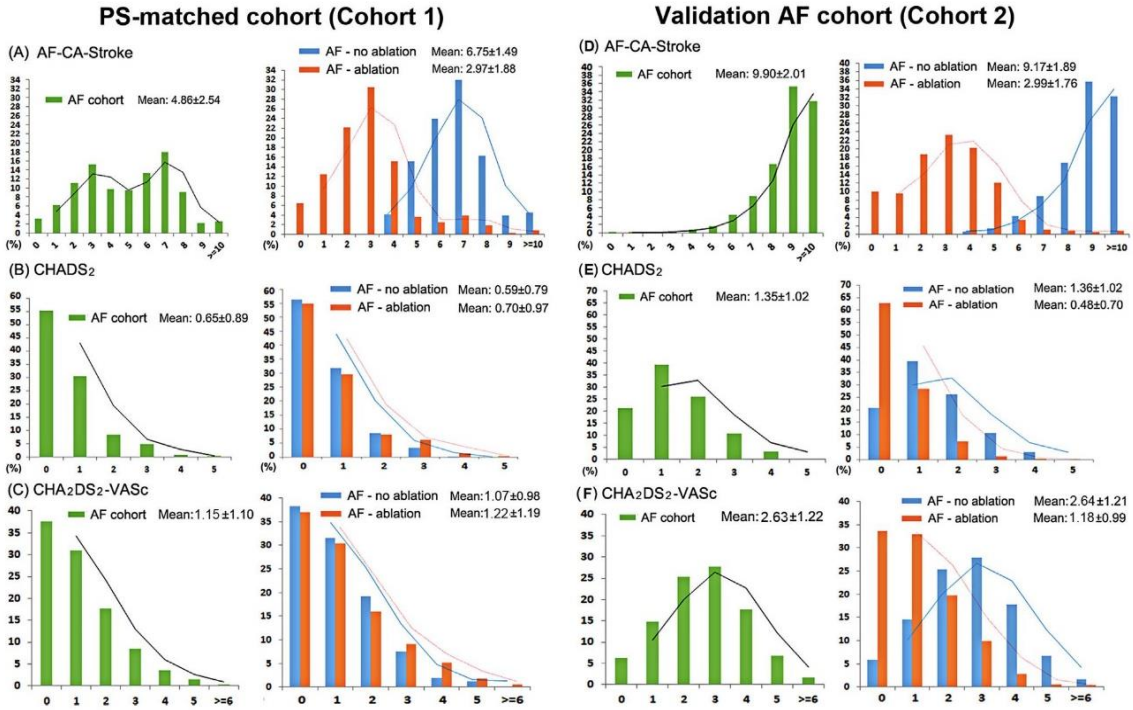

Fig. 4. Distributions among various soring systems and AF groups in the propensity-score (PS) matched cohort, for the scoring systems of (A) AF-CA-Stroke, (B) $CHADS_2$, and (C) CHA_2DS_2-VASc; and in the validation AF cohort in Taiwan, for the scoring systems of (D) AF-CA-Stroke, (E) $CHADS_2$, and (F) CHA_2DS_2-VASc. Trend line: moving average of stroke rate by every 2-unit score.

score, and CHA_2DS_2-VASc score might be used for stroke risk stratification in Asians as with Caucasians [29]. Previous studies suggested that patients with AF ablation with $CHADS_2$ score of "0" or CHA_2DS_2-VASc score of < 2 were indeed classified as low stroke risk [13], especially in patients with AF ablation [12,14].

In the era of catheter ablation, several observational studies in different countries have reported that AF ablation was an effective therapy in AF patients at various ages with multiple co-morbidities [30,31]. In AF patients receiving ablation, they had significantly decreased risks of stroke, AF-related complications, and mortality than AF patients receiving antiarrhythmic drugs but without AF ablation [32,33]. In the largest randomized (CABANA) trial for comparing the effects between antiarrhythmic drugs and AF ablation by using intention-to-treat analysis, AF ablation did not significantly reduce stroke risks in AF ablation group [34]. The reason of non-significant ablation effect on reducing stroke risk could be the crossovers between antiarrhythmic drugs and AF ablation during follow-up, which may affect the final outcomes.

This study firstly showed that the status of receiving AF ablation is a significant factor in the new scoring system with equivalent scores of 4 points in the risk stratification of the future stroke risk. Second, when assessing the risk of stroke after an ablation in low-risk patients based on AF-CA-Stroke scores, 19.5% in Cohort 1 and 15.3% in Cohort 2 were classified as moderate-to-high-risk group based on CHA_2DS_2-VASc scores, but classified as a low-risk group based on AF-CA-Stroke scores. The long-term outcome in terms of cardiovascular risk was confirmed (Table 4). In Cohort 1, the 1-year stroke rate was 0% for patients with AF ablation in the low-risk group according to AF-CA-Stroke and CHA_2DS_2-VASc score; whereas in Cohort 2, the 1-year stroke rates were 2.3–2.5% based on AF-CA-Stroke and CHA_2DS_2-VASc scores. That is, both AF-CA-Stroke and CHA_2DS_2-VASc scores can be used for assessing low stroke risk in AF patients in Asia. Based on the AF-CA-Stroke score, around 80–85% patients may take benefits form AF ablation procedures with lower stroke risks, and they may not be necessary to receive oral anticoagulants after receiving successful AF ablations (however, only around 65% AF patients were grouped as low risk group based on the CHA_2DS_2-VASc scores in this study). We suggest that long-term anticoagulants may be discontinued in around 80% of patients with AF ablation based on AF-CA-Stroke scores, irrespective of the recurrence state of ablation.

4.4. Limitations

This were several limitations in this study. First, the diagnoses were based on ICD-9-CM codes, which were established by the physicians and re-confirmed by a certified coding specialist, we could not exclude the possibility of miscoding. Second, information regarding the AF subtypes, AF recurrences, methods of AF ablation were not available in this study. Whether the above-mentioned status might affect the stroke outcome remains unclear. However, in the sub-analysis of this study using the TVGH AF ablation dataset in Cohort 1 (AF types were available only in AF ablation group in Cohort 1), AF patients with persistent AF were not associated with increased stroke risk. And we used AF-related admissions as the surrogate of AF recurrences, AF-related admissions in AF ablation group did not significantly affect the incident stroke risk. Third, the uses of medications such as anti-coagulation and anti-arrhythmic drugs may affect the stroke outcomes. However, due to this study was a cohort study, medication uses varied among patients. Besides, the study aim was to demonstrate a scoring system using the conventional risk factors plus the status of catheter

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Table 4
Stroke rates during various follow-up periods based on risk groups and ablation status in Cohort 1 and Cohort 2.

All patients	AF-CA-Stroke score				CHA_2DS_2-VASc			
	Scores: 0–4	Scores: 5–8	Scores: >8	All	Scores: 0–1	Scores: 2–4	Scores: >4	All
PS-matched cohort (Cohort 1)	N = 716 (45.5%)	N = 783 (49.7%)	N = 75 (4.8%)	N = 1574	N = 1080 (68.7%)	N = 465 (29.5%)	N = 29 (1.8%)	N = 1574
1-year stroke	0.1%	4.7%	10.7%	2.8%	1.9%	4.5%	6.9%	2.8%
5-year stroke	0.2%	14.2%	38.7%	8.9%	6.0%	14.2%	31.0%	8.9%
10-year stroke	0.4%	22.7%	56.0%	14.2%	10.0%	21.5%	51.7%	14.2%
Validation cohort (Cohort 2)	N = 2525 (1.7%)	N = 45931 (31.2%)	N = 98769 (67.1%)	N = 147225	N = 30871 (21.0%)	N = 104015 (70.6%)	N = 12339 (8.4%)	N = 147225
1-year stroke	1.9%	7.0%	18.3%	14.5%	5.9%	14.7%	34.4%	14.5%
5-year stroke	5.0%	17.3%	33.2%	27.8%	14.4%	28.5%	55.1%	27.8%
10-year stroke	6.7%	21.8%	36.6%	31.5%	18.4%	32.2%	58.4%	31.5%
AF – no ablation	AF-CA-Stroke score				CHA_2DS_2-VASc			
	Scores: 0–4	Scores: 5–8	Scores: >8	All	Scores: 0–1	Scores: 2–4	Scores: >4	All
PS-matched cohort (Cohort 1)	N = 33 (4.2%)	N = 688 (87.4%)	N = 66 (8.4%)	N = 787	N = 550 (69.9%)	N = 227 (28.8%)	N = 10 (1.3%)	N = 787
1-year stroke	1.0%	4.3%	10.6%	4.6%	3.8%	6.6%	0.0%	4.6%
5-year stroke	4.1%	13.7%	37.9%	15.1%	11.8%	22.5%	30.0%	15.1%
10-year stroke	8.6%	21.7%	51.5%	23.8%	19.6%	32.6%	50.0%	23.8%
Validation cohort (Cohort 2)	N = 972 (0.7%)	N = 45599 (31.3%)	N = 98757 (68.0%)	N = 145328	N = 29607 (20.4%)	N = 103396 (71.1%)	N = 12325 (8.5%)	N = 145328
1-year stroke	1.0%	6.9%	18.3%	14.6%	6.1%	14.7%	34.3%	14.6%
5-year stroke	2.6%	17.2%	33.2%	28.0%	14.7%	28.5%	55.1%	28.0%
10-year stroke	3.7%	21.7%	36.6%	31.7%	18.8%	32.2%	58.4%	31.7%
AF – ablation	AF-CA-Stroke score				CHA_2DS_2-VASc			
	Scores: 0–4	Scores: 5–8	Scores: >8	All	Scores: 0–1	Scores: 2–4	Scores: >4	All
PS-matched cohort (Cohort 1)	N = 683 (86.8%)	N = 95 (12.1%)	N = 9 (1.1%)	N = 787	N = 530 (67.3%)	N = 238 (30.3%)	N = 19 (2.4%)	N = 787
1-year stroke	0.0%	7.4%	22.2%	1.0%	0.0%	2.5%	10.5%	1.0%
5-year stroke	0.0%	18.1%	44.4%	2.7%	0.0%	6.3%	31.6%	2.7%
10-year stroke	0.0%	29.7%	88.9%	4.6%	0.0%	10.9%	52.6%	4.6%
Validation cohort (Cohort 2)	N = 1553 (81.9%)	N = 332 (17.5%)	N = 12 (0.6%)	N = 1897	N = 1264 (66.6%)	N = 619 (32.7%)	N = 14 (0.7%)	N = 1897
1-year stroke	2.5%	18.3%	66.7%	5.2%	2.3%	9.7%	64.3%	5.2%
5-year stroke	6.5%	29.1%	75.0%	11.5%	6.1%	21.2%	78.6%	11.5%
10-year stroke	8.6%	31.4%	75.0%	14.4%	8.7%	24.6%	78.6%	14.4%

AF: atrial fibrillation; PS: propensity-score.

ablation for stroke management, as a result, we did not consider the effects of medication uses for constructing the scoring system. Finally, changes in therapy may occur over time due to changed status of ablation, underlying diseases, and age, the AF-CA-Stroke score shall be re-assessed annually. Because of lacking data on the comparisons between the novel and conventional scoring systems, it is difficult to conclude that the new scoring system might generate when applied to other populations. However, we provided 1-year, 5-year, and 10-year outcomes using a nationwide cohort with validation to support our study findings.

The large number of population-based AF cohort and the long-term follow-up were the advantages of our study in constructing a clinical model-based scoring system. The status of AF ablation in the PS-match cohort was provided by a medical center in Taiwan, and then, the cohort was linked to the NHIRD, regardless ablation outcomes of the study patients. The ablation strategy and the outcome may be different among centers; nevertheless, we still exhibited good discrimination ability for risk stratifications of stroke in patients with AF as calculated using the new scores.

5. Conclusion

A newly constructed clinical model-based point scoring system is useful in identifying risk stratifications of stroke in patients with AF using clinical factors, including various age stratifications and catheter ablation status. These clinical factors shall be considered as risk stratification for stroke prevention.

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Declaration of Competing Interest

None of the authors have any conflicts of interest or financial relationships related to the study.

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Dear Dr. Lin:

It is a pleasure to accept your manuscript entitled "Risks of Ventricular Tachyarrhythmia and Mortality in Patients with Amyloidosis– A Long-term Cohort Study" in its current fo Sinica.

Thank you for your fine contribution. On behalf of the Editors of the Acta Cardiologica Sinica, we look forward to your continued contributions to the Journal. You will receive g future.

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Risks of Ventricular Tachyarrhythmia and Mortality in Patients with Amyloidosis – A Long-Term Cohort Study

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Background: The presence of ventricular tachycardia (VT) is associated with higher mortality. The annual incidence of VT after a diagnosis of amyloidosis and the associated cardiovascular (CV) outcomes have not been well assessed in a large cohort.

Methods: A total of 12,139 amyloidosis patients were identified from the Taiwan National Health Insurance Research Database. Non-amyloidosis group was matched 1:1 for age, gender, hypertension, and diabetes mellitus (DM) to the amyloidosis group using a propensity score. Analysis of the risk of CV outcomes was conducted. We also analyzed the incidence of cardiac amyloidosis (CA).

Results: The incidence rates of amyloidosis and CA were 6.54 and 0.61 per 100,000 person-years, respectively. Multivariable analysis revealed that the risk of VT was higher in both the amyloidosis [hazard ratio (HR): 7.90; 95% confidence interval (CI): 4.49-13.9] and CA (HR: 153.3, 95% CI: 54.3-432.7) groups. In the amyloidosis group, the risk of heart failure (HF)-related hospitalization, CV death, and all-cause death was also higher. Amyloidosis was associated with a higher CV mortality rate following VT (HR: 1.50; 95% CI: 1.07-2.12). The onset of a new VT event in patients with amyloidosis was associated with HF, DM, chronic liver disease, and anti-arrhythmic drug use.

Conclusions: In this nationwide cohort study, the incidence rates of amyloidosis and CA were 6.54 and 0.61 per 100,000 person-years, respectively. The long-term risks of VT and CV mortality were higher in the patients with amyloidosis and CA. The patients with amyloidosis had a poorer prognosis following VT events, highlighting the importance of continuous monitoring in these patients.

Key Words: Amyloidosis • Cardiomyopathy • Cardiovascular death • Ventricular tachyarrhythmia

INTRODUCTION

Amyloidosis is a rare disorder of protein misfolding that is characterized by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs.[1] However, not every misfolded protein fibril is deposited in the heart of an individual with amyloidosis. Most cases of cardiac amyloidosis (CA) are caused by one of two proteins, light chain (AL) or transthyretin (ATTR). Embedded amyloid fibrils in the heart cause stiffness and proteotoxicity to the myocardium, which results in heart failure (HF), arrhythmia, and sudden cardiac death.[2] In

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one case series, 62% of ATTR amyloidosis patients had atrial fibrillation (AF).[3] The incidence of ventricular tachycardia (VT) and the associated outcomes in patients with amyloidosis, however, are not well-documented.

This study aimed to explore the incidence of new-onset VT and cardiovascular (CV) outcomes in patients with amyloidosis after long-term follow-up using a representative national cohort, and also to assess the outcomes of VT in these patients. The risk factors contributing to VT were also evaluated, which has not been explored in previous studies.

METHODS

Database

In this study, we used the Taiwan National Health Insurance Research Database (NHIRD) to investigate the risks of VT and CV events in patients with amyloidosis during long-term follow-up (2000 to 2016). The Taiwan Collaboration Centre of Health Information Application, Ministry of Health and Welfare, provided the entire dataset used for this study. The National Health Insurance program in Taiwan covers 27 million people and over 99% of the total population. The NHIRD includes information on outpatient visits, hospitalizations and prescribed medications. We also used data from the National Death Registry, which contains information on the primary and contributing causes of death, as well as the date of death for all citizens. Previous studies have verified the accuracy of the coding.[4,5] The study protocol was reviewed and approved by our institutional review board (IRB Number: 2021-09-014BC). Additionally, we obtained permission from the National Research Institute for the Department of Health and the Health Promotion Administration, Ministry of Health and Welfare.

Study design and participants

The study flow chart of this retrospective, cohort, population-based study is shown in Supplementary Figure 1. A total of 12,139 patients aged 18-85 years diagnosed with amyloidosis between 2000 and 2006 were identified from the NHIRD, using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 277.3. Co-morbidities were obtained from the medical claims data based on ICD-9-CM codes. All of the enrolled patients had a diagnosis of amyloidosis documented at least twice in outpatient records or at least once in inpatient records. CA was defined as amyloidosis coupled with one of the possible cardiac manifestations of amyloidosis, including HF, cardiomyopathy, or AF.[6,7]

VT was defined as ventricular tachycardia, ventricular flutter and fibrillation, and cardiac arrest (ICD 9-CM: 427.1, 427.4, and 427.5, respectively). The study excluded patients with an implantable cardioverter defibrillator, prior history of tuberculosis (ICD 9-CM code: 011.9), those with other systemic inflammatory diseases or connective tissue disorders [ICD-9-CM codes: Reiter's syndrome (099.3), Hodgkin disease (201.9), multiple myeloma (203.0), familial Mediterranean fever (277.31), Crohn's disease (555), ulcerative colitis (556), systemic lupus erythematosus (710), rheumatoid arthritis (714), and ankylosing spondylitis (720.0)], and those with VT.

An independent control group of 150,000 individuals without a diagnosis of amyloidosis during the induction period of five years, without prior structural heart disease, and aged 18-85 years was selected between 2000 and 2006 for comparison. Propensity score (PS) was used to match the same number of controls with the same number of amyloidosis patients to minimize the impact of imbalanced distributions between cases and controls (Supplementary Figure 1).

Furthermore, we collected data regarding the following characteristics: age (years), sex, hypertension (ICD-9-CM codes: 401-405), diabetes mellitus (DM) (ICD-9-CM code: 250), chronic obstructive pulmonary disease (ICD-9-CM codes: 490-496), chronic kidney disease (ICD-9-CM codes: 584-585), congestive heart failure (ICD-9-CM code: 428), hyperlipidemia (ICD-9-CM code: 272), thyroid diseases (ICD-9-CM code: 242), prior acute coronary diseases (ICD-9-CM codes: 410-411), prior stroke (ICD-9-CM codes: 430-438), chronic liver disease (ICD-9-CM code: 571), and cancer (ICD-9-CM codes: 140-208).

Study endpoints during follow-up

The follow-up period ended when the subjects died or had CV outcomes beyond 2015. Study outcomes included time to new-onset VT, AF-related hospitalization, HF-related hospitalization, CV death (ICD-9-CM codes: 390-450), cardiac death (ICD-9-CM codes: 390-429), and all-cause mortality. HF-related hospitalization was de-

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fined as hospitalization for either a primary diagnosis of HF or with HF as one of the first two secondary diagnoses (ICD-9-CM codes: 428, 428.0, 428.1, and 428.9). Time to implantation of a pacemaker or implantable cardioverter-defibrillator (ICD) implantation was checked. The National Death Registry in Taiwan was used to confirm deaths, and mortality data were traced until the end of 2016.

Statistical analysis

The Student's t-test was used to compare normally distributed continuous variables, while the Mann-Whitney U test was used to compare non-normally distributed continuous variables. Categorical values were expressed as absolute numbers (n) and percentages (%), and statistical comparisons were performed using the chi-square test. Incidence rates were calculated as the number of cases per 10,000 person-years (PYs). Confounders were minimized using 1:1 PS matching. Age, sex, hypertension, and DM were matched 1:1 under identical PS with a 0.15 caliper.

Event-free survival curves were plotted using the Kaplan-Meier method, and the significance of the results was determined using the log-rank test. Conditional Cox proportional hazards regression analysis was used to compare hazard ratio (HR) with 95% confidence intervals (CIs) for the outcomes. Multivariable analysis was used to identify the independent predictors of new-onset VT and mortality during the long-term follow-up. Two different models were used to adjust for potential confounders (Model 1: age and sex; Model 2: Model 1 plus hypertension, DM, congestive HF, hyperlipidemia, chronic kidney disease, liver disease, chronic obstructive pulmonary disease, thyroid disease, prior coronary artery disease, prior stroke, and cancer). A two-tailed alpha level of < 0.05 was considered statistically significant. The analysis was conducted using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

In total, 12,139 patients with amyloidosis and the same number of non-amyloidosis subjects were identified between 2000 and 2006 (Supplementary Figure 1). The incidence rate of amyloidosis was 6.54/100,000 person-years. The baseline characteristics are shown in Table 1. Of the 12,139 patients, 1,130 met the criteria of CA, and the incidence rate was 0.61/100,000 person-years. Compared to the patients with non-cardiac amyloidosis, those with CA were older, more predominantly male, and had a greater number of comorbid conditions (Table 2).

Incidence of cardiovascular events

The incidence rate of VT was 8.57 per 10,000 PYs in the amyloidosis group, and 3.37 per 10,000 PYs in the control group ($p = 0.014$) after a median follow-up of 12 years (interquartile range:11.3-12.0) (Table 3). The incidence rates of AF-related hospitalization (30.2 vs. 11.0 per 10,000 PYs), HF-related hospitalization (53.9 vs. 21.2 per 10,000 PYs), CV death (53.0 vs. 33.1 per 10,000 PYs), and all-cause mortality (229.9 vs. 154.5 per 10,000 PYs) were higher in the patients with amyloidosis than in the controls (Table 3).

Compared to the patients with non-cardiac amyloidosis, the incidence of VT was significantly higher among those with CA (113.8 vs. 0.69 per 10,000 PYs) (Table 4). The incidence rates of CV death (495.2 vs. 31.3 per 10,000 PYs) and all-cause mortality (1532.9 vs. 165.9 per 10,000 PYs) were also higher in the patients with CA than in those with non-cardiac amyloidosis.

Cardiovascular outcomes

Supplementary Figures 2A-E show the Kaplan-Meier event-free survival curves for new-onset VT events, AF, HF admission, CV death, and all-cause mortality of the patients with and without amyloidosis. Compared to the control group, the amyloidosis group had a higher rate of new-onset VT events ($p < 0.001$, Supplementary Figure 2A), AF ($p < 0.001$, Supplementary Figure 2B), HF-related admission ($p < 0.001$, Supplementary Figure 2C), CV death ($p < 0.001$, Supplementary Figure 2D), and all-cause mortality ($p < 0.001$, Supplementary Figure 2E). Notably, the risk of new-onset VT in the two groups was comparable during the first 7.5 years, and then diverged later (Supplementary Figure 2A).

After multivariable adjustments, an increased risk of VT events was observed in the patients with amyloidosis (adjusted HR: 7.90, 95% CI: 4.49-13.9; $p < 0.001$). In addition, the patients with amyloidosis had a higher risk of

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Table 1. Baseline characteristics of the study population

Variables	Original cohort			Propensity-score matched cohort		
	No amyloidosis (N = 106648)	Amyloidosis (N = 12139)	p value	No amyloidosis (N = 12139)	Amyloidosis (N = 12139)	p value
Age (years)	49.8 ± 17.6	52.1 ± 16.1	< 0.001	52.1 ± 16.1	52.1 ± 16.1	> 0.99
Male gender (n, %)	45509 (42.7%)	5971 (49.2%)	< 0.001	5971 (49.2%)	5971 (49.2%)	> 0.99
Cardiac amyloidosis (diagnosis during follow-up; n, %)	0 (0.00%)	1130 (9.31%)	< 0.001	0 (0.00%)	1130 (9.31%)	< 0.001
Underlying diseases (n, %)						
Hypertension	48951 (45.9%)	5024 (41.4%)	< 0.001	5024 (41.4%)	5024 (41.4%)	> 0.99
Diabetes mellitus	24037 (22.5%)	2348 (19.3%)	< 0.001	2348 (19.3%)	2348 (19.3%)	> 0.99
Atrial fibrillation	1098 (1.03%)	2 (0.02%)	< 0.001	123 (1.01%)	2 (0.02%)	< 0.001
Conduction disturbance	174 (0.16%)	0 (0.00%)	< 0.001	18 (0.15%)	0 (0.00%)	< 0.001
Cardiomyopathy	253 (0.24%)	4 (0.03%)	< 0.001	27 (0.22%)	4 (0.03%)	< 0.001
Coronary artery disease	1576 (1.48%)	0 (0.00%)	< 0.001	161 (1.33%)	0 (0.00%)	< 0.001
Stroke/TIA	10948 (10.3%)	13 (0.11%)	< 0.001	1208 (10.0%)	13 (0.11%)	< 0.001
Congestive heart failure	4052 (3.80%)	18 (0.15%)	< 0.001	431 (3.6%)	18 (0.15%)	< 0.001
Valvular heart disease	1084 (1.02%)	3 (0.02%)	< 0.001	93 (0.77%)	3 (0.02%)	< 0.001
Chronic kidney disease	2429 (2.28%)	59 (0.49%)	< 0.001	272 (2.24%)	59 (0.49%)	< 0.001
Hyperlipidemia	21786 (20.4%)	28 (0.23%)	< 0.001	2311 (19.0%)	28 (0.23%)	< 0.001
Hyperuricemia	12510 (11.7%)	19 (0.16%)	< 0.001	1439 (11.9%)	19 (0.16%)	< 0.001
Chronic liver disease	16907 (15.9%)	48 (0.40%)	< 0.001	1970 (16.2%)	48 (0.40%)	< 0.001
COPD	20227 (19.0%)	26 (0.21%)	< 0.001	2479 (20.4%)	26 (0.21%)	< 0.001
Thyroid disease	2118 (1.99%)	7 (0.06%)	< 0.001	243 (2.00%)	7 (0.06%)	< 0.001
Cancer	6034 (5.66%)	47 (0.39%)	< 0.001	776 (6.39%)	47 (0.39%)	< 0.001
Medication uses (n, %)						
ACEi	31220 (29.3%)	3380 (9.77%)	0.001	3198 (26.3%)	3380 (27.8%)	0.009
ARB	28081 (26.3%)	3220 (10.3%)	0.64	2811 (23.2%)	3220 (26.5%)	< 0.001
CCB	18984 (17.8%)	2068 (17.0%)	0.037	1894 (15.6%)	2068 (17.0%)	0.003
Beta-blockers	54449 (51.1%)	5274 (47.2%)	< 0.001	6065 (50.0%)	5274 (47.2%)	< 0.001
AADs	7496 (7.03%)	883 (7.27%)	0.32	838 (6.90%)	883 (7.27%)	0.26
AAD: Ia	573 (0.54%)	86 (0.71%)	0.016	60 (0.49%)	86 (0.71%)	0.031
AAD: Ib	3630 (3.40%)	395 (3.25%)	0.39	407 (3.35%)	395 (3.25%)	0.67
AAD: Ic	1236 (1.16%)	182 (1.50%)	0.001	132 (1.09%)	182 (1.50%)	0.005
AAD: III	2854 (2.68%)	366 (3.02%)	0.029	319 (2.63%)	366 (3.02%)	0.07
Anti-platelet	40155 (37.7%)	4462 (36.8%)	0.054	4395 (36.2%)	4462 (36.8%)	0.37
Warfarin	2302 (2.16%)	309 (2.55%)	0.006	239 (1.97%)	309 (2.55%)	0.002

AAD, antiarrhythmic agents; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

AF (adjusted HR: 6.21, 95% CI: 4.38-8.78; p < 0.001), HF-related hospitalization (adjusted HR: 54.7, 95% CI: 37.1-80.7; p < 0.001), CV death (adjusted HR: 5.09, 95% CI: 4.23-6.12; p < 0.001), and all-cause mortality (adjusted HR: 5.11, 95% CI: 4.69-5.57; p < 0.001) (Table 5). The risk of VT in the patients with CA was significantly higher than in those with non-cardiac amyloidosis (adjusted HR: 153.3, 95% CI: 54.3-432.7; p < 0.001). The patients with CA also had a higher risk of CV death (adjusted HR: 1.34, 95% CI: 1.02-1.78; p = 0.04) (Table 6), but not all-cause mortality (adjusted HR: 1.03, 95% CI: 0.88-1.20; p = 0.75).

No ICDs were implanted in the study population during follow-up. The patients with amyloidosis had a higher incidence of pacemaker implantation than those without amyloidosis (1.26% vs. 0.91%; p = 0.008). In addition, more patients with CA had a pacemaker implanted than those with non-cardiac amyloidosis (8.94% vs. 0.47%; p < 0.001).

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Table 2. Baseline characteristics for patients with cardiac amyloidosis and non-cardiac amyloidosis

Variables	Patients with amyloidosis (Total N = 12139)		
	Non-cardiac (N = 11009)	Cardiac (N = 1130)	p value
Age (years)	50.3 ± 15.5	69.1 ± 10.2	< 0.001
Male gender (n, %)	5140 (46.7%)	831 (73.5%)	< 0.001
Underlying diseases (n, %)			
Hypertension	4057 (36.9%)	967 (85.6%)	< 0.001
Diabetes mellitus	1883 (17.1%)	465 (41.2%)	< 0.001
Atrial fibrillation	0 (0.00%)	2 (0.18%)	0.009
Conduction disturbance	0 (0.00%)	0 (0.00%)	Na
Cardiomyopathy	0 (0.00%)	4 (0.35%)	< 0.001
Coronary artery disease	0 (0.00%)	0 (0.00%)	Na
Stroke/TIA	8 (0.07%)	5 (0.44%)	0.005
Congestive heart failure	0 (0.00%)	18 (1.59%)	< 0.001
Valvular heart disease	2 (0.02%)	1 (0.09%)	0.25
Chronic kidney disease	38 (0.35%)	21 (1.86%)	< 0.001
Hyperlipidemia	23 (0.21%)	5 (0.44%)	0.18
Hyperuricemia	15 (0.14%)	4 (0.35%)	0.09
Chronic liver disease	42 (0.38%)	6 (0.53%)	0.45
COPD	17 (0.15%)	9 (0.80%)	< 0.001
Thyroid disease	5 (0.05%)	2 (0.18%)	0.50
Cancer	40 (0.36%)	7 (0.62%)	0.20
Medication uses (n, %)			
ACEi	2643 (24.0%)	737 (65.2%)	< 0.001
ARB	2490 (22.6%)	730 (64.6%)	< 0.001
CCB	1548 (14.1%)	520 (46.0%)	< 0.001
Beta-blockers	4926 (44.7%)	798 (70.6%)	< 0.001
AADs	547 (4.97%)	336 (29.7%)	< 0.001
AAD: Ia	53 (0.48%)	33 (2.92%)	< 0.001
AAD: Ib	293 (2.66%)	102 (9.03%)	< 0.001
AAD: Ic	103 (0.94%)	79 (6.99%)	< 0.001
AAD: III	155 (1.41%)	211 (18.7%)	< 0.001
Anti-platelet	3573 (32.5%)	889 (78.7%)	< 0.001
Warfarin	148 (1.33%)	161 (14.2%)	< 0.001

AAD, antiarrhythmic agents; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; Na, not available; TIA, transient ischemic attack.

Predictors of the occurrence of ventricular arrhythmias

After multivariable adjustments, a baseline history of HF (HR: 1.86, 95% CI: 1.22-2.85, p = 0.004), DM (HR: 1.61, 95% CI: 1.08-2.41, p = 0.02), chronic liver disease (HR: 7.33, 95% CI: 2.24-24.0, p = 0.001), and anti-arrhythmic drug use (HR: 1.60, 95% CI: 1.02-2.51, p = 0.04) were independently associated with new-onset VT in the patients with amyloidosis (Table 7). In the patients with amyloidosis, new-onset VT was an independent risk factor for CV mortality after multivariable adjustments (HR: 1.50, 95% CI: 1.07-2.12; p = 0.02) (Table 8).

DISCUSSION

Main findings

The main findings of this study were: (1) the incidence rates of amyloidosis and CA were 6.54 and 0.61 per 100,000 PYs, respectively; (2) patients with amyloidosis had a significantly higher incidence of VT, AF, HF-related hospitalization, CV death, and all-cause mortality during long-term follow-up; the patients with CA also had a significantly higher incidence of VT than those with non-cardiac amyloidosis; (3) HF-related hospitalization, DM, and chronic liver disease, use were associated with new-onset VT in the patients with amyloidosis; and (4) new-onset VT was associated with higher CV mortality in the patients with amyloidosis.

Incidence of amyloidosis and CA

Amyloidosis is a relatively rare disease, and there are currently no data on the nationwide epidemiology

Table 3. Cumulative event rate, incidence rate, and crude risk of cardiovascular events in patients with and without amyloidosis

Outcomes	Variables	Total numbers	PYs	Event (%)	p value	Incidence rate (per 10,000 PYs, 95% CI)	Crude HR (95% CI)	p value
Ventricular tachycardia	No amyloidosis	12139	287575	97 (0.80%)	0.014	3.37 (2.70-7.12)	1 (reference)	-
	With amyloidosis	12139	156334	134 (1.10%)		8.57 (7.12-10.0)	6.91 (4.20-11.4)	< 0.001
Atrial fibrillation	No amyloidosis	12139	286990	316 (2.60%)	< 0.001	11.0 (9.80-12.2)	1 (reference)	
	With amyloidosis	12139	152596	460 (3.79%)		30.2 (27.4-32.9)	5.01 (3.75-6.69)	< 0.001
Heart failure-related admission	No amyloidosis	12139	286988	608 (5.01%)	< 0.001	21.2 (19.5-22.9)	1 (reference)	-
	With amyloidosis	12139	153399	826 (6.80%)		53.9 (50.2-57.5)	6.19 (5.12-7.50)	< 0.001
Cardiovascular death	No amyloidosis	12139	143935	447 (3.93%)	< 0.001	33.1 (30.2-36.1)	1 (reference)	-
	With amyloidosis	12139	112615	597 (4.92%)		53.0 (48.8-57.3)	5.32 (4.57-6.18)	< 0.001
All-cause mortality	No amyloidosis	12139	143935	2224 (18.3%)	< 0.001	154.5 (148.1-160.9)	1 (reference)	-
	With amyloidosis	12139	112615	2589 (21.3%)		229.9 (221.0-238.8)	4.39 (4.09-4.70)	< 0.001

CI, confidence interval; HR, hazard ratio; PYs, person-years.

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Table 4. Cumulative event rate, incidence rate, and crude risk of cardiovascular events in amyloidosis patients with or without cardiac type

Outcomes	Variables	Total numbers	PYs	Event (%)	p value	Incidence rate (per 10,000 PYs, 95% CI)	Crude HR (95% CI)	p value
Ventricular	Non-cardiac	11009	145434	10 (0.09%)	< 0.001	0.69 (0.26-1.11)	1 (reference)	-
tachycardia	Cardiac	1130	10900	124 (11.0%)		113.8 (93.7-133.8)	53.9 (19.9-146.4)	< 0.001
Cardiovascular	Non-cardiac	11009	107344	336 (3.05%)	< 0.001	31.3 (28.0-34.6)	1 (reference)	-
death	Cardiac	1130	5271	209 (18.5%)		495.2 (435.1-555.2)	1.75 (1.49-2.06)	< 0.001
All-cause mortality	Non-cardiac	11009	107344	1781 (16.2%)	< 0.001	165.9 (158.2-173.6)	1 (reference)	-
	Cardiac	1130	5271	808 (71.5%)		1532.9 (1427.2-1638.6)	1.02 (0.94-1.11)	0.60

CI, confidence interval; HR, hazard ratio; PYs, person-years.

Table 5. Adjusted hazard ratio for long-term outcomes in patients with amyloidosis

Outcomes	Model	Hazard ratio*	95% confidence interval		p value
Ventricular tachycardia	1	6.90	4.19	11.4	< 0.001
	2	7.90	4.49	13.9	< 0.001
Atrial fibrillation	1	5.26	3.92	7.05	< 0.001
	2	6.21	4.38	8.78	< 0.001
Heart failure-related admission	1	6.54	5.38	7.93	< 0.001
	2	54.7	37.1	80.7	< 0.001
Cardiovascular death	1	5.43	4.67	6.31	< 0.001
	2	5.09	4.23	6.12	< 0.001
All-cause mortality	1	4.40	4.11	4.72	< 0.001
	2	5.11	4.69	5.57	< 0.001

* Hazard ratios were analyzed for amyloidosis patients versus controls.
Model 1: Adjusted for age and sex.
Model 2: Model 1 + hypertension, diabetes mellitus, congestive heart failure, hyperlipidemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, thyroid disease, prior coronary artery disease, prior stroke, cancer.

Table 6. Adjusted hazard ratio for long-term outcomes in patients with cardiac amyloidosis

Outcomes	Model	Hazard ratio*	95% confidence interval		p value
Ventricular tachycardia	1	61.2	22.4	167.0	< 0.001
	2	153.3	54.3	432.7	< 0.001
Cardiovascular death	1	1.63	1.39	1.93	< 0.001
	2	1.34	1.02	1.78	0.04
All-cause mortality	1	1.00	0.92	1.09	0.99
	2	1.03	0.88	1.20	0.75

* Hazard ratios were analyzed for amyloidosis patients versus controls.
Model 1: Adjusted for age and sex.
Model 2: Model 1 + hypertension, diabetes mellitus, congestive heart failure, hyperlipidemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, thyroid disease, prior coronary artery disease, prior stroke, cancer.

of amyloidosis. Most international epidemiological studies are based on death certificate data and are highly focused on specific types of amyloidosis.[8-11] In our data, the incidence rate of amyloidosis (including both localized and systemic amyloidosis) was 6.54 per 100,000 PYs in a nationwide cohort.

The first study to identify the incidence and prevalence of CA among Medicare beneficiaries in the United States was reported by Gilstrap et al., who found that among hospitalized patients over 65 years of age, the incidence rate of CA was 17 per 100,000 PYs.[6] It should be noted that the data collected from the Medicare data-

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Table 7. Characteristics of amyloidosis patients with and without ventricular arrhythmia

Variables	Without VT (N = 12005)	With VT (N = 134)	p value	Univariable		Multivariable*	
				Hazard ratio (95% CI)	p value	Adjusted hazard ratio (95% CI)	p value
Age (years old)	51.9 ± 16.0	66.4 ± 12.2	< 0.001	1.003 (0.99-1.02)	0.77		
Male (n, %)	5875 (48.9%)	96 (71.6%)	< 0.001	1.05 (0.67-1.65)	0.82		
Pacemaker	140 (1.17%)	(9.70%)	< 0.001	2.60 (1.39-4.85)	0.003	1.46 (0.76-2.81)	0.25
Underlying diseases							
Atrial fibrillation	430 (3.58%)	30 (22.4%)	< 0.001	2.17 (1.40-3.38)	0.001	1.27 (0.77-2.81)	0.35
History of heart failure	15 (0.12%)	3 (2.24%)	0.012	4.68 (1.16-18.9)	0.031	1.86 (1.22-2.85)	0.004
Hypertension	4918 (41.0%)	106 (79.1%)	< 0.001	1.65 (1.01-2.68)	0.044	0.81 (0.36-1.80)	0.60
Diabetes mellitus	2285 (19.0%)	63 (47.0%)	< 0.001	1.86 (1.27-2.72)	0.001	1.61 (1.08-2.41)	0.02
Stroke	13 (0.10%)	0 (0.00%)	> 0.99	Na	Na		
Chronic kidney disease	53 (0.44%)	6 (4.48%)	< 0.001	2.46 (0.78-7.45)	0.12		
Chronic liver disease	45 (0.37%)	3 (2.24%)	0.016	4.34 (1.38-13.7)	0.012	7.33 (2.24-24.0)	0.001
COPD	24 (0.20%)	2 (1.49%)	0.033	2.67 (0.66-10.8)	0.17		
Thyroid disease	7 (0.06%)	0 (0.00%)	> 0.99	Na	Na		
Hyperlipidemia	28 (0.23%)	0 (0.00%)	> 0.99	Na	Na		
Cancer	47 (0.39%)	0 (0.00%)	> 0.99	Na	Na		
Medication uses							
ACEi	3294 (27.4%)	86 (64.2%)	< 0.001	1.76 (1.18-2.64)	0.006	1.47 (0.83-2.61)	0.19
ARB	3143 (26.2%)	77 (57.5%)	< 0.001	1.43 (0.96-2.09)	0.08	0.91 (0.55-1.49)	0.70
CCB	2007 (16.7%)	61 (45.5%)	< 0.001	1.59 (1.09-2.33)	0.017	1.12 (0.72-1.73)	0.61
Beta-blockers	5635 (46.9%)	89 (66.4%)	< 0.001	0.83 (0.57-1.23)	0.35		
AADs	838 (6.98%)	45 (33.6%)	< 0.001	2.30 (1.53-3.45)	< 0.001	1.60 (1.02-2.51)	0.04
Anti-platelet	4365 (36.4%)	97 (72.4%)	< 0.001	1.45 (0.95-2.24)	0.09	0.97 (0.60-1.58)	0.91
Warfarin	288 (2.40%)	21 (15.7%)	< 0.001	2.49 (1.48-4.17)	< 0.001	1.55 (0.88-2.72)	0.13

* Adjusted for variables with p < 0.10 in the univariable analysis.

AAD, antiarrhythmic agents; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Na, not available; TIA, transient ischemic attack; VT, ventricular tachycardia.

base were highly selective and only included inpatient resources in their study. In contrast, we found a CA incidence of 0.61 per 100,000 PYs, more in agreement with the data published recently in Danish national registries.[6] The difference between our findings and those reported by the Danish national registries may be explained by the selection and age of patients. Additionally, our data were retrieved from 2000 to 2006, a period during which CA was not well diagnosed. Finally, the population in the Danish national registries was solely Caucasian, whilst our study provides the first nationwide assessment of amyloidosis and CA in a Han population.

New-onset VT and CV events in the patients with amyloidosis and CA

Few studies have investigated the incidence of VT in patients with amyloidosis. Using Holter monitoring, Palladini et al. and Dubrey et al. reported VT in 18% of 51 and 26.7% of 195 patients with AL amyloidosis, respectively.[12,13] Goldsmith et al. analyzed types of arrhythmia in 24 patients with AL amyloidosis undergoing stem cell transplantation, and found that sustained VT occurred in 12.5% of the patients.[14] A study using implanted loop monitors showed that VT was identifiable only in one patient (5%) with AL amyloidosis during a median follow-up period of 308 days.[15] However, those studies were confined to a small population of highly selected subjects, which rendered the true incidence of ventricular arrhythmia impossible to determine.

To the best of our knowledge, this is the first study to demonstrate the long-term follow-up of CV events in patients with amyloidosis and CA using a nationwide co-

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Table 8. Characteristics of amyloidosis patients with and without cardiovascular death

Variables	Without CVD (N = 11524)	With CVD (N = 597)	p value	Univariable		Multivariable*	
				Hazard ratio (95% CI)	p value	Adjusted hazard ratio (95% CI)	p value
Age (years old)	51.1 ± 15.7	70.7 ± 9.42	< 0.001	1.03 (1.02-1.04)	< 0.001	1.02 (1.01-1.03)	< 0.001
Male (n, %)	5498 (47.6%)	473 (79.2%)	< 0.001	1.26 (1.03-1.53)	< 0.001	1.06 (0.86-1.31)	0.56
Type: cardiac amyloidosis	869 (7.53%)	261 (43.7%)	< 0.001	1.75 (1.49-2.06)	< 0.001	1.30 (0.91-1.86)	0.15
Pacemaker	111 (0.96%)	42 (7.04%)	< 0.001	2.04 (1.49-2.80)	< 0.001	1.36 (0.98-1.89)	0.07
Underlying diseases							
Ventricular tachycardia related admission	93 (0.81%)	41 (6.87%)	< 0.001	1.93 (1.40-2.65)	< 0.001	1.50 (1.07-2.12)	0.02
Atrial fibrillation	348 (3.02%)	112 (18.8%)	< 0.001	1.63 (1.33-2.01)	< 0.001	1.01 (0.77-1.34)	0.92
Heart failure related admission	626 (5.42%)	200 (33.5%)	< 0.001	1.63 (1.38-1.94)	< 0.001	1.03 (0.74-1.42)	0.88
Hypertension	4548 (39.4%)	476 (79.7%)	< 0.001	1.56 (1.28-1.90)	< 0.001	1.08 (0.78-1.49)	0.63
Diabetes mellitus	2134 (18.5%)	214 (35.8%)	< 0.001	0.92 (0.78-1.09)	0.35		
Stroke	10 (0.09%)	3 (0.50%)	0.023	1.57 (0.50-4.88)	0.44		
Chronic kidney disease	46 (0.40%)	13 (2.18%)	< 0.001	2.23 (1.29-3.88)	0.004	2.41 (1.36-4.26)	0.003
Chronic liver disease	45 (0.39%)	3 (0.50%)	0.51	0.63 (0.20-1.96)	0.43		
COPD	20 (0.17%)	6 (1.00%)	0.001	1.32 (0.59-2.95)	0.50		
Thyroid disease	7 (0.06%)	0 (0.00%)	> 0.99	Na	Na		
Hyperlipidemia	25 (0.22%)	3 (0.50%)	0.16	1.46 (0.47-4.54)	0.51		
Cancer	44 (0.38%)	3 (0.50%)	0.50	0.51 (0.16-1.58)	0.24		
Medication uses							
ACEi	3010 (26.1%)	370 (62.0%)	< 0.001	1.42 (1.21-1.68)	< 0.001	1.05 (0.84-1.31)	0.66
ARB	2880 (25.0%)	340 (57.0%)	< 0.001	1.27 (1.08-1.50)	0.004	0.93 (0.76-1.13)	0.45
CCB	1838 (15.9%)	230 (38.5%)	< 0.001	1.41 (1.20-1.67)	< 0.001	1.08 (0.90-1.31)	0.41
Beta-blockers	5347 (46.3%)	377 (63.1%)	< 0.001	0.98 (0.83-1.16)	0.81		
AADs	747 (6.47%)	136 (22.8%)	< 0.001	1.63 (1.35-1.98)	< 0.001	1.25 (1.02-1.55)	0.033
Anti-platelet	4013 (34.8%)	449 (75.2%)	< 0.001	1.71 (1.42-2.06)	< 0.001	1.33 (1.08-1.64)	0.007
Warfarin	251 (2.17%)	58 (9.72%)	< 0.001	1.36 (1.03-1.79)	0.029	0.93 (0.69-1.26)	0.64

* Adjusted for variables with p < 0.10 in the univariable analysis.

AAD, antiarrhythmic agents; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular death; Na, not available; TIA, transient ischemic attack.

hort. Our findings indicated that the patients with amyloidosis had a 7.9-fold increased risk of developing VT compared to those without amyloidosis, and that the patients with CA had a 153.3-fold increased risk of new-onset VT compared to those with non-cardiac amyloidosis. We also demonstrated for the first time that a higher risk of VT was observed 7.5 years after the patients were diagnosed with amyloidosis. Furthermore, we also demonstrated that VT contributed to a significantly higher CV death rate. Consistent with previous studies,[12,14] VT was an independent risk factor with a 1.5-fold increase in CV mortality after adjusting for other confounders, compared to the amyloidosis patients without VT. Preventing and treating these ventricular arrhythmic events are crucial to improve the prognosis of patients with amyloidosis.

Predictors of VT in amyloidosis

Our results demonstrated that a history of HF had predictive value for new-onset VT. Falk et al. reported that patients with amyloidosis who presented with VT were more likely to have a history of HF and abnormal echocardiographic findings,[16] which is consistent with our findings. An enlarged left ventricular (LV) chamber and impaired LV systolic function could result in structural remodeling and diseased substrate formation, which may explain the occurrence of VT at the late stage of amyloidosis with cardiac involvement.[17]

Some reports have demonstrated that oxidative stress in the presence of liver disease and DM is associated with ventricular instability and QT prolongation,[18-20] which may contribute to VT. However, the correlation between amyloidosis and DM with the risk of VT remains unclear.

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No published study has linked chronic liver disease, amyloidosis, and VT risk, and therefore further studies are needed to investigate these relationships.

Furthermore, VT has also been linked to the use of AADs. AADs are used to control the rate or rhythm of AF in patients with amyloidosis.[3,20] Patients receiving AADs may experience more new-onset VT because amyloidosis affects both atriums and ventricles. Therefore, this may explain why the incidence of VT is higher in patients taking AADs for AF. While AADs may reduce the recurrence of VT, their efficacy is rarely promising. Moreover, AADs are well known to cause proarrhythmic effects because of QTc prolongation, which can also lead to new-onset VT in patients with amyloidosis.[21]

Clinical implications

Our study found that patients with amyloidosis and CA had a significantly higher incidence of VT, and they also had a significantly greater incidence of CV mortality following VT than those without VT. AADs are conventionally used for the treatment of VT. Beta-blockers are widely used to suppress VT, but they may be harmful to patients with CA because of a consequent loss of cardiac output.[21] Furthermore, our results showed neither a protective effect of AADs against VT occurrence nor benefits on CV or all-cause mortality. As previously mentioned, the role of AADs in patients with amyloidosis is not conclusive, and they may even pose a risk for VT and CV death. Currently, the implantation of an ICD is controversial in patients with amyloidosis. Owing to the lack of survival benefit from ICD implantation in patients with CA with an advanced stage of HF,[22,23] it is important that these patients should be closely monitored over the long term once amyloidosis has been diagnosed to minimize adverse outcomes. The decisions of pharmacotherapies or ICD implantation should be carefully considered and discussed between the patient and physician with expertise at the earlier stage, especially for those carrying high-risk features, such as HF, DM, and chronic liver disease.

Study limitations

There are several limitations in our study. First, the study was retrospective in nature, and therefore there may be inherent bias. Despite the use of PS matching, some variables between the non-amyloidosis and amyloidosis groups remained inconsistent. However, we used multivariable regression to confirm the adjusted effect sizes. Moreover, we enrolled a large sample from a nationwide cohort with long-term follow-up. In addition, since amyloidosis was diagnosed using an ICD-9 code from the NHIRD, there may have been diagnosis and procedure coding errors. However, amyloidosis is a rare disease, and only physicians who are familiar with this disease would be capable of making this diagnosis. A certified coding specialist also confirmed the diagnosis to reduce the possibility of misclassification. Moreover, our medical records should reflect an accurate diagnosis of VT since it is a life-threatening condition. Third, no additional information was available from the NHIRD which could differentiate localized from systemic amyloidosis. Fourth, the definition of CA was based on the code for amyloidosis plus the codes for one of HF/cardiomyopathy/AF, and this definition is not 100% sensitive or specific, so it will both include patients without CA and miss patients with CA.

CONCLUSION

Amyloidosis and CA may have increased the risk of VT during the follow-up period of over 10 years in this study, and the presence of new-onset VT was an independent risk factor for CV mortality in the patients with amyloidosis. Accordingly, patients with amyloidosis should continue to undergo cardiac evaluations during long-term follow-up. Providing early interventions for patients at risk of VT may improve their prognosis.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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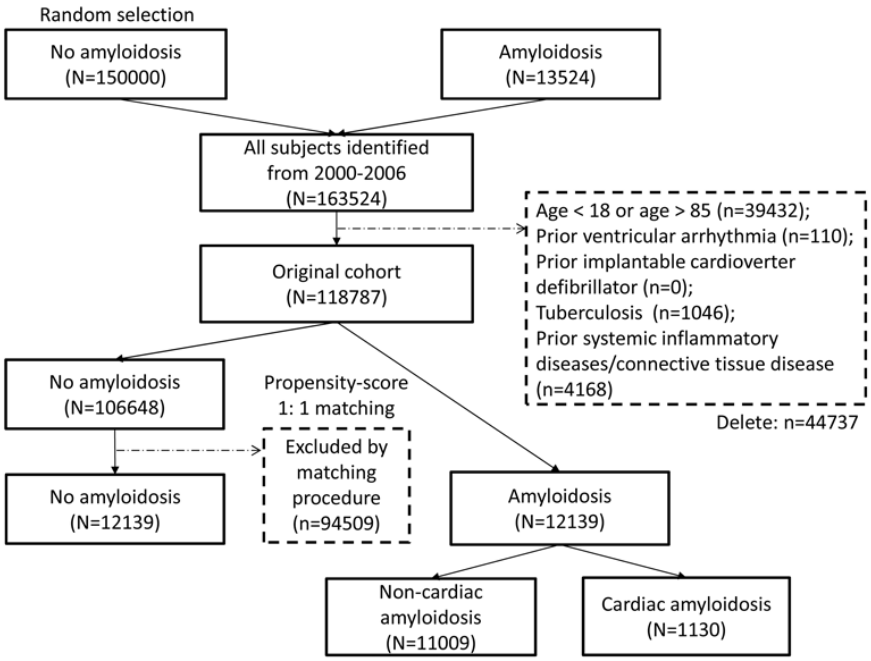
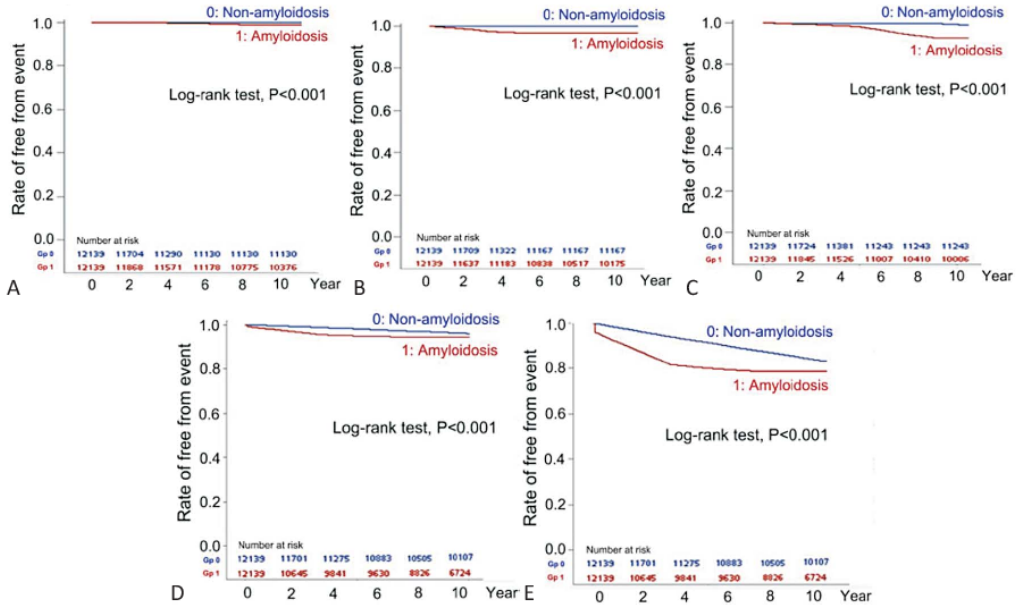
SUPPLEMENTARY MATERIAL



Supplementary Figure 1. *Flowchart of the study cohort.*



Supplementary Figure 2. *Kaplan-Meier event-free survival curves for new-onset events of ventricular tachycardia (VT) (A), atrial fibrillation (AF) (B), heart failure (HF) related admission (C), cardiovascular death (D), and all-cause mortality (E). A significantly higher risk of new-onset VT, AF, HF related admission, cardiovascular death, and all-cause mortality in patients with amyloidosis compared to the control group. The risk of new-onset VT for the two groups was initially comparable for up to 7.5 years and then separated during the later period (A).*

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