BMJ Open

Higher risk of future events, mortality, and greater healthcare use among patients with increasingly recurrent atherosclerotic cardiovascular disease events in Taiwan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064219
Article Type:	Original research
Date Submitted by the Author:	07-May-2022
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Keywords:	Coronary heart disease < CARDIOLOGY, Cardiac Epidemiology < CARDIOLOGY, EPIDEMIOLOGY

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Higher risk of future events, mortality, and greater healthcare use among patients with increasingly recurrent atherosclerotic cardiovascular disease events in Taiwan

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Funding

The project was funded by Amgen Taiwan Limited.

Disclaimer

Wei-Ju Chen and Yea-Harn Yang are employees of Amgen Taiwan Limited. Chia-Yun Hsu, Wen-Jone Chen, Hung-Ju Lin, Ho-Min Chen and Fei-Yuan Hsiao received a grant from Amgen Taiwan Limited.

Abstract: words (Max: 250): 241 words

Text word counts: 3707 words (excluding the title, author names/affiliations, abstract, keywords, figures/tables and references)

Figure counts: 6 figures

Table counts: 1 table

Others: 4 supplemental figures & 2 supplemental tables

References: 25

ABSTRACT (word count: 241)

Objectives:

This was a retrospective longitudinal analysis using Taiwan's National Health Insurance Research Database. We described the occurrence of recurrent atherosclerotic cardiovascular disease (ASCVD) events within 3 years after a new-onset event, and the associated disease burden, and statin prescribing in ASCVD patients in Taiwan.

Methods:

We identified patients with a new-onset ASCVD event (index event) during 2012 and 2014 and followed up their recurrent ASCVD events. For each index and recurrent event, patients were observed for 12 months after admission to quantify risks of mortality, recurrent events, treatment and healthcare use.

Results:

We identified 97,321, 120,914 and 14,794 patients with new-onset coronary heart disease (CHD), cerebrovascular disease (CBVD) and peripheral artery disease (PAD), respectively. The proportion of patients developing recurrent events during follow-up increased with each additional event. The proportions of developing first, second and third recurrent events were: 22.5, 25.6 and 30.9% for CHD; 20.9, 26.2 and 32.4% for CBVD; and 40.2, 41.4 and 43.6% for PAD, respectively. Statin prescribing was suboptimal, ranging from 63.4% (CHD patients) to 34.5% (PAD patients) at time of index event. Most patients had the same type of ASCVD for their recurrent events as their new-onset event. Survival rates decreased with each recurrent event (p <0.05 for all three ASCVD groups).

Conclusion:

Compared with new-onset ASCVD events, recurrent events are associated with a higher risk of mortality and recurrent ASCVD, and greater healthcare use. The results highlight the importance of preventing recurrent ASCVD events.

Keywords (up to 6): atherosclerosis, cardiovascular diseases, peripheral arterial disease, actuarial analysis mortality

INTRODUCTION

Cardiovascular disease (CVD) and cerebrovascular disease (CBVD) are the major causes of death globally.[1] Worldwide, the estimated numbers of deaths due to ischaemic heart disease and stroke in 2019 were 9.14 million and 6.55 million, respectively,[2] and the annual global economic cost of CVD is expected to rise to 1,044 billion USD by 2030.[3] The estimated economic cost of stroke and congestive heart disease in low to middle income countries is estimated at 5000 USD per episode.[4] Taiwan has not been spared this burden – local data show CVD was the second and CBVD the fourth leading cause of death in 2019, with standardized mortality rates of 43.6 and 26.7 per 100,000 persons, respectively.[5]

Atherosclerotic cardiovascular disease (ASCVD) comprises acute coronary syndrome, myocardial infarction (MI), unstable angina, coronary or other arterial revascularization, transient ischaemic attack and peripheral artery disease (PAD).[6] By promoting healthy dietary choices, advocating physical activity to achieve weight control, and controlling individual cardiovascular risk factors, such as cholesterol (particularly low-density lipoprotein [LDL]), blood pressure and blood glucose, physicians may help their patients prevent or slow the development of ASCVD.[6]

Patients who have had a first ASCVD event have an increased risk for future events compared to those with no events.[6] Therefore, the US and European cholesterol guidelines have highlighted the importance of secondary prevention to prevent recurrent ASCVD events.[6,7] The 2018 American Heart Association guidelines recommend high-intensity statin therapy for secondary prevention, and proprotein convertase subtilisin/kexin type 9 (PSCK9) inhibitors and ezetimibe are recommended options for patients who are

contraindicated for high-intensity statins or do not achieve LDL cholesterol targets on maximally tolerated statins.[6] Despite these recommendations, patients with a history of CVD events are often undertreated. Data from Europe show 80% of such patients are not at LDL target, and in low-to-middle income countries fewer than 10% of patients are on multidrug treatment.[8]

Prior studies have indicated that some ASCVD patients develop recurrent events within a relatively short period.[9-11] For example, in a US study comprising 48,688 Medicare beneficiaries with index acute MI, the recurrence rate remained relatively high for patients experiencing acute MI or coronary heart disease (CHD), at 68.5 and 124.9 per 1,000 person-years, respectively, during 2007–2009.[9] In a cohort of 7,870 patients with acute MI enrolled in the Osaka Acute Coronary Insufficiency Study (OACIS), 353 patients (4.5%) experienced recurrent MI with a median follow-up of 3.9 years.[10] Another study of 196,765 patients with ischaemic stroke in the Swedish Stroke Register (Riksstroke) reported that 11.3% had a recurrent ischaemic stroke within 1 year.[12] In addition, as different ASCVD events share common risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus and smoking, some studies suggest that the recurrent event may not be identical to the index event. For example, 1.4% of patients discharged after acute MI experienced a stroke event during the next 12 months.[13] Therefore assessing for other types of recurrent ASCVD events in addition to the index event type may produce a more complete picture of recurrent event risk, but examples of such an approach in the literature are rare.

Although the development of recurrent ASCVD events has been investigated, most existing studies observe event rates and outcomes associated with the first ASCVD recurrence; data on event rates beyond the first recurrence are limited. The epidemiology of ASCVD

events and the treatment patterns of these patients are not well understood in Taiwan. First, it is not known if recurrent ASCVD events incur a higher burden to patients in terms of healthcare use or mortality. Secondly, it is not clear whether these high-risk patients receive lipid-lowering treatment as recommended by the international guidelines. Therefore, the aim of this study is to evaluate the temporal pattern and healthcare burden of recurrent ASCVD events within 3 years following a new-onset ASCVD event (index event) in patients in Taiwan. For each ASCVD event (index, first and second recurrent events), we followed up to 18 months after admission to estimate risk of mortality and recurrent events. Healthcare use was also estimated following each event using the same landmark approach.

METHODS

Data source

This study used data from Taiwan's National Health Insurance Research Database (NHIRD) from 1 January 2010 to 31 December 2017, provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW). Taiwan's National Health Insurance (NHI) system is a mandatory, single-payer health insurance programme, which provides comprehensive benefits including inpatient care, ambulatory care, dental care and prescription drugs to its beneficiaries. Over 99% of Taiwan's 23 million people are covered by the NHI. The NHIRD is a database of uniquely-identified claims and transactions for all covered services used by patients enrolled in the programme. It provides patient-level information for research, including demographic, clinical, medical resource use (ambulatory care claims, emergency room [ER] claims and inpatient claims) and treatment patterns. All traceable personal identifiers were encrypted to protect patient confidentiality.[14]

Ethics statement

This study was reviewed and approved by the Research Ethics Committee of National Taiwan University Hospital (NTUH-REC-201710059W). Informed consent from patients was waived since the data were retrospectively collected and the identification data from NHIRD were encrypted for confidentiality.

Study design

This was a retrospective longitudinal analysis using Taiwan's NHIRD. **Figure 1** illustrates the study design. We identified patients with a new-onset ASCVD event (index event) and followed up their recurrent ASCVD events (first, second and third recurrent events). The date of the new-onset event was defined as the index date. The 2-year baseline period before the index date was examined to ensure patients had no history of prior ASCVD and to ascertain baseline characteristics. The observation period for recurrent events was from the index date (inclusive of index date) to death or 3 years after the index date, whichever came first.

For each ASCVD event (index, first and second recurrent event), we observed patients for 12 months after admission to estimate risks of mortality and recurrent events, and healthcare use. Sensitivity analyses using follow-up durations of 6 and 18 months were performed.

Study population

All patients in the NHIRD with a primary ASCVD event during 1 January 2012 through 31 December 2014 and aged 20 years or above were included in this study. An ASCVD event was defined as a hospitalization with a primary or a first secondary discharge diagnosis of

ASCVD. In addition, no history of hospitalization with any ASCVD diagnosis within 2 years prior to the index event was required to guarantee new-onset events (index event).

We categorized patients with new-onset ASCVDs into three categories using International Classification of Diseases version 9 and 10 (ICD-9/10-CM) codes: (1) those with CHD, including MI (ICD-9-CM codes 410.x, 412; ICD-10-CM codes I21, I22, I25.2), angina (ICD-9-CM codes 411.1, 413.x; ICD-10-CM code I20) and other ischaemic heart disease (ICD-9-CM codes 411.0, 411.8x; ICD-10-CM code I24); (2) those with CBVD, including ischaemic stroke (ICD-9-CM codes 433.x1, 434.x1; ICD-10-CM code I63) and transient ischaemic attack (ICD-9-CM codes 435.8, 435.9; ICD-10-CM codes G45.0–G45.2, G45.8–G45.9); and (3) those with PAD (ICD-9-CM codes 250.7x, 440.2x, 440.8, 440.9, 443.9, 444.2x, 444.9; ICD-10-CM codes E10.5, E11.5, I70.2–I70.9, I73.9, I74.3, I74.5, I75). Patients diagnosed with more than one type of ASCVD in new-onset hospitalization were excluded to avoid interaction effects of dual ASCVD events on outcome measurements.

Study variables

Index event and recurrent event

This study identified the index event as the date of new-onset ASCVD events and defined recurrent ASCVD events as occurring within the 3 years of follow-up after the index event (sequentially characterized as a first, second or third recurrent event). Recurrent ASCVD events, defined as a hospitalization with the primary or the first secondary discharge diagnosis of ASCVD, were also classified as CHD events, CBVD events or PAD events. Length of hospital stay of each event was calculated in days. Time between events was calculated in days between the discharge date of the event and the admission date of the next event. Follow-up time of each event was calculated in months from the discharge of each event until the end of study follow-up.

Risk of mortality and recurrent event

Following each ASCVD event, mortality was identified using the National Death Registry (linked to the NHIRD by encrypted personal identities). Recurrent events were identified using the definition mentioned above. Risk of mortality associated with a recurrent event was followed up from discharge after each event to occurrence of the outcome or 31 December 2017, whichever came first.

Healthcare use

Healthcare use following each ASCVD event (index, first and second recurrent event), excluding use for the event itself, was estimated for 12 months following discharge after the event. Healthcare use was estimated by calculating the number of outpatient visits, ER visits and re-admissions. Sensitivity analyses using follow-up durations of 6 and 18 months were performed.

Statin use

Proportions of patients prescribed statins following each ASCVD event (index, first and second recurrent event) were calculated for 12 months following admission for the event. During the study period (2012–2017), statins were used as the major lipid-lowering therapy in the Taiwan NHI system, while ezetimibe was reimbursed when used in combination with statin treatment.[15] Therefore, we only described statin use in this study. Sensitivity analyses using follow-up durations of 6 and 18 months were performed.

Statistical analysis

Variables were summarized through descriptive analyses, including tabular and graphical

display of mean, standard deviation, median and interquartile range for continuous variables, and frequency and percentage for categorical variables.

Following each ASCVD event, risk of all-cause mortality and risk of recurrent event over time were estimated and compared across patients who developed designated subsequent events. For example, among patients with new-onset CHD, the risk of all-cause mortality for the index event was calculated from the time of index event till the end of observation; the mortality risk for the first subsequent event was calculated from the time they developed the first recurrent event till the end of observation, similarly for those developed with the second recurrent event (**Supplement 1**). The data were presented as Kaplan-Meier survival curves. For estimating risk of recurrent events, we conducted Fine and Gray analysis to account for competing risks of death.

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-sided p <0.05 were considered statistically significant.

Patient and public involvement

No patients were actively involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of the study.

RESULTS

Study population

We identified 111,399, 133,538 and 21,572 patients who were hospitalized with a diagnosis of CHD, CBVD or PAD, respectively, between 1 January 2012 and 31 December 2014. We

excluded patients with a history of ASCVD in the 2 years prior to the index event and patients younger than 20 years of age. Patients with multiple ASCVD types at the index event were excluded (985 patients in the CHD cohort; 1,068 patients in the CBVD cohort; and 353 patients in the PAD cohort). Therefore, we analysed the records of 97,321, 120,914 and 14,794 patients with new-onset CHD, CBVD and PAD, respectively (Selection flow of study population in **Supplement 2**). Baseline characteristics showed that 68.5%, 59.5% and 57.7% of patients were male, with median age 65, 71 and 74 years in the CHD, CBVD and PAD groups, respectively (**Table 1**).

Table 1. Patient demographics and characteristics of each event

	Index event		1st recurrent event		2nd recurrent event		3rd recurrent event	
[a] CHD								
Patients, n	97,321		21,902		5,601		1,731	
Male, n (%)	66,690	(68.5)						
Age, y, median (Q1–Q3)	65	(56–77)						
Length of stay, days								
Median (Q1–Q3)	4	(2–6)	3	(2–7)	4	(2–8)	5	(2–9)
Time from last event to the current event, days								
Median (Q1–Q3)	NA		213	(56–500)	176	(55–384)	124	(43–303)
Follow-up, months								
Median (Q1–Q3)	36	(36–36)	24	(11–33)	16	(6–26)	13	(5–21)
[b] CBVD								
Patients, n	120,914		25,337		6,644		2,153	
Male, n (%)	71,934	(59.5)						
Age, y, median (Q1–Q3)	71	(61–80)						
Length of stay, days								
Median (Q1–Q3)	7	(4–13)	8	(4–19)	9	(5–23)	11	(5–26)
Time from last event to the current event, days								
Median (Q1–Q3)	NA		162	(30–502)	99	(34–306)	72	(35–210)
Follow up, months								
Median (Q1–Q3)	36	(33–36)	24	(10–34)	19	(8–30)	18	(7–29)
[c] PAD								
Patients, n	14,794		5,951		2,463		1,073	

Male, n (%)	8,534	(57.7)						
Age, y, median (Q1–Q3)	74	(63–82)						
Length of stay, days								
Median (Q1–Q3)	8	(3–16)	7	(3–15)	7	(3–15)	7	(3–15)
Time from last event to the current event, days								
Median (Q1–Q3)	NA		112	(37–366)	112	(39–297)	115	(42–287)
Follow up, months								
Median (Q1–Q3)	36	(14–36)	22	(8–33)	17	(6–27)	13	(5–23)

[a] CBVD: cerebrovascular disease;

[b] CHD: coronary heart disease;

[c] PAD: Peripheral arterial disease;

Index event and recurrent events

Among the new-onset patients, 22.5% of patients with CHD (21,902/97,321), 21.0% of patients with CBVD (25,337/120,914) and 40.2% of patients with PAD (5,951/14,794) had at least one recurrent event **(Table 1)**. The proportion of patients developing a recurrent event during follow-up increased with each additional event that occurred (the proportions developing the first, second and third recurrent events were: 22.5%, 25.6% and 30.9% for CHD; 21.0%, 26.2% and 32.4% for CBVD; and 40.2%, 41.4% and 43.6% for PAD; **Figure 2**).

With more recurrent events, there was a trend towards a shorter median time to next event in patients with CHD (213 days from index event to first recurrent event; 176 days from first to second recurrent event; 124 days from second to third recurrent event) or CBVD (162 days; 99 days; 72 days), but not in those with PAD (112 days; 112 days; 115 days). The median length of hospital stay showed little change between events in CHD and PAD groups, whereas an increasing trend was observed in CBVD group (from 7 days for index event to 11 days for third recurrent event).

Most patients had the same type of ASCVD for their recurrent events as for their index

event; 66–81% of patients with new-onset CHD had CHD at first recurrence, whereas this percentage was 80–84% for CBVD and 76–78% for PAD (**Figure 2**). When assessing these data by ASCVD type, the proportion of PAD events increased with each additional event in the CHD group (from 6% for the first recurrent event to 19% for the third recurrent event) and CBVD group (from 4% for the first recurrent event to 9% for the third recurrent event). In contrast, the proportions of CHD and CBVD remained stable across recurrences in the non-CHD (CBVD/PAD) and non-CBVD (CHD/PAD) groups, respectively (**Figure 2**).

Risk of mortality and recurrence rate following each event

For patients with PAD with one recurrent event, the mortality rate was 40.5%; patients with CHD or CBVD with one recurrent event, had mortality rates of 21.8% and 25.8%, respectively. The survival rates decreased as recurrent events accumulated (p <0.05 for all three ASCVD groups; **Figure 3**). The 1-year survival rates following the index event, first recurrent event and second recurrent event in the CHD group were 85.9%, 84.4% and 79.8%, respectively (**Supplement 3)**. For patients with CBVD or PAD, 1-year survival rates were highest after the index event, compared with later events, and survival rates were similar following the first and second recurrent event (CBVD: 85.9%, 83.0% and 83.3%, respectively; PAD: 77.0%, 73.7% and 72.5%, respectively.

Higher rates of developing another recurrent event were observed when patients experienced more recurrent events (p <0.05 for all three ASCVD groups; **Figure 4**). The 1-year recurrent event rates following the index event, first and second recurrent event were 14.7%, 19.6% and 27.3%, respectively, in the CHD group (**Supplement 4)**. A similar trend was observed for the CBVD and PAD groups (CBVD: 14.0%, 21.6% and 29.8%, respectively; PAD: 30.1%, 34.1% and 37.6%, respectively). The risk of having an event

increased significantly within the first 6 months after each event (**Figure 4**).

Healthcare use

Cumulative rates of hospital re-admission and ER visit increased with increasing recurrent events. For example, in the CHD group, the 1-year re-admission rates following the index, first and second recurrent events were 43.1%, 47.6% and 55.3%, respectively and the proportions visiting the ER were 46.4%, 51.9% and 57.8%, respectively (**Figure 5**). The rate of outpatient visits remained over 90% for all patient groups and events. Similarly high rates of healthcare usage were observed even if only hospital visits related to CV health were considered (**Supplement 5**).

Statin use

Statin prescriptions after each event remained relatively stable in all patient groups: 63.4–68.4% in the CHD group, 49.5–51.9% in the CBVD group and 34.5–40.8% in the PAD group within 12 months following the index event and the second recurrent event (**Figure 6**). Patients with index CHD were most frequently prescribed statins compared with patients with index CBVD or index PAD. Similar trends were evident when assessed at 0–6 or 0–18 months from the event (**Supplement 6**)

DISCUSSION

Our study demonstrates a higher risk of recurrence, mortality and increasing healthcare use among patients with occurrence of each additional recurrent ASCVD events; 22.5% of patients with CHD (21,902/97,321), 21.0% of patients with CBVD (25,337/120,914) and 40.2% of patients with PAD (5,951/14,794) at index had at least one recurrence during 3-year follow-up. Patients were more likely to have a recurrent event if they had already

experienced a recurrence, and this risk increased with increasing episodes of recurrence. In addition, the study found a trend towards a shorter median time to next event in patients in Taiwan with CHD or CBVD, but a similar median time between PAD events.

A notable finding is the suboptimal prescription of statins among patients in Taiwan with ASCVD events. Only 34.5% of patients with PAD, 63.4% of patients with CHD and 49.5% of patients with CBVD received statins in the 12 months after the index event. This finding is similar to US database studies, where approximately 45% of patients with ASCVD were not on lipid-lowering therapy.[16,17] The particularly low statin prescribing rates for PAD patients are also evident in US data; data from PAD patients collected 2005–2012 found only 33.1% were using statins.[18] The low statin prescribing rate among PAD patients in our study may contribute to the increased risk of recurrent events in these patients relative to their counterparts with CBVD or CHD. While our data show moderately higher statin prescribing as patients accumulate recurrent events, statin prescribing rates remained suboptimal overall (63–66% for the CHD group, 50–52% for the CBVD group and 35–41% for the PAD group). These data highlight undertreatment in ASCVD management in Taiwan, despite multiple studies confirming that lowering LDL cholesterol with high-intensity statins or PCSK9 inhibitors effectively reduces the risk of primary and secondary cardiovascular events.[19-21] Raising local awareness of the recommendations for secondary prevention in international guidelines may help address this problem.

Unlike previous studies,[9-12] which only focused on the first recurrent event and a single event type, our study provides a more complete picture regarding the patterns of multiple recurrent events and their associated burden. To the best of our knowledge, our study is the first in Asia investigating the burden of recurrent cardiovascular events. A recent study

in Finland has also evaluated multiple recurrent events including different event types, with some similar findings to our study. In Finnish CVD patients, each additional event caused increased risk of a recurrent event, and the median time of recurrence decreased with increasing numbers of events.[22]

The pattern of recurrent events showed that patients were more likely to develop the same type of ASCVD in the recurrent events. In our study, 66–81% of patients with new-onset CHD had CHD at first recurrence, whereas this percentage was 80–84% for CBVD and 76–78% for PAD. These findings are in line with a previous real-world study showing survivors of MI and ischaemic stroke are at immediate risk of having an additional cardiovascular event, in most cases of the same type as previously experienced by the patient.[23] Nevertheless, our data suggest that around one quarter of patients could experience a recurrent event of a different type to their initial event. Notably, PAD accounted for a larger proportion of recurrent event among patients with index CHD or CBVD event. Therefore, patients receiving treatment for secondary prevention should be educated on recognizing signs and symptoms of different types of events, not just their index event.

Our study revealed an increased risk of death with cumulative recurrent events at different follow-up periods (6, 12 and 18 months) across different types of index events; such data are relatively limited in existing literature.[22,23] Furthermore, among all three types of ASCVD we studied, patients with PAD had the highest risk of death and highest incidence of recurrent events with cumulative recurrent events, which is in line with findings from previous studies.[24,25] These data indicate an urgent need to improve secondary prevention in patients with ASCVD, especially those with PAD.

There are several limitations to our study. First, since the study used administrative records, we were unable to evaluate healthcare use that was not covered by the NHI, such as out-of-pocket payment. Second, our study only focused on recurrent events developing in the 3 years after the index date, and we were unable to capture recurrent events occurring beyond that. Moreover, the risk of mortality and developing recurrent events might be underestimated due to the limited follow-up period after the first and second recurrent event. Third, generalizability of our study may be limited by its study population, as we only included patients with new-onset ASCVD leading to hospitalization. Therefore, this study is likely to have included patients with ASCVD with higher severity or morbidity. Despite the above limitations, the use of claims data from the NHI database in this study provided comprehensive records on ASCVD occurrence, treatment pattern and healthcare use. The database covers over 99% of the population of Taiwan and is representative of Taiwan's general population; this allowed us to comprehensively investigate patients with ASCVD from the general population in Taiwan.

In a large population of patients in Taiwan we observed a higher risk of mortality with increasing recurrent events, as well as increased risk of developing further recurrent ASCVD events, and greater healthcare use, representing an increase in the disease burden. Our data also show suboptimal rates of statin use in these patients highlighting an opportunity to improve secondary prevention in this population.

Conflict of interest

Wei-Ju Chen and Yea-Harn Yang are employees of Amgen Taiwan Limited. Chia-Yun Hsu, Wen-Jone Chen, Hung-Ju Lin, Ho-Min Chen, Chieh-Min Chen and Fei-Yuan Hsiao received a grant from Amgen Taiwan Limited.

Funding

The project was funded by Amgen Taiwan Limited and N/A for the grant number.

Authors' contributions

Hsu CY, Chen WJ, Lin HJ, and Hsiao FY contributed to the study concept and design of the research; Hsu CY, Chen WJ, Yang YH, Chen CM and Hsiao FY performed the research; Ho-Min Chen analysed the data; all authors wrote and approved the manuscript.

Acknowledgements

We thank the National Health Insurance Administration (NHIA) and Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, for making the databases used in this study available. However, the content of this article does not represent any official position of the NHIA or HWDC. The authors have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Medical writing assistance was provided by MIMS (Hong Kong) Ltd., which was funded by Amgen Taiwan in compliance with Good Publication Practice 3 ethical guidelines (Battisti et al. *Ann Intern Med*. 2015;163:461–4) and the STROBE checklist for the reporting of observational studies (https://www.equator-network.org/reporting-guidelines/strobe/).

Data availability

The data underlying this article cannot be shared publicly due to ethical and legal restrictions from Taiwan authorities. The data can be accessed by qualified researchers with permission from the Health and Welfare Data Science Center (HWDC), Ministry of

Health and available only through HWDC facilities.

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FIGURE LEGENDS

Figure 1. Study design.

ASCVD: atherosclerotic cardiovascular disease.

Figure 2. Recurrent event types by index events type

ASCVD: atherosclerotic cardiovascular disease; CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Figure 3. Survival rates following each event.

CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Figure 4. Cumulative recurrent event rates following each event.

CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

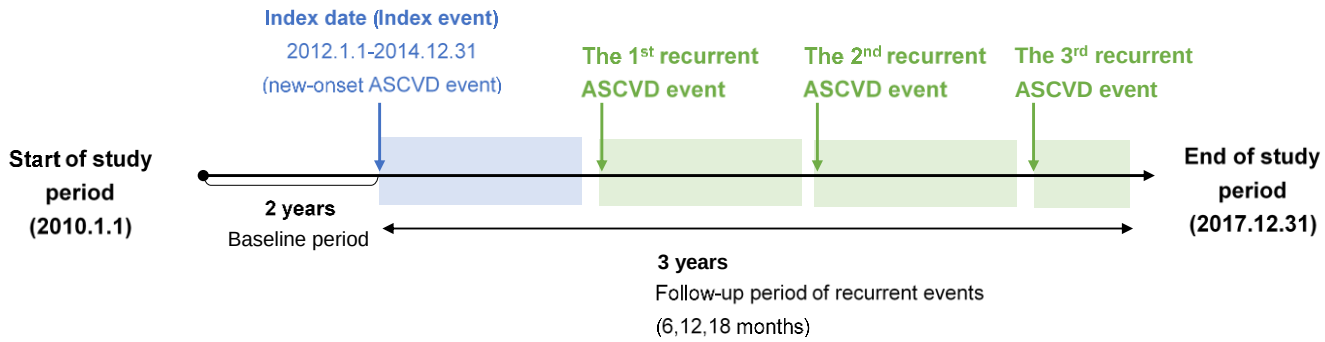
Figure 5. Proportion of patients having healthcare use following each event during a 12-month follow-up

CBVD: cerebrovascular disease; CHD: coronary heart disease; ER: emergency room; OPD: outpatient department; PAD: peripheral artery disease.

Figure 6. Proportion of statin prescription following each event during a 12-month follow-up

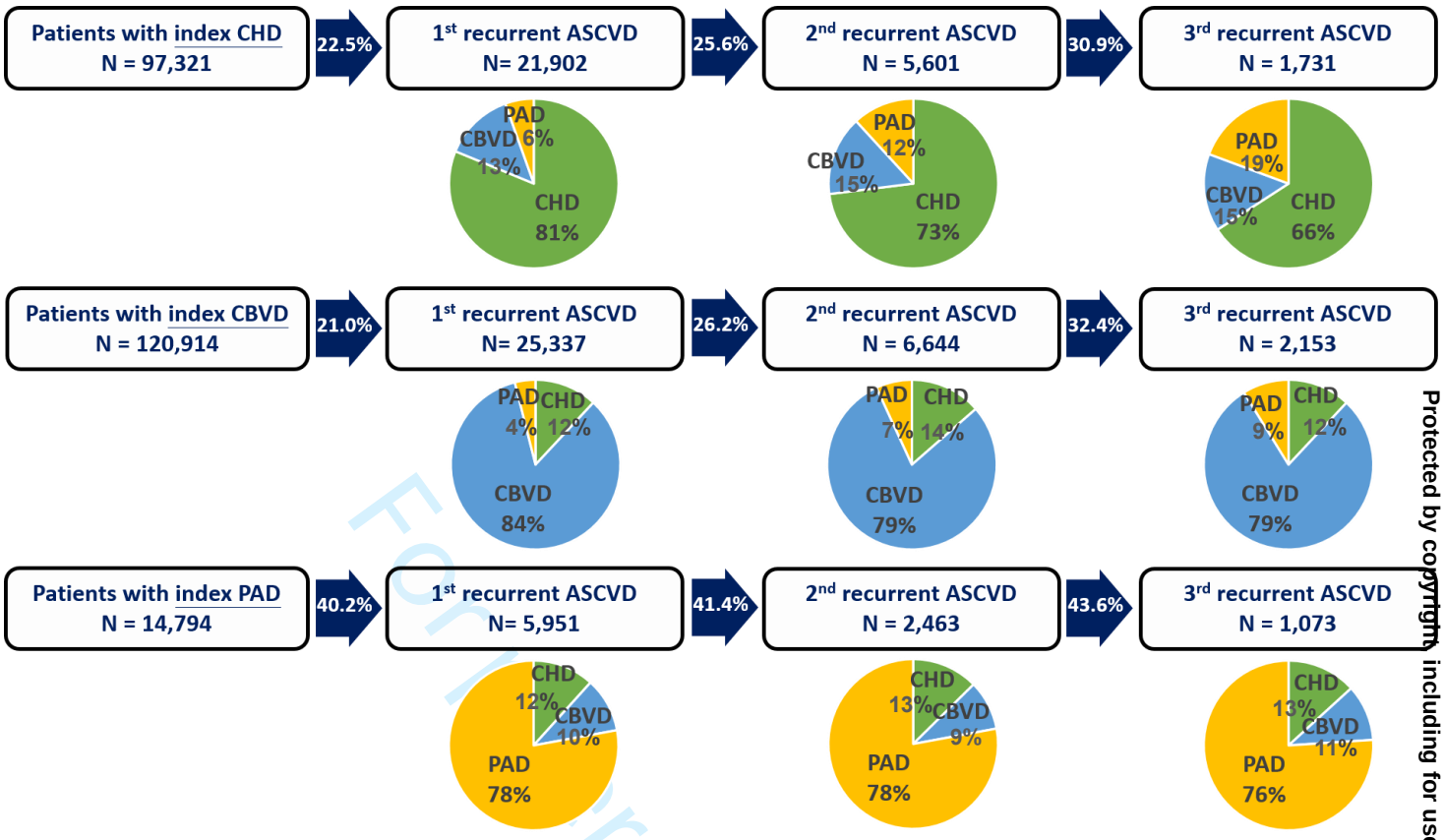
CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Figure 1. Study design



ASCVD: atherosclerotic cardiovascular disease.

Figure 2. Recurrent event types by index events type



ASCVD: atherosclerotic cardiovascular disease; CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Figure 3. Survival rates following each event

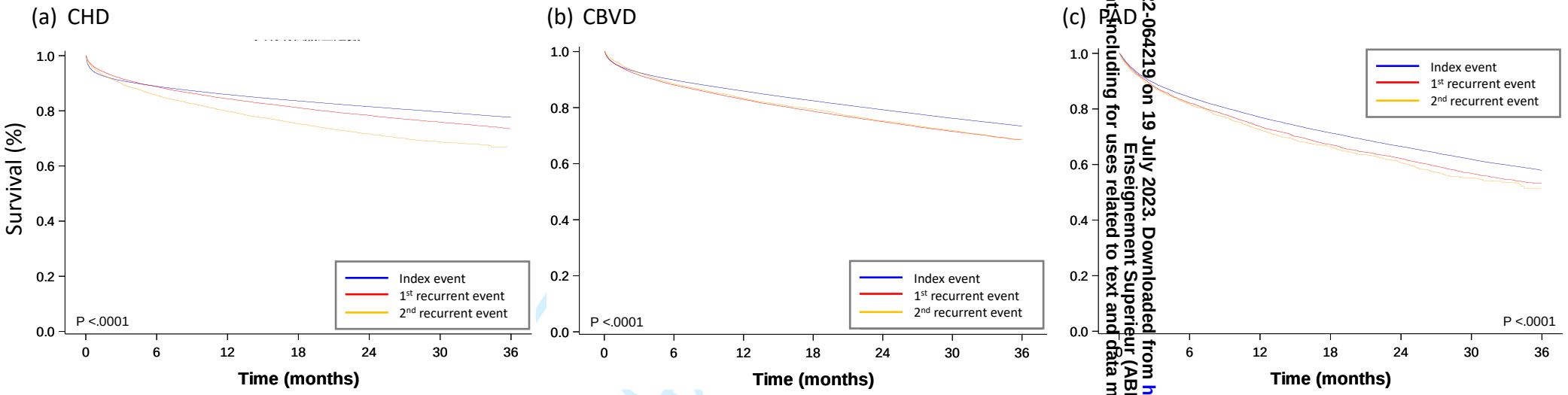


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Figure 4. Cumulative recurrent event rates following each event

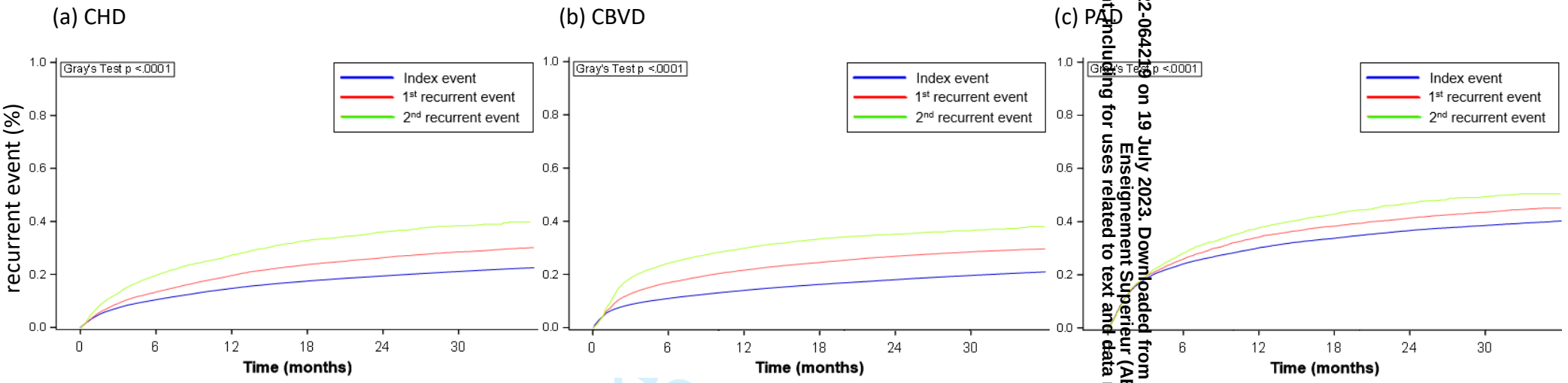

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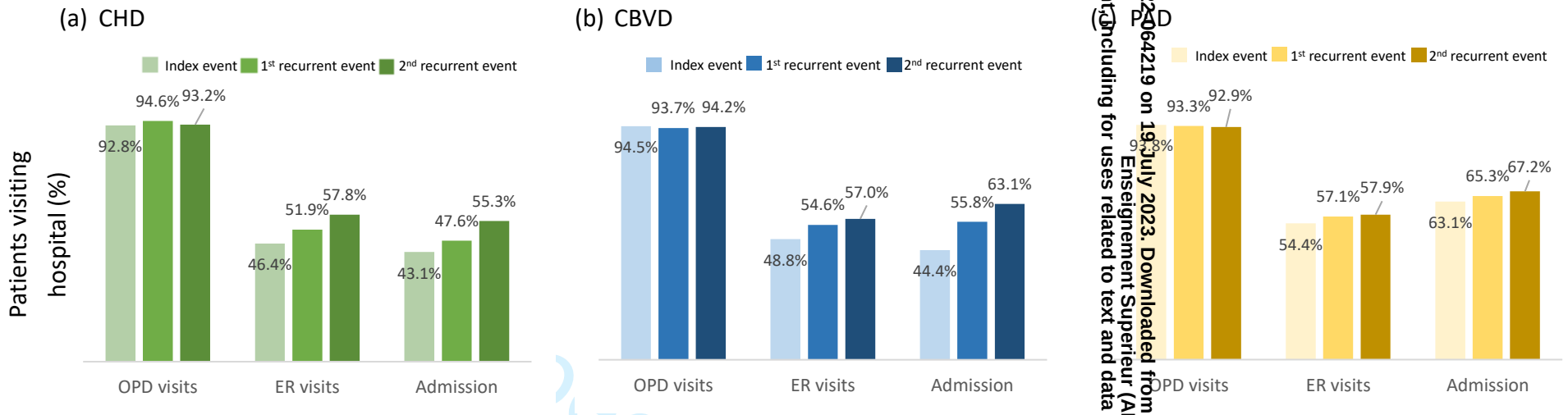
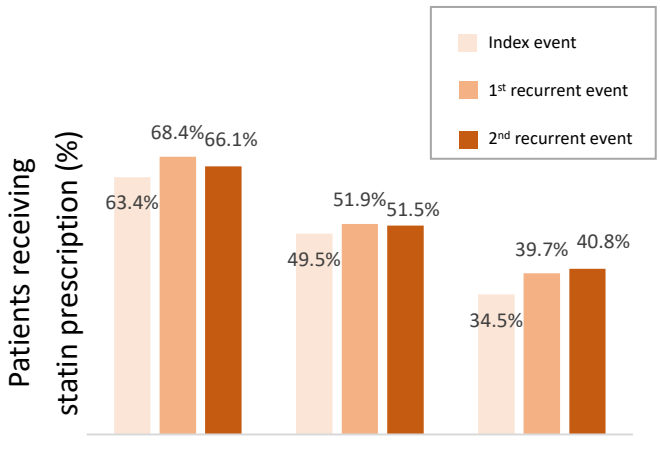
Figure 5. Proportion of patients having healthcare use following each event during a 12-month follow-up



CBVD: cerebrovascular disease; CHD: coronary heart disease; ER: emergency room; OPD: outpatient department; PAD: peripheral artery disease.

Figure 6. Proportion of statin prescription following each event during a 12-month follow-up



CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Online supplement

Higher risk of future events, mortality and greater healthcare use among patients with increasingly recurrent atherosclerotic cardiovascular disease events in Taiwan

Chia-Yun Hsu[1], Wen-Jone Chen[2], Hung-Ju Lin[2], Ho-Min Chen[1], Yea-Harn Yang[3], Wei-Ju Chen[3], Chieh-Min Chen[4], Fei-Yuan Hsiao[4,5,6*]

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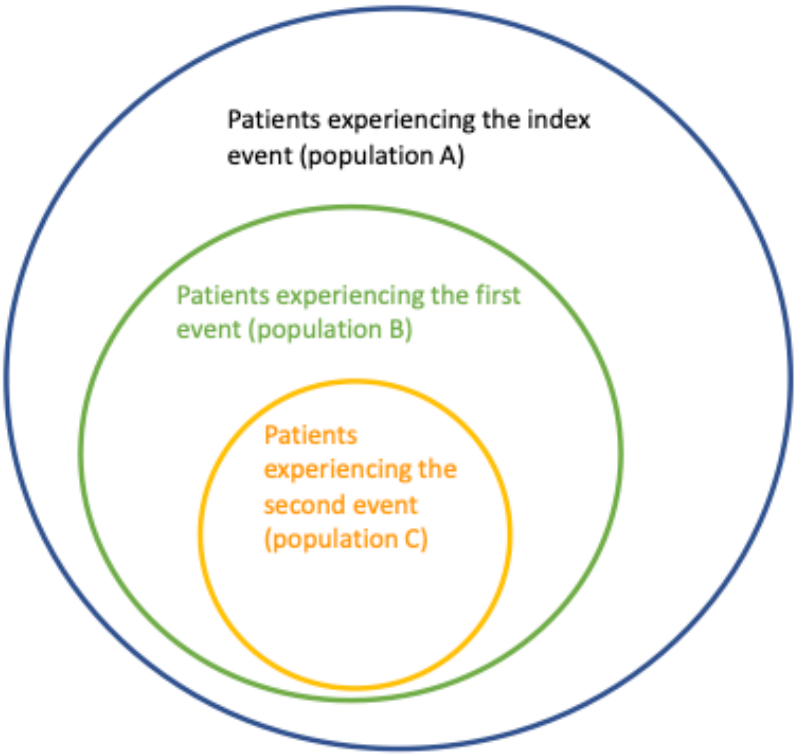
Supplement 1 (Figure). Definition of subsequent events

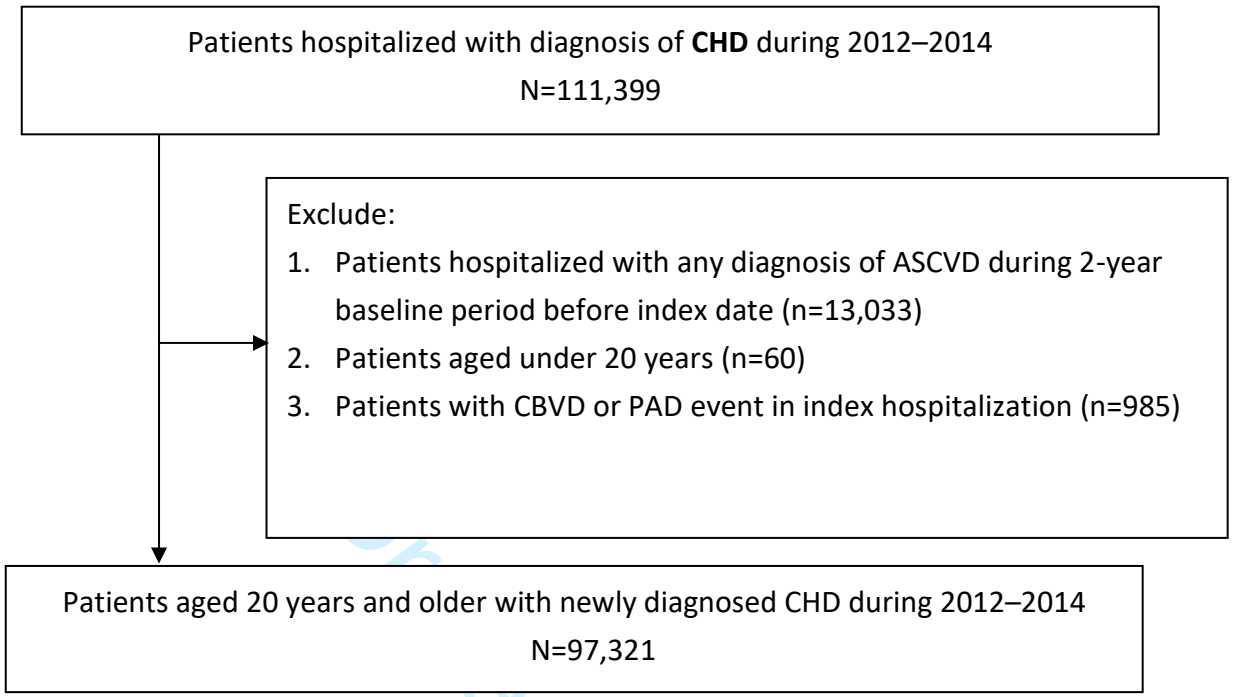


(Size of the circles is not proportional to the number of actual data)

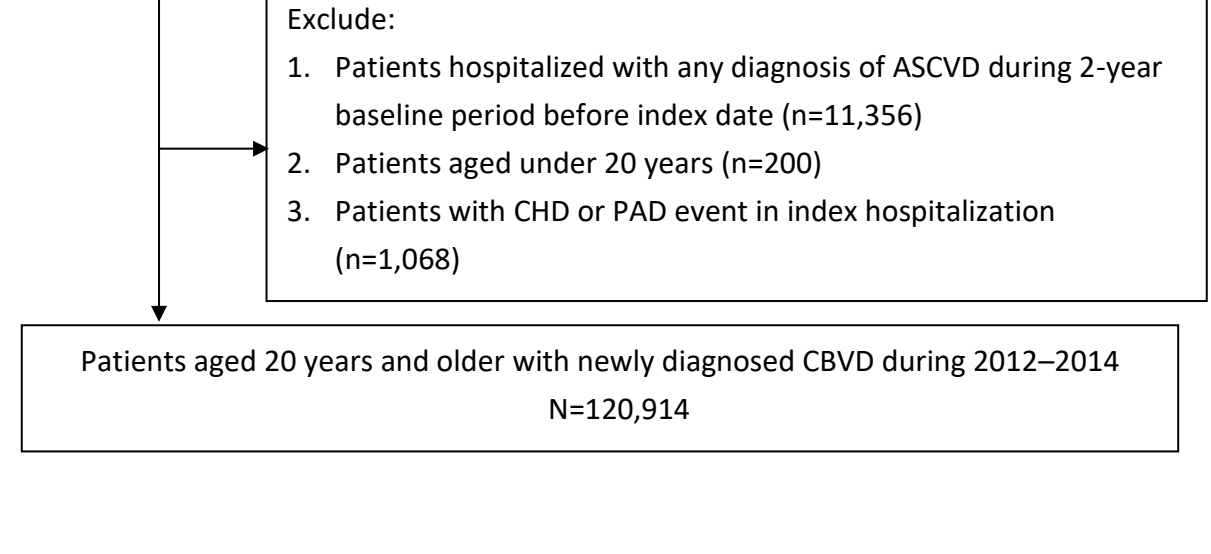
Patients with an index event (population A), were further defined into subsets if they experienced a first recurrent event (population B) and a second recurrent event (population C). Post-event mortality was calculated and compared between each of these populations.

Supplement 2 (Figure) Selection flow of study population

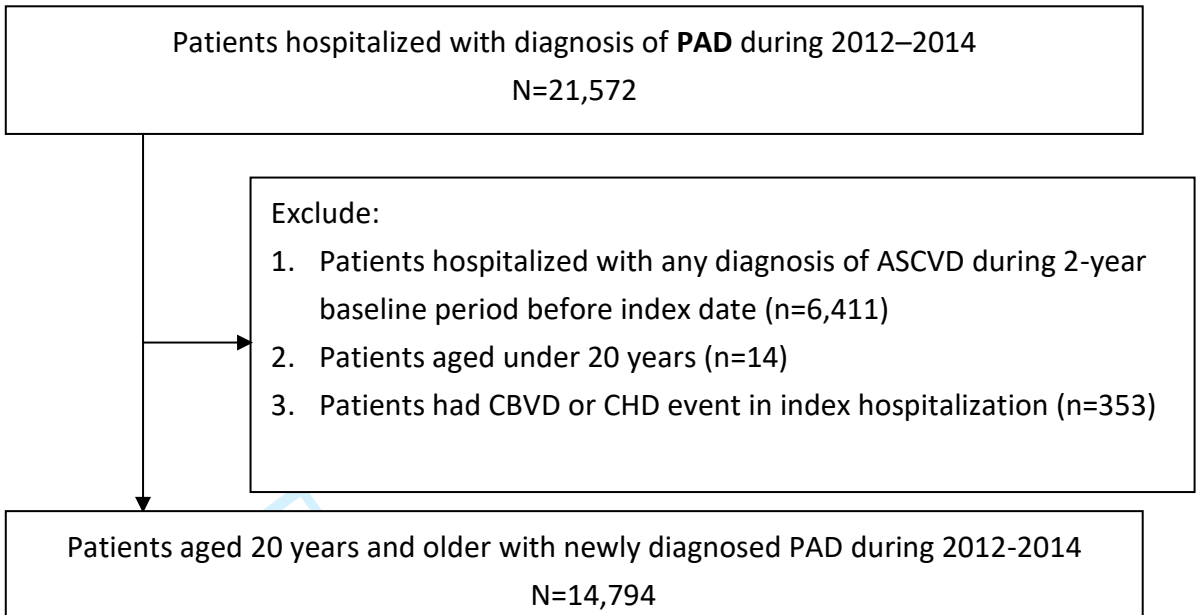
(a) Patients with new-onset CHD



(b) Patients with new-onset CBVD



(c) Patients with new-onset PAD



CBVD, cerebrovascular disease; CHD, coronary heart disease PAD, peripheral artery disease

Supplement 3 (Table). Probability of survival estimated by Kaplan–Meier method

	Patients, n	Deaths, n	(%)	Probability of survival			
				6 mo	12 mo	18 mo	24 mo
Coronary heart disease							
Index event	97,321	21,773	(22.4)	0.889	0.859	0.836	0.815
First recurrent event	21,902	4,769	(21.8)	0.887	0.844	0.811	0.784
Second recurrent event	5,601	1,376	(24.6)	0.856	0.798	0.753	0.716
Cerebrovascular disease							
Index event	120,914	32,125	(26.6)	0.899	0.859	0.824	0.792
First recurrent event	25,337	6,540	(25.8)	0.881	0.830	0.787	0.750
Second recurrent event	6,644	1,528	(23.0)	0.884	0.833	0.795	0.753
Peripheral artery disease							
Index event	14,794	6,217	(42.0)	0.842	0.770	0.713	0.665
First recurrent event	5,951	2,412	(40.5)	0.821	0.737	0.672	0.622
Second recurrent event	2,463	924	(37.5)	0.817	0.725	0.663	0.607

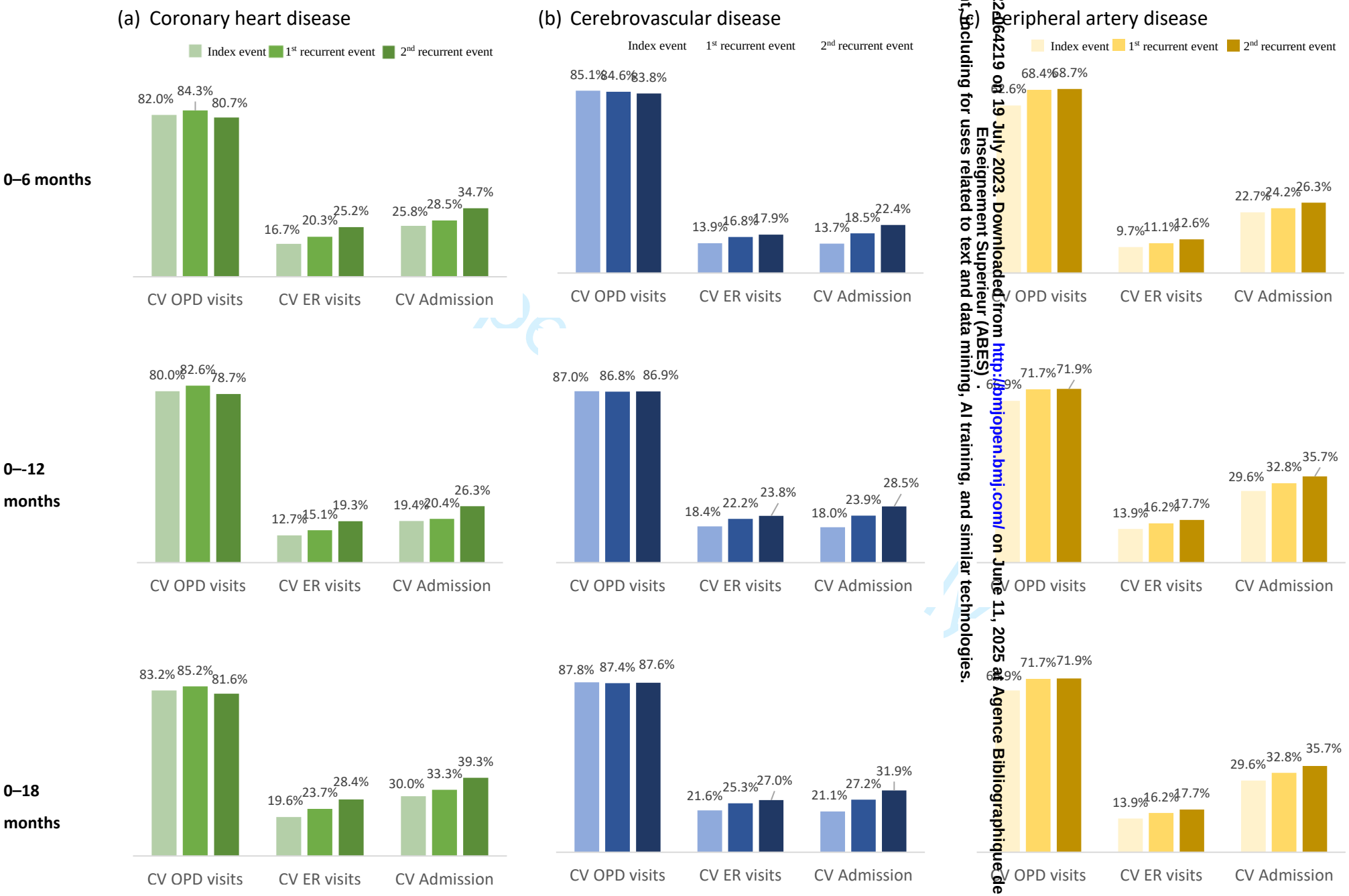
mo, months.

Supplement 4 (Table). Cumulative incidence rate of recurrent events considering competing risk estimated by Fine and Gray method

	Patients, n	Events, n	(%)	Event rate			
				6 mo	12 mo	18 mo	24 mo
Coronary heart disease							
Index event	97,321	21,902	(22.5)	0.104	0.147	0.175	0.194
First recurrent event	21,902	5,601	(25.6)	0.134	0.196	0.237	0.263
Second recurrent event	5,601	1,731	(30.9)	0.196	0.273	0.327	0.360
Cerebrovascular disease							
Index event	120,914	25,337	(20.9)	0.110	0.140	0.162	0.180
First recurrent event	25,337	6,644	(26.2)	0.169	0.216	0.245	0.268
Second recurrent event	6,644	2,153	(32.4)	0.242	0.298	0.333	0.351
Peripheral artery disease							
Index event	14,794	5,951	(40.2)	0.241	0.301	0.338	0.367
First recurrent event	5,951	2,463	(41.4)	0.259	0.341	0.383	0.413
Second recurrent event	2,463	1,073	(43.6)	0.281	0.376	0.428	0.470

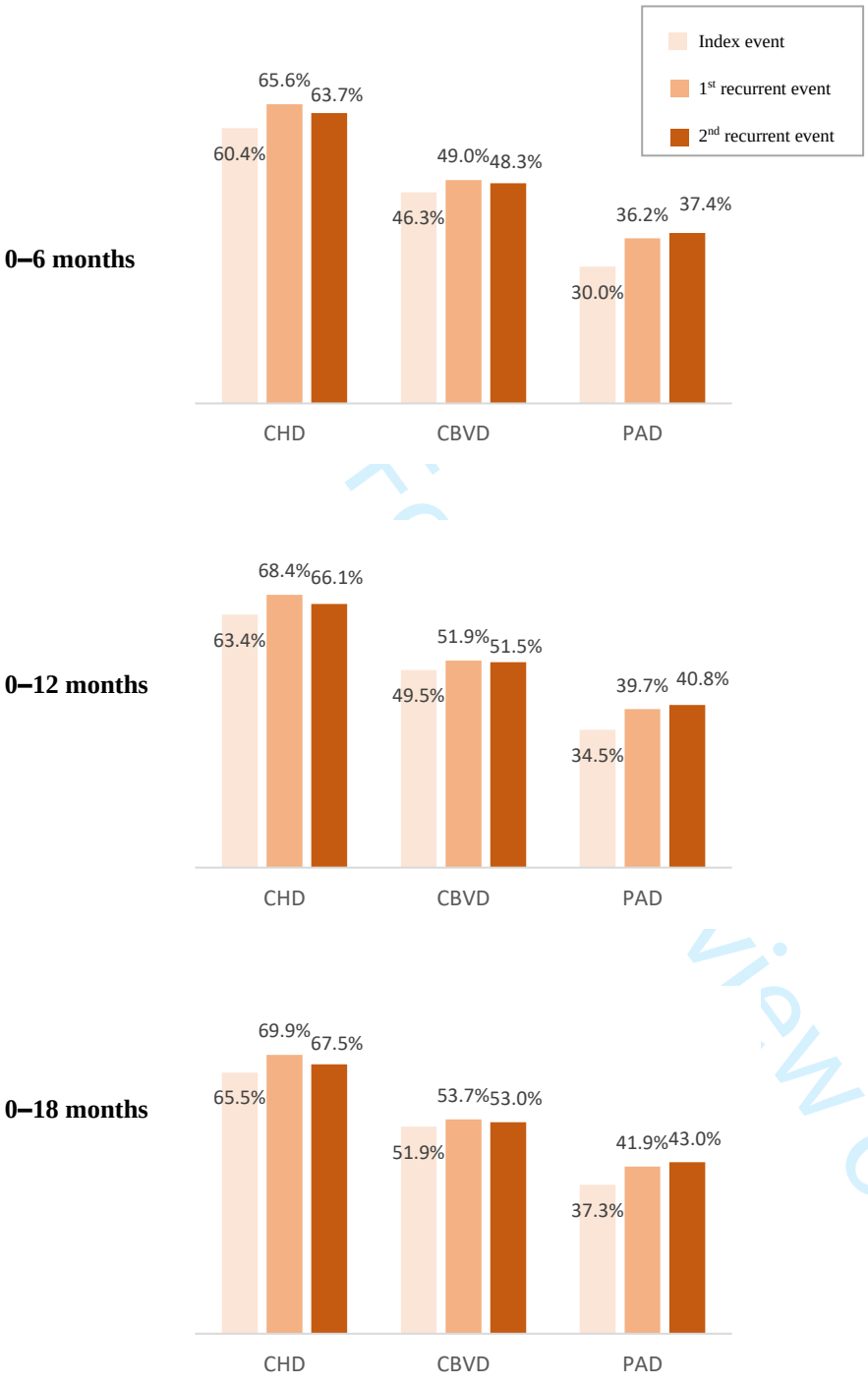
mo, months.

Supplement 5 (Figure). Percentage of patients having cardiovascular-related healthcare use following each event.



CV, cardiovascular disease; ER, emergency room OPD: outpatient department

Supplement 6 (Figure). Percentage of patients prescribed with statin following each event



CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12-14
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-14

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Higher risk of future events, mortality, and greater healthcare use among patients with increasingly recurrent atherosclerotic cardiovascular disease events in Taiwan: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064219.R1
Article Type:	Original research
Date Submitted by the Author:	17-Nov-2022
Complete List of Authors:	Hsu, Chia-Yun; National Taiwan University CHEN, WEN-JONE; National Taiwan University Hospital, Internal Medicine; National Taiwan University Hospital, Emergency Medicine Lin, Hung-Ju; National Taiwan University Hospital, Department of Internal Medicine, National Taiwan University Hospital Chen, Ho-Min; National Taiwan University Hospital Hsin-Chu Branch, Center for Critical Care Medicine Yang, Yea-Harn; Amgen Taiwan Limited Chen, Wei-Ju; Amgen Taiwan Limited Chen, Chieh-Min; National Taiwan University Hsiao, Fei-Yuan; National Taiwan University; National Taiwan University Hospital, Department of Pharmacy
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Cardiovascular medicine
Keywords:	Coronary heart disease < CARDIOLOGY, Cardiac Epidemiology < CARDIOLOGY, EPIDEMIOLOGY

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Higher risk of future events, mortality, and greater healthcare use among patients with increasingly recurrent atherosclerotic cardiovascular disease events in Taiwan: a retrospective cohort study

Chia-Yun Hsu[1], Wen-Jone Chen[2], Hung-Ju Lin[2], Ho-Min Chen[1], Yea-Harn Yang[3], Wei-Ju Chen[3], Chieh-Min Chen[4], Fei-Yuan Hsiao[4,5,6*]

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Running head: Patients with recurrent ASCVD events in Taiwan

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Fax: Not available

Abstract: 295 words

Text word counts: 3303 words (excluding the title, author names/affiliations, abstract, keywords, figures/tables and references)

Figure counts: 5 figures

Table counts: 1 table

Others: 5 supplemental figures & 2 supplemental tables

References: 20

ABSTRACT (word count: 295)

Objectives:

To describe the occurrence of recurrent atherosclerotic cardiovascular disease (ASCVD) events within 3 years after a new-onset event, and the associated disease burden, and statin prescribing in ASCVD patients in Taiwan.

Design: Retrospective cohort study.

Setting: This was a retrospective cohort study using Taiwan's National Health Insurance Research Database (NHIRD).

Participants:

In total, 111,399, 133,538 and 21,572 patients who were hospitalized with diagnosis of coronary heart disease (CHD), cerebrovascular disease (CBVD) and peripheral artery disease (PAD), respectively, between 1 January 2012 and 31 December 2014.

Primary and secondary outcome measures:

For each index and recurrent event, patients were observed for 12 months after admission to quantify risks of mortality, recurrent events, statin treatment and healthcare use.

Results:

We identified 97,321, 120,914 and 14,794 patients with new-onset coronary heart disease (CHD), cerebrovascular disease (CBVD) and peripheral artery disease (PAD), respectively. The proportions of developing first, second and third recurrent events were: 22.5, 25.6 and 30.9% for CHD; 20.9, 26.2 and 32.4% for CBVD; and 40.2, 41.4 and 43.6% for PAD, respectively. Most patients had the same type of ASCVD for their recurrent events as their new-onset event. The mortality rates increased with each recurrent event (p <0.05 for all three ASCVD groups). The rates of hospital re-admission and ER visit increased with increasing recurrent events. For example, in the CHD group, the 1-year re-admission rates following the index, first and second recurrent events were 43.1%, 47.6% and 55.3%,

respectively and the proportions of visiting ER were 46.4%, 51.9% and 57.8%, respectively. Statin prescribing was suboptimal at time of index event and recurrent events.

Conclusion:

Recurrent ASCVD events were associated with a higher risk of recurrent event and mortality and greater healthcare use. However, statin prescriptions at index event and after each recurrent event were suboptimal.

Keywords (up to 6): atherosclerotic cardiovascular disease (ASCVD) events, recurrent event, mortality, healthcare use, statin

Strengths and limitations of this study:

- This retrospective cohort study using Taiwan's national health insurance claims data, which provides nationwide estimates of recurrent atherosclerotic cardiovascular disease (ASCVD) events.
- The methodology is noteworthy in capturing up to third recurrent ASCVD events and its associated mortality and healthcare use due to its longitudinal study design.
- As with all studies using claims data, healthcare uses that are not covered by the national health insurance are not captured in this study.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) comprises acute coronary syndrome, myocardial infarction (MI), unstable angina, coronary or other arterial revascularization, transient ischaemic attack and peripheral artery disease (PAD).[1] Patients who have had a first ASCVD event have an increased risk for future events compared to those with no events.[1]

Prior studies have indicated that some ASCVD patients develop recurrent events within a relatively short period.[2-4] For example, in a US study comprising 48,688 Medicare beneficiaries with index acute MI, the recurrence rate remained relatively high for patients experiencing acute MI or coronary heart disease (CHD), at 68.5 and 124.9 per 1,000 person-years, respectively, during 2007–2009.[2] In a cohort of 7,870 patients with acute MI enrolled in the Osaka Acute Coronary Insufficiency Study (OACIS), 353 patients (4.5%) experienced recurrent MI with a median follow-up of 3.9 years.[3] Another study of 196,765 patients with ischaemic stroke in the Swedish Stroke Register (Riksstroke) reported that 11.3% had a recurrent ischaemic stroke within 1 year.[5]

In addition, as different ASCVD events share common risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus and smoking, some studies have suggest that the recurrent event may not be identical to the index event. For example, 1.4% of patients discharged after acute MI experienced a stroke event during the next 12 months.[6] Therefore assessing for other types of recurrent ASCVD events in addition to the index event type may produce a more complete picture of recurrent event risk, but examples of such an approach in the literature are rare.

Although the development of recurrent ASCVD events has been investigated, most existing studies observe event rates and outcomes associated with the first ASCVD recurrence; data on event rates beyond the first recurrence are limited. The epidemiology of ASCVD events and the treatment patterns of these patients are not well understood, particularly in Taiwan. First, it is not known if recurrent ASCVD events incur a higher burden to patients in terms of healthcare use or mortality. Secondly, it is not clear whether these high-risk patients receive lipid-lowering treatment as recommended by the international guidelines[1, 7]. Previous studies have suggested that patients with a history of CVD events are often undertreated. Data from Europe show 80% of such patients are not at LDL target, and in low-to-middle income countries fewer than 10% of patients are on multidrug treatment.[8]

Therefore, the aim of this study is to evaluate the temporal pattern and healthcare burden of recurrent ASCVD events within 3 years following a new-onset ASCVD event (index event) in patients in Taiwan. For each ASCVD event (index, first and second recurrent events), we followed up to 18 months after admission to estimate risk of mortality and recurrent events. Healthcare use was also estimated following each event using the same landmark approach.

METHODS

Data source

This retrospective cohort study used data from Taiwan's National Health Insurance Research Database (NHIRD) from 1 January 2010 to 31 December 2017, provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW). Taiwan's National Health Insurance (NHI) system is a mandatory, single-payer health insurance programme, which provides comprehensive benefits including inpatient care, ambulatory care, dental care and prescription drugs to its beneficiaries. Over 99% of Taiwan's 23 million

people are covered by the NHI. The NHIRD is a database of uniquely-identified claims and transactions for all covered services used by patients enrolled in the programme. It provides patient-level information for research, including demographic, clinical, medical resource use (ambulatory care claims, emergency room [ER] claims and inpatient claims) and treatment patterns. All traceable personal identifiers were encrypted to protect patient confidentiality.[9]

Study design

This was a retrospective longitudinal study using Taiwan's NHIRD. **Figure 1** illustrates the study design. We identified patients with a new-onset ASCVD event (index event) and followed up their recurrent ASCVD events (first, second and third recurrent events). The date of the new-onset event was defined as the index date. The 2-year baseline period before the index date was examined to ensure patients had no history of prior ASCVD and to ascertain baseline characteristics. The observation period for recurrent events was from the index date (inclusive of index date) to death or 3 years after the index date, whichever came first.

For each ASCVD event (index, first and second recurrent event), we observed patients for 12 months after admission to estimate risks of mortality and recurrent events, and healthcare use. Sensitivity analyses using follow-up durations of 6 and 18 months were performed.

Study population

All patients in the NHIRD with a primary ASCVD event during 1 January 2012 through 31 December 2014 and aged 20 years or above were included in this study. An ASCVD event was defined as a hospitalization with a primary or a first secondary discharge diagnosis of ASCVD. In addition, no history of hospitalization with any ASCVD diagnosis within 2 years prior to the index event was required to guarantee new-onset events (index event).

We categorized patients with new-onset ASCVDs into three categories using International Classification of Diseases version 9 and 10 (ICD-9/10-CM) codes: (1) those with CHD, including MI (ICD-9-CM codes 410.x, 412; ICD-10-CM codes I21, I22, I25.2), angina (ICD-9-CM codes 411.1, 413.x; ICD-10-CM code I20) and other ischaemic heart disease (ICD-9-CM codes 411.0, 411.8x; ICD-10-CM code I24); (2) those with CBVD, including ischaemic stroke (ICD-9-CM codes 433.x1, 434.x1; ICD-10-CM code I63) and transient ischaemic attack (ICD-9-CM codes 435.8, 435.9; ICD-10-CM codes G45.0–G45.2, G45.8–G45.9); and (3) those with PAD (ICD-9-CM codes 250.7x, 440.2x, 440.8, 440.9, 443.9, 444.2x, 444.9; ICD-10-CM codes E10.5, E11.5, I70.2–I70.9, I73.9, I74.3, I74.5, I75). Patients diagnosed with more than one type of ASCVD in new-onset hospitalization were excluded to avoid interaction effects of dual ASCVD events on outcome measurements.

In total, we identified 111,399, 133,538 and 21,572 patients who were hospitalized with a diagnosis of CHD, CBVD or PAD, respectively, between 1 January 2012 and 31 December 2014.

Study variables

Index event and recurrent event

This study identified the index event as the date of new-onset ASCVD events and defined recurrent ASCVD events as occurring within the 3 years of follow-up after the index event (sequentially characterized as a first, second or third recurrent event). Recurrent ASCVD events, defined as a hospitalization with the primary or the first secondary discharge diagnosis of ASCVD, were also classified as CHD events, CBVD events or PAD events. Length of hospital stay of each event was calculated in days. Time between events was calculated in days between the discharge date of the event and the admission date of the

next event. Follow-up time of each event was calculated in months from the discharge of each event until the end of study follow-up.

Risk of mortality and recurrent event

Following each ASCVD event, mortality was identified using the National Death Registry (linked to the NHIRD by encrypted personal identities). Recurrent events were identified using the definition mentioned above. Risk of mortality associated with a recurrent event was followed up from discharge after each event to occurrence of the outcome or 31 December 2017, whichever came first.

Healthcare use

Healthcare use following each ASCVD event (index, first and second recurrent event), excluding use for the event itself, was estimated for 12 months following discharge after the event. Healthcare use was estimated by calculating the number of outpatient visits, ER visits and re-admissions. Sensitivity analyses using follow-up durations of 6 and 18 months were performed.

Statin use

Proportions of patients prescribed statins following each ASCVD event (index, first and second recurrent event) were calculated for 12 months following admission for the event. During the study period (2012–2017), statins were used as the major lipid-lowering therapy in the Taiwan NHI system, while ezetimibe was reimbursed when used in combination with statin treatment.[10] Therefore, we only described statin use in this study. Sensitivity analyses using follow-up durations of 6 and 18 months were performed.

Statistical analysis

Variables were summarized through descriptive analyses, including tabular and graphical display of mean, standard deviation, median and interquartile range for continuous variables, and frequency and percentage for categorical variables.

Following each ASCVD event, risk of all-cause mortality and risk of recurrent event over time were estimated and compared across patients who developed designated subsequent events. For example, among patients with new-onset CHD, the risk of all-cause mortality for the index event was calculated from the time of index event till the end of observation; the mortality risk for the first subsequent event was calculated from the time they developed the first recurrent event till the end of observation, similarly for those developed with the second recurrent event (**Supplement 1**). The data were presented as Kaplan-Meier survival curves. For estimating risk of recurrent events, we conducted Fine and Gray analysis to account for competing risks of death.

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-sided p <0.05 were considered statistically significant.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Study population

We identified 111,399, 133,538 and 21,572 patients who were hospitalized with a diagnosis of CHD, CBVD or PAD, respectively, between 1 January 2012 and 31 December 2014. We

excluded patients with a history of ASCVD in the 2 years prior to the index event and patients younger than 20 years of age. Patients with multiple ASCVD types at the index event were excluded (985 patients in the CHD cohort; 1,068 patients in the CBVD cohort; and 353 patients in the PAD cohort). Therefore, we analysed the records of 97,321, 120,914 and 14,794 patients with new-onset CHD, CBVD and PAD, respectively (Selection flow of study population in **Supplement 2**). Baseline characteristics showed that 68.5%, 59.5% and 57.7% of patients were male, with median age 65, 71 and 74 years in the CHD, CBVD and PAD groups, respectively (**Table 1**).

Index event and recurrent events

Among the new-onset patients, 22.5% of patients with CHD (21,902/97,321), 21.0% of patients with CBVD (25,337/120,914) and 40.2% of patients with PAD (5,951/14,794) had at least one recurrent event **(Table 1)**. The proportion of patients developing a recurrent event during follow-up increased with each additional event that occurred (the proportions developing the first, second and third recurrent events were: 22.5%, 25.6% and 30.9% for CHD; 21.0%, 26.2% and 32.4% for CBVD; and 40.2%, 41.4% and 43.6% for PAD; **Supplement 3).**

With more recurrent events, there was a trend towards a shorter median time to next event in patients with CHD (213 days from index event to first recurrent event; 176 days from first to second recurrent event; 124 days from second to third recurrent event) or CBVD (162 days; 99 days; 72 days), but not in those with PAD (112 days; 112 days; 115 days). The median length of hospital stay showed little change between events in CHD and PAD groups, whereas an increasing trend was observed in CBVD group (from 7 days for index event to 11 days for third recurrent event).

Most patients had the same type of ASCVD for their recurrent events as for their index

event; 66–81% of patients with new-onset CHD had CHD at first recurrence, whereas this percentage was 80–84% for CBVD and 76–78% for PAD (**Supplement 3**). When assessing these data by ASCVD type, the proportion of PAD events increased with each additional event in the CHD group (from 6% for the first recurrent event to 19% for the third recurrent event) and CBVD group (from 4% for the first recurrent event to 9% for the third recurrent event). In contrast, the proportions of CHD and CBVD remained stable across recurrences in the non-CHD (CBVD/PAD) and non-CBVD (CHD/PAD) groups, respectively (**Supplement 3**).

Risk of mortality and recurrence rate following each event

For patients with PAD with one recurrent event, the mortality rate was 40.5%; patients with CHD or CBVD with one recurrent event, had mortality rates of 21.8% and 25.8%, respectively. The survival rates decreased as recurrent events accumulated (p <0.05 for all three ASCVD groups; **Figure 2**). The 1-year survival rates following the index event, first recurrent event and second recurrent event in the CHD group were 85.9%, 84.4% and 79.8%, respectively **(Supplement 4)**. For patients with CBVD or PAD, 1-year survival rates were highest after the index event, compared with later events, and survival rates were similar following the first and second recurrent event (CBVD: 85.9%, 83.0% and 83.3%, respectively; PAD: 77.0%, 73.7% and 72.5%, respectively.

Higher rates of developing another recurrent event were observed when patients experienced more recurrent events (p <0.05 for all three ASCVD groups; **Figure 3**). The 1-year recurrent event rates following the index event, first and second recurrent event were 14.7%, 19.6% and 27.3%, respectively, in the CHD group (**Supplement 5)**. A similar trend was observed for the CBVD and PAD groups (CBVD: 14.0%, 21.6% and 29.8%, respectively; PAD: 30.1%,

34.1% and 37.6%, respectively). The risk of having an event increased significantly within the first 6 months after each event (**Figure 3**).

Healthcare use

Cumulative rates of hospital re-admission and ER visit increased with increasing recurrent events. For example, in the CHD group, the 1-year re-admission rates following the index, first and second recurrent events were 43.1%, 47.6% and 55.3%, respectively and the proportions visiting the ER were 46.4%, 51.9% and 57.8%, respectively (**Figure 4**). The rate of outpatient visits remained over 90% for all patient groups and events. Similarly high rates of healthcare usage were observed even if only hospital visits related to CV health were considered (**Supplement 6**).

Statin use

Statin prescriptions after each event were suboptimalin all patient groups: 63.4–68.4% in the CHD group, 49.5–51.9% in the CBVD group and 34.5–40.8% in the PAD group within 12 months following the index event and the second recurrent event (**Figure 5**). Patients with index CHD were most frequently prescribed statins compared with patients with index CBVD or index PAD. Similar trends were evident when assessed at 0–6 or 0–18 months from the event (**Supplement 7**)

DISCUSSION

Our study demonstrates a higher risk of recurrence, mortality and increasing healthcare use among patients with occurrence of each additional recurrent ASCVD events; 22.5% of patients with CHD (21,902/97,321), 21.0% of patients with CBVD (25,337/120,914) and 40.2% of patients with PAD (5,951/14,794) at index had at least one recurrence during 3-

year follow-up. Patients were more likely to have a recurrent event if they had already experienced a recurrence, and this risk increased with increasing episodes of recurrence. In addition, the study found a trend towards a shorter median time to next event in patients in Taiwan with CHD or CBVD, but a similar median time between PAD events.

A notable finding is the suboptimal prescription of statins among patients in Taiwan with ASCVD events. Only 34.5% of patients with PAD, 63.4% of patients with CHD and 49.5% of patients with CBVD received statins in the 12 months after the index event. This finding is similar to US database studies, where approximately 45% of patients with ASCVD were not on lipid-lowering therapy.[11, 12] The particularly low statin prescribing rates for PAD patients are also evident in US data; data from PAD patients collected 2005–2012 found only 33.1% were using statins.[13] The low statin prescribing rate among PAD patients in our study may contribute to the increased risk of recurrent events in these patients relative to their counterparts with CBVD or CHD. While our data show moderately higher statin prescribing as patients accumulate recurrent events, statin prescribing rates remained suboptimal overall (63–66% for the CHD group, 50–52% for the CBVD group and 35–41% for the PAD group). These data highlight undertreatment in ASCVD management in Taiwan, despite multiple studies confirming that lowering LDL cholesterol with high-intensity statins or PCSK9 inhibitors effectively reduces the risk of primary and secondary cardiovascular events.[14-16] Raising local awareness of the recommendations for secondary prevention in international guidelines may help address this problem.

Unlike previous studies,[2-5] which only focused on the first recurrent event and a single event type, our study provides a more complete picture regarding the patterns of multiple recurrent events and their associated burden. To the best of our knowledge, our study is the first in

Asia investigating the burden of recurrent cardiovascular events. A recent study in Finland has also evaluated multiple recurrent events including different event types, with some similar findings to our study. In Finnish CVD patients, each additional event caused increased risk of a recurrent event, and the median time of recurrence decreased with increasing numbers of events.[17]

The pattern of recurrent events showed that patients were more likely to develop the same type of ASCVD in the recurrent events. In our study, 66–81% of patients with new-onset CHD had CHD at first recurrence, whereas this percentage was 80–84% for CBVD and 76–78% for PAD. These findings are in line with a previous real-world study showing survivors of MI and ischaemic stroke are at immediate risk of having an additional cardiovascular event, in most cases of the same type as previously experienced by the patient.[18] Nevertheless, our data suggest that around one quarter of patients could experience a recurrent event of a different type to their initial event. Notably, PAD accounted for a larger proportion of recurrent event among patients with index CHD or CBVD event. Therefore, patients receiving treatment for secondary prevention should be educated on recognizing signs and symptoms of different types of events, not just their index event.

Our study revealed an increased risk of death with cumulative recurrent events at different follow-up periods (6, 12 and 18 months) across different types of index events; such data are relatively limited in existing literature.[17, 18] Furthermore, among all three types of ASCVD we studied, patients with PAD had the highest risk of death and highest incidence of recurrent events with cumulative recurrent events, which is in line with findings from previous studies.[19, 20] These data indicate an urgent need to improve secondary prevention in patients with ASCVD, especially those with PAD.

There are several limitations to our study. First, since the study used administrative records, we were unable to evaluate healthcare use that was not covered by the NHI, such as out-of-pocket payment. In addition, socioeconomic factor or life style factors (such as diet or exercise) are not available in Taiwan's national health insurance claims data. Second, our study only focused on recurrent events developing in the 3 years after the index date, and we were unable to capture recurrent events occurring beyond that. Moreover, the risk of mortality and developing recurrent events might be underestimated due to the limited follow-up period after the first and second recurrent event. Third, generalizability of our study may be limited by its study population, as we only included patients with new-onset ASCVD leading to hospitalization. Therefore, this study is likely to have included patients with ASCVD with higher severity or morbidity. Fourth, as we intended to capture the natural course of recurrent atherosclerotic cardiovascular disease events, we did not include other control variables beside age and sex in our competing risk model analyses. Despite the above limitations, the use of claims data from the NHI database in this study provided comprehensive records on ASCVD occurrence, treatment pattern and healthcare use. The database covers over 99% of the population of Taiwan and is representative of Taiwan's general population; this allowed us to comprehensively investigate patients with ASCVD from the general population in Taiwan.

In a large population of patients in Taiwan we observed a higher risk of mortality with increasing recurrent events, as well as increased risk of developing further recurrent ASCVD events, and greater healthcare use, representing an increase in the disease burden. Our data also show suboptimal rates of statin use in these patients highlighting an opportunity to improve secondary prevention in this population.

Acknowledgements

We thank the National Health Insurance Administration (NHIA) and Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, for making the databases used in this study available. However, the content of this article does not represent any official position of the NHIA or HWDC. The authors take responsibility for the integrity of the data and the accuracy of the data analysis. Medical writing assistance was provided by MIMS (Hong Kong) Ltd., which was funded by Amgen Taiwan in compliance with Good Publication Practice 3 ethical guidelines (Battisti et al. *Ann Intern Med*. 2015;163:461–4) and the STROBE checklist for the reporting of observational studies (https://www.equator-network.org/reporting-guidelines/strobe/).

Author contributions

Chia-Yun Hsu, Wen-Jone Chen, Hung-Ju Lin, Wei-Ju Chen, Yea-Harn Yang and Fei-Yuan Hsiao contributed to the study concept and design of the research; Chia-Yun Hsu, Chieh-Min Chen and Fei-Yuan Hsiao performed the research; Ho-Min Chen analysed the data; all authors wrote and approved the manuscript.

Funding

The project was funded by Amgen Taiwan Limited. The title of the project was burden of subsequent cardiovascular event among patients with cardiovascular disease in Taiwan.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: Wei-Ju Chen and Yea-Harn Yang are employees of Amgen Taiwan Limited. Chia-Yun Hsu, Wen-Jone Chen, Hung-Ju Lin, Ho-Min Chen, Chieh-Min Chen and Fei-Yuan Hsiao received a grant from Amgen Taiwan Limited.

Patient consent for publication

Not applicable.

Ethics approval

This study was reviewed and approved by the Research Ethics Committee of National Taiwan University Hospital (NTUH-REC-201710059W). Informed consent from patients was waived since the data were retrospectively collected and the identification data from NHIRD were encrypted for confidentiality.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

The data underlying this article cannot be shared publicly due to ethical and legal restrictions from Taiwan authorities. The data can be accessed by qualified researchers with permission from the Health and Welfare Data Science Center (HWDC), Ministry of Health and available only through HWDC facilities.

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FIGURE LEGENDS

Figure 1. Study design.

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CBVD, cerebrovascular disease; PAD, peripheral artery disease.

Figure 2. Survival rates following each event.

CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Figure 3. Cumulative recurrent event rates following each event.

CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Figure 4. Proportion of patients having healthcare use following each event during a 12-month follow-up

CBVD: cerebrovascular disease; CHD: coronary heart disease; ER: emergency room; OPD: outpatient department; PAD: peripheral artery disease.

Figure 5. Proportion of statin prescription following each event during a 12-month follow-up

CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

TABLES

Table 1. Patient demographics and characteristics of each event

	Index event		1st recurrent event		2nd recurrent event		3rd recurrent event	
CHD								
Patients, n	97,321		21,902		5,601		1,731	
Male, n (%)	66,690	(68.5)						
Age, y, median (Q1–Q3)	65	(56–77)						
Length of stay, days								
Median (Q1–Q3)	4	(2–6)	3	(2–7)	4	(2–8)	5	(2–9)
Time from last event to the current event, days								
Median (Q1–Q3)	NA		213	(56–500)	176	(55–384)	124	(43–303)
Follow-up, months								
Median (Q1–Q3)	36	(36–36)	24	(11–33)	16	(6–26)	13	(5–21)
CBVD								
Patients, n	120,914		25,337		6,644		2,153	
Male, n (%)	71,934	(59.5)						
Age, y, median (Q1–Q3)	71	(61–80)						
Length of stay, days								
Median (Q1–Q3)	7	(4–13)	8	(4–19)	9	(5–23)	11	(5–26)
Time from last event to the current event, days								
Median (Q1–Q3)	NA		162	(30–502)	99	(34–306)	72	(35–210)
Follow up, months								
Median (Q1–Q3)	36	(33–36)	24	(10–34)	19	(8–30)	18	(7–29)
PAD								
Patients, n	14,794		5,951		2,463		1,073	
Male, n (%)	8,534	(57.7)						
Age, y, median (Q1–Q3)	74	(63–82)						
Length of stay, days								
Median (Q1–Q3)	8	(3–16)	7	(3–15)	7	(3–15)	7	(3–15)
Time from last event to the current event, days								
Median (Q1–Q3)	NA		112	(37–366)	112	(39–297)	115	(42–287)
Follow up, months								
Median (Q1–Q3)	36	(14–36)	22	(8–33)	17	(6–27)	13	(5–23)

CBVD: cerebrovascular disease; CHD: coronary heart disease; Q: quartile.

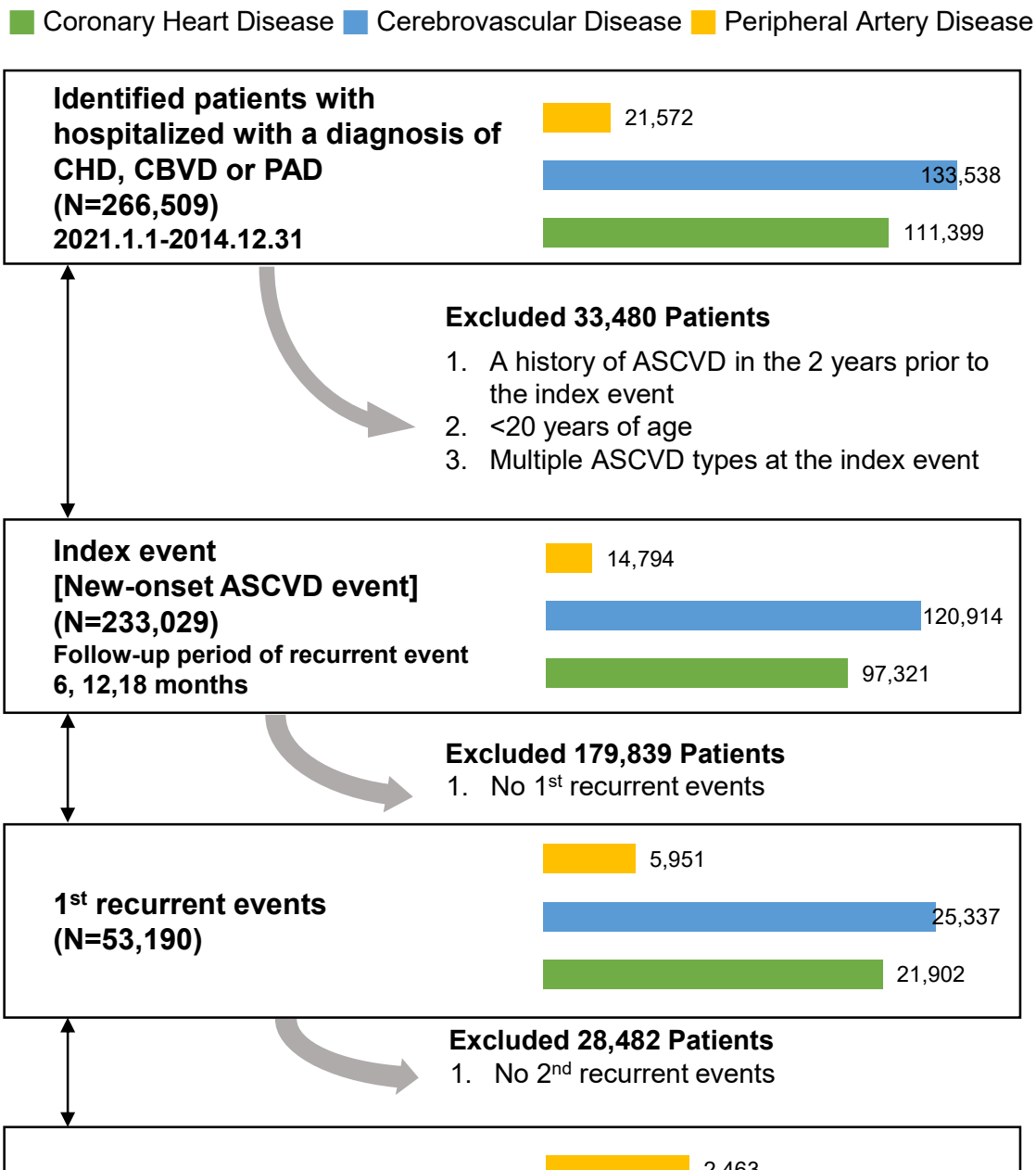
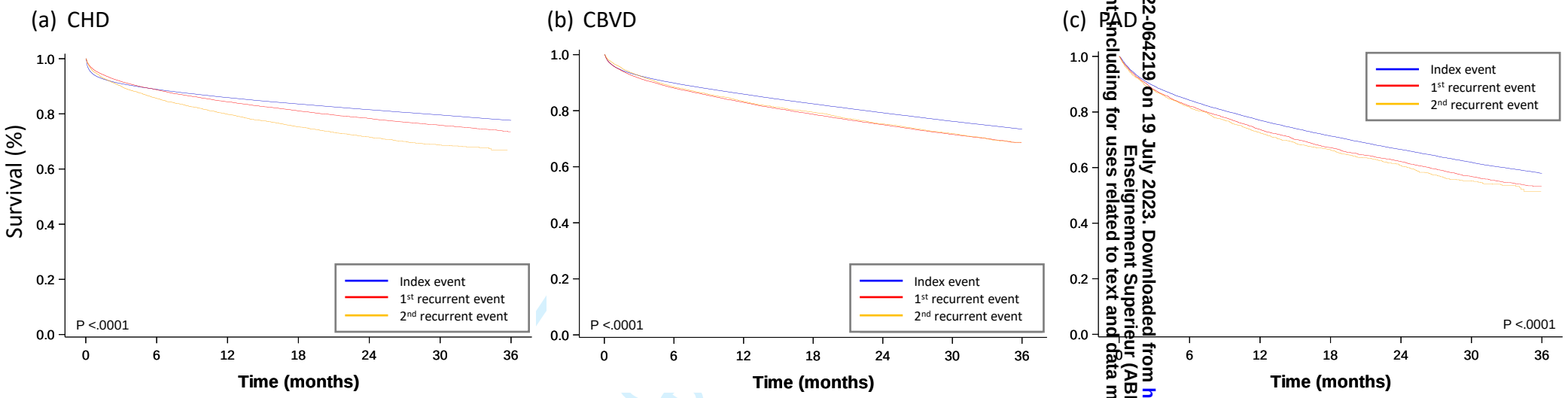


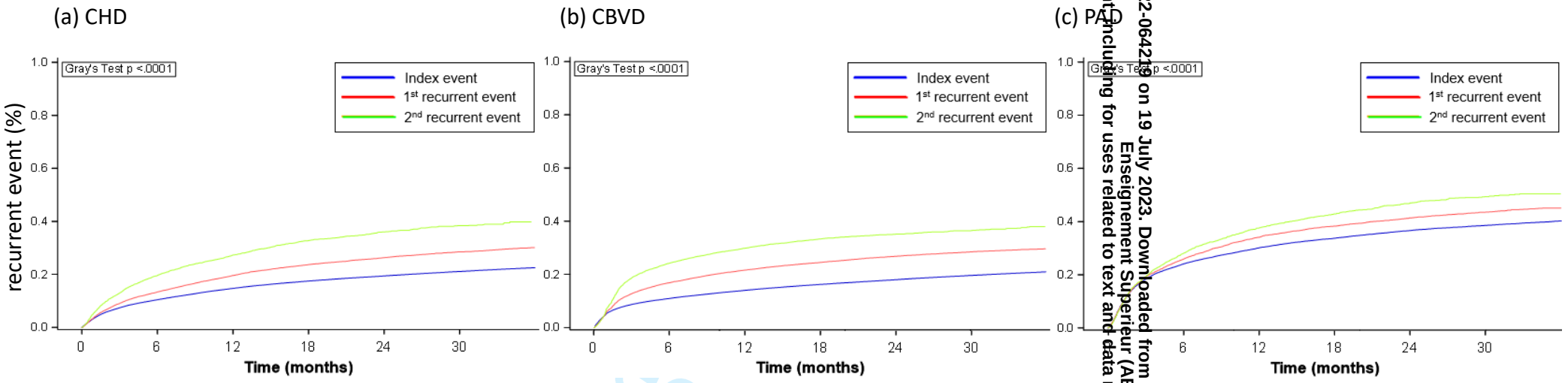
Figure 1. Study design . ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CBVD, cerebrovascular disease; PAD, peripheral artery disease.

Figure 2. Survival rates following each event



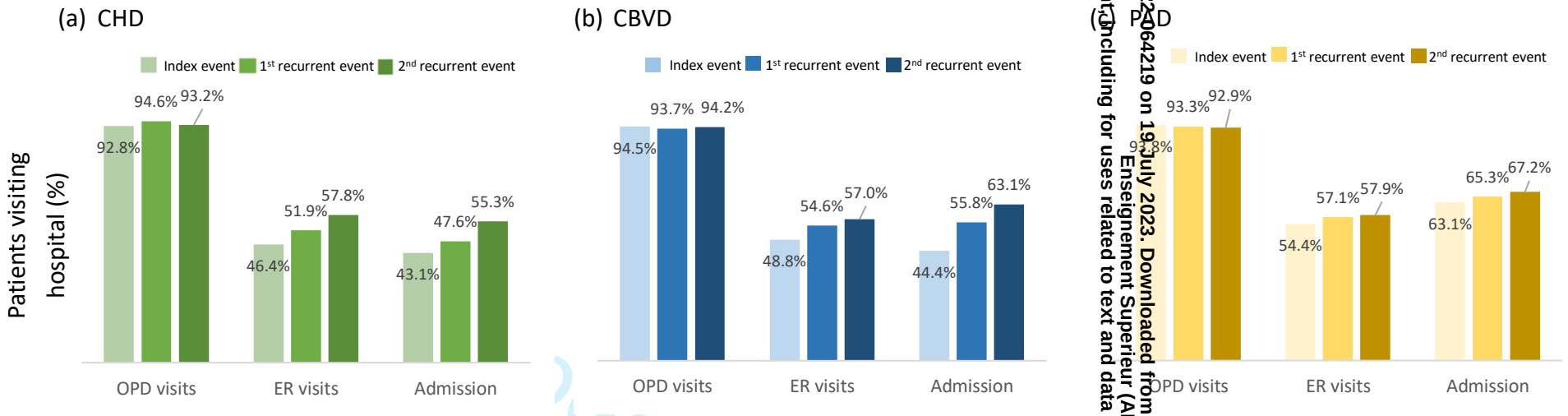
CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Figure 3. Cumulative recurrent event rates following each event



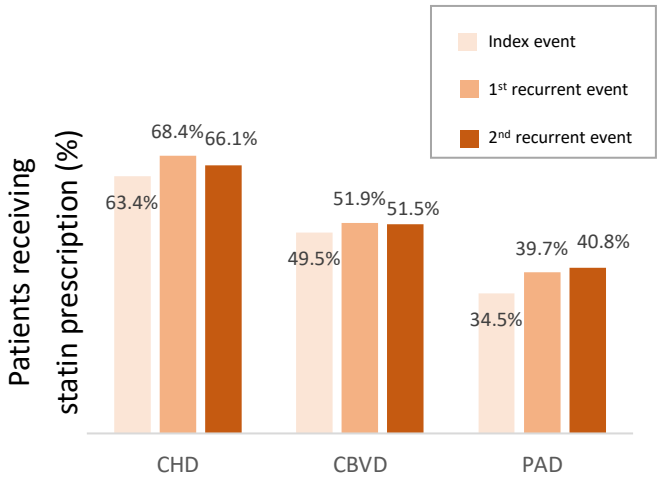
CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Figure 4. Proportion of patients having healthcare use following each event during a 12-month follow-up



CBVD: cerebrovascular disease; CHD: coronary heart disease; ER: emergency room; OPD: outpatient department; PAD: peripheral artery disease.

Figure 5. Proportion of statin prescription following each event during a 12-month follow-up



CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

Online supplement

Higher risk of future events, mortality, and greater healthcare use among patients with increasingly recurrent atherosclerotic cardiovascular disease events in Taiwan: a retrospective cohort study

Chia-Yun Hsu[1], Wen-Jone Chen[2], Hung-Ju Lin[2], Ho-Min Chen[1], Yea-Harn Yang[3], Wei-Ju Chen[3], Chieh-Min Chen[4], Fei-Yuan Hsiao[4,5,6*]

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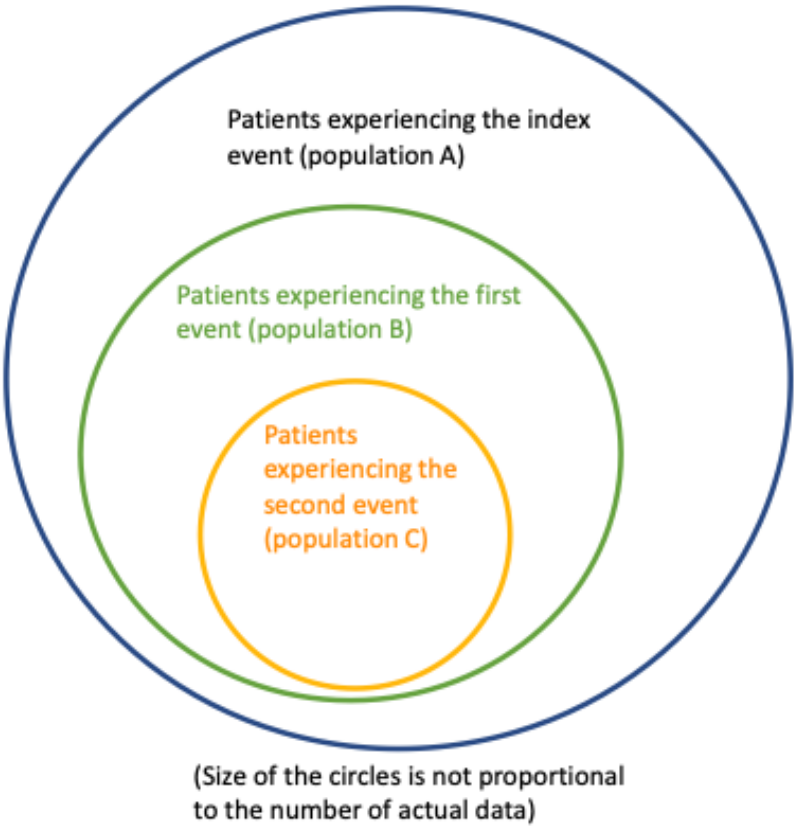
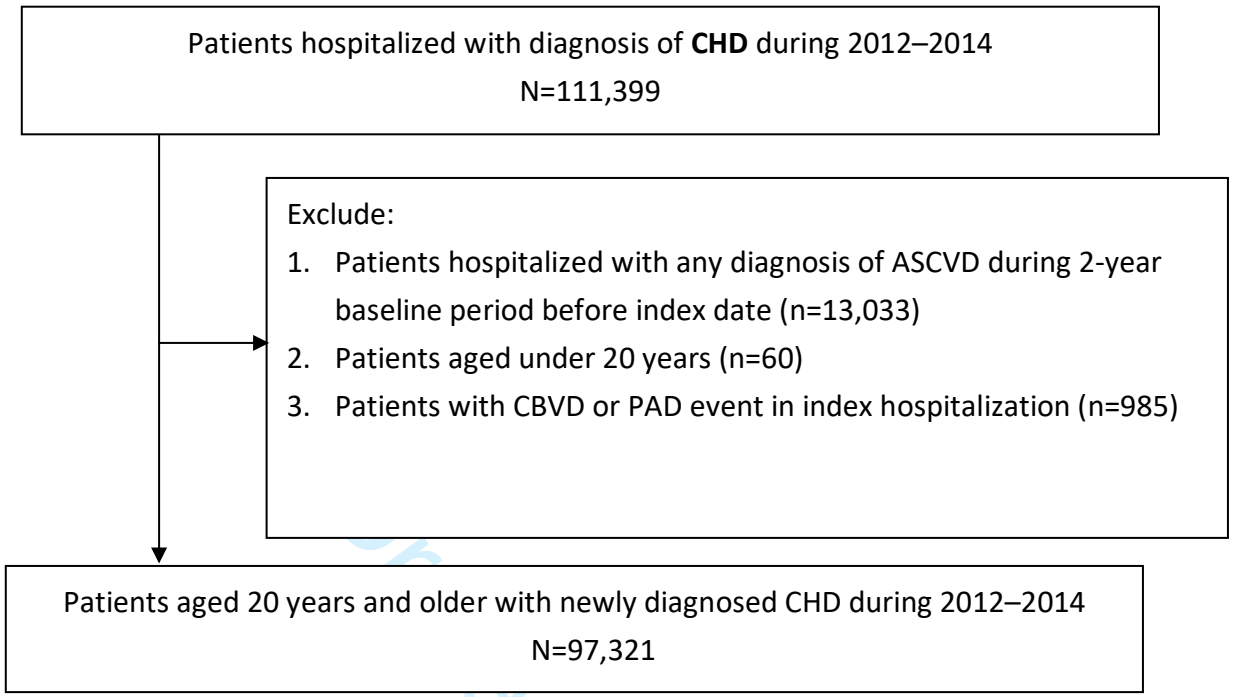
Supplement 1 (Figure). Definition of subsequent events



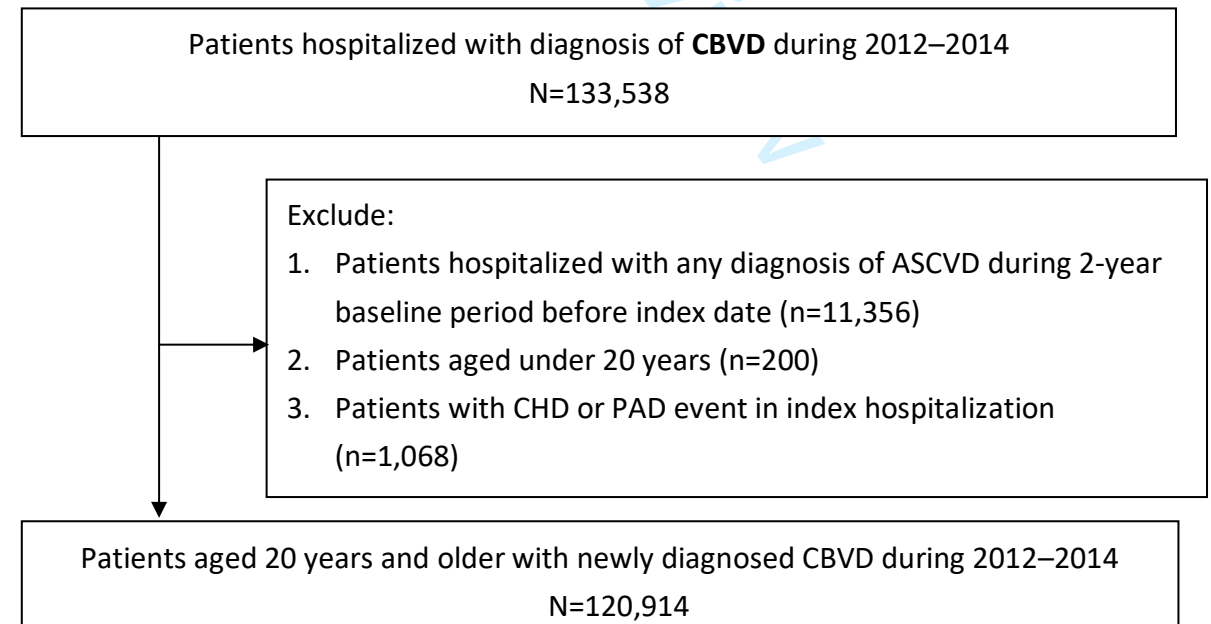
Patients with an index event (population A), were further defined into subsets if they experienced a first recurrent event (population B) and a second recurrent event (population C). Post-event mortality was calculated and compared between each of these populations.

Supplement 2 (Figure). Selection flow of study population

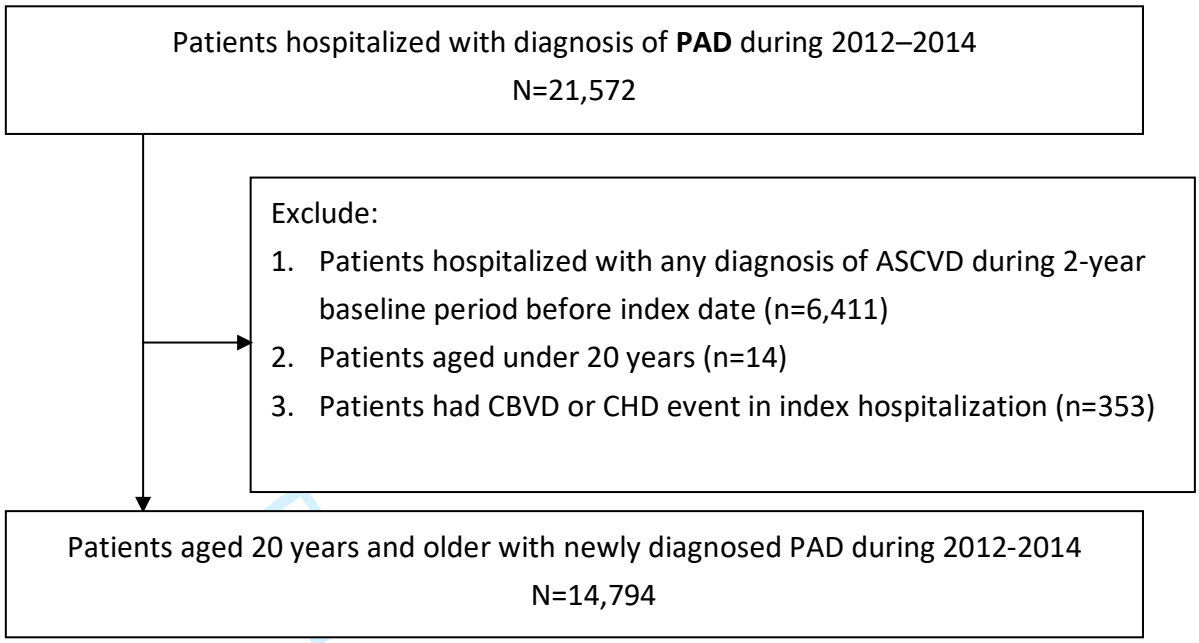
(a) Patients with new-onset CHD



(b) Patients with new-onset CBVD

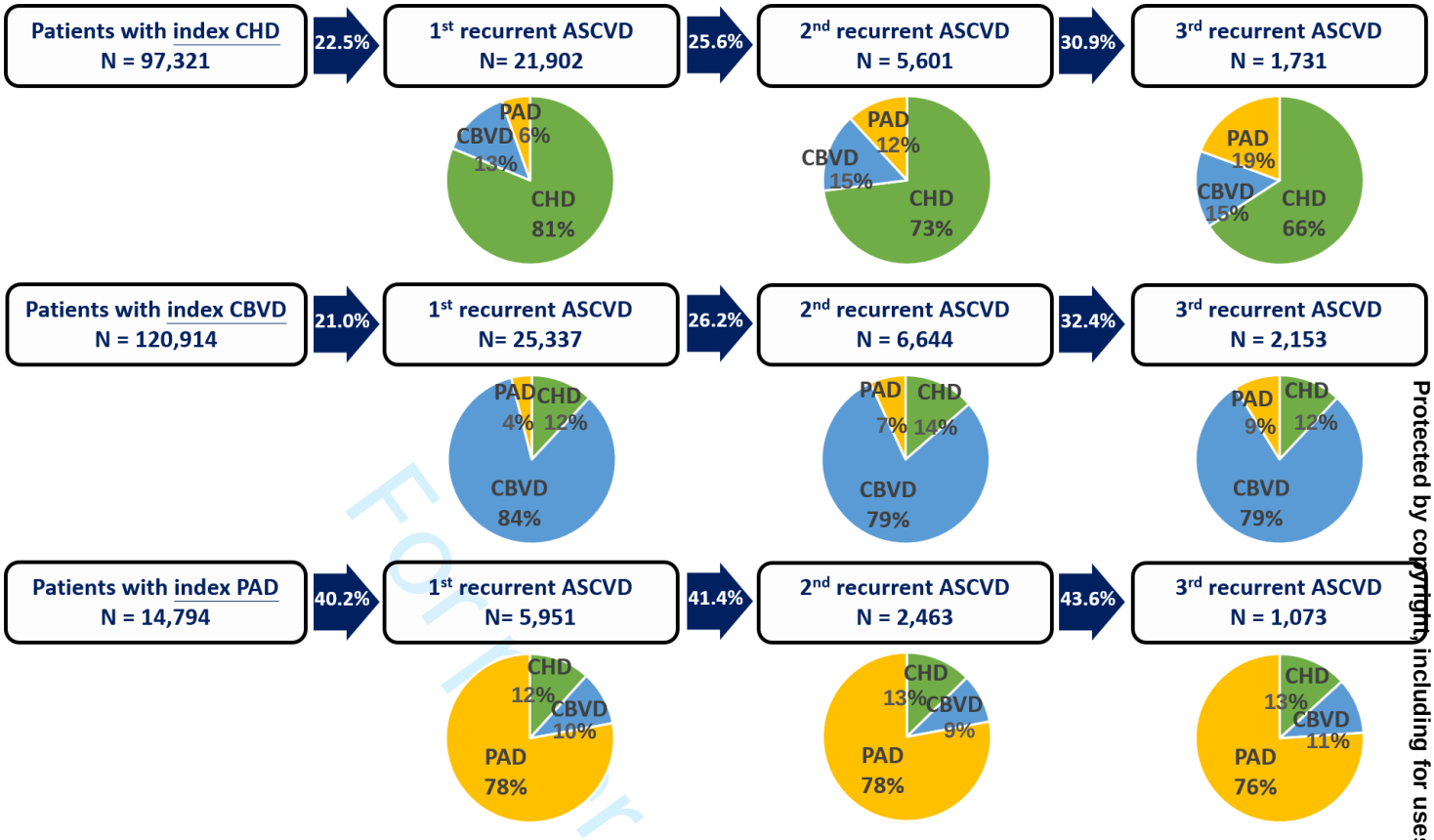


(c) Patients with new-onset PAD



CBVD, cerebrovascular disease; CHD, coronary heart disease PAD, peripheral artery disease

Supplement 3 (Figure). Recurrent event types by index events type



ASCVD: atherosclerotic cardiovascular disease; CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease

Supplement 4 (Table). Probability of survival estimated by Kaplan–Meier method

	Patients, n	Deaths, n	(%)	Probability of survival			
				6 mo	12 mo	18 mo	24 mo
Coronary heart disease							
Index event	97,321	21,773	(22.4)	0.889	0.859	0.836	0.815
First recurrent event	21,902	4,769	(21.8)	0.887	0.844	0.811	0.784
Second recurrent event	5,601	1,376	(24.6)	0.856	0.798	0.753	0.716
Cerebrovascular disease							
Index event	120,914	32,125	(26.6)	0.899	0.859	0.824	0.792
First recurrent event	25,337	6,540	(25.8)	0.881	0.830	0.787	0.750
Second recurrent event	6,644	1,528	(23.0)	0.884	0.833	0.795	0.753
Peripheral artery disease							
Index event	14,794	6,217	(42.0)	0.842	0.770	0.713	0.665
First recurrent event	5,951	2,412	(40.5)	0.821	0.737	0.672	0.622
Second recurrent event	2,463	924	(37.5)	0.817	0.725	0.663	0.607

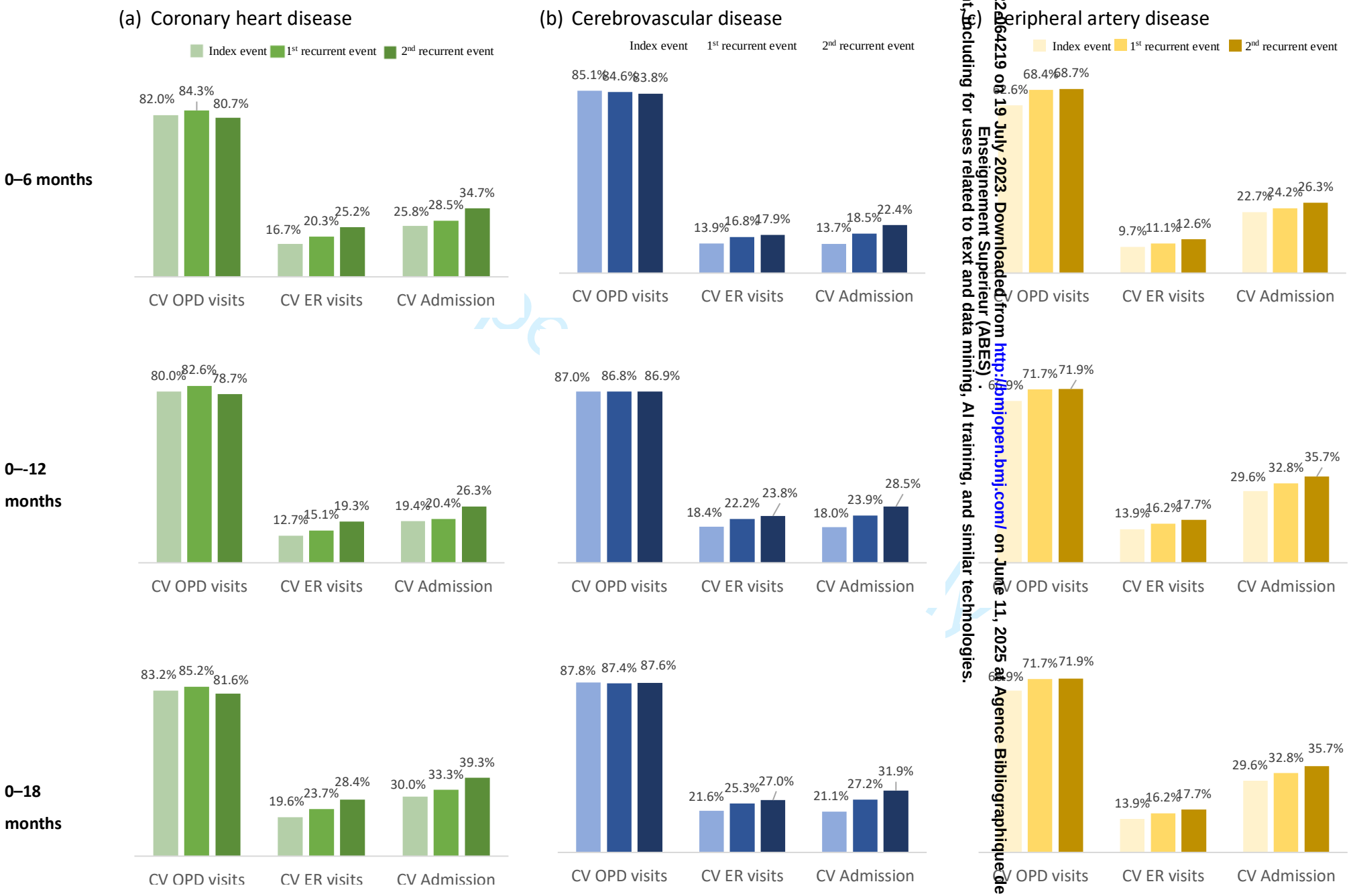
mo, months.

Supplement 5 (Table). Cumulative incidence rate of recurrent events considering competing risk estimated by Fine and Gray method

	Patients, n	Events, n	(%)	Event rate			
				6 mo	12 mo	18 mo	24 mo
Coronary heart disease							
Index event	97,321	21,902	(22.5)	0.104	0.147	0.175	0.194
First recurrent event	21,902	5,601	(25.6)	0.134	0.196	0.237	0.263
Second recurrent event	5,601	1,731	(30.9)	0.196	0.273	0.327	0.360
Cerebrovascular disease							
Index event	120,914	25,337	(20.9)	0.110	0.140	0.162	0.180
First recurrent event	25,337	6,644	(26.2)	0.169	0.216	0.245	0.268
Second recurrent event	6,644	2,153	(32.4)	0.242	0.298	0.333	0.351
Peripheral artery disease							
Index event	14,794	5,951	(40.2)	0.241	0.301	0.338	0.367
First recurrent event	5,951	2,463	(41.4)	0.259	0.341	0.383	0.413
Second recurrent event	2,463	1,073	(43.6)	0.281	0.376	0.428	0.470

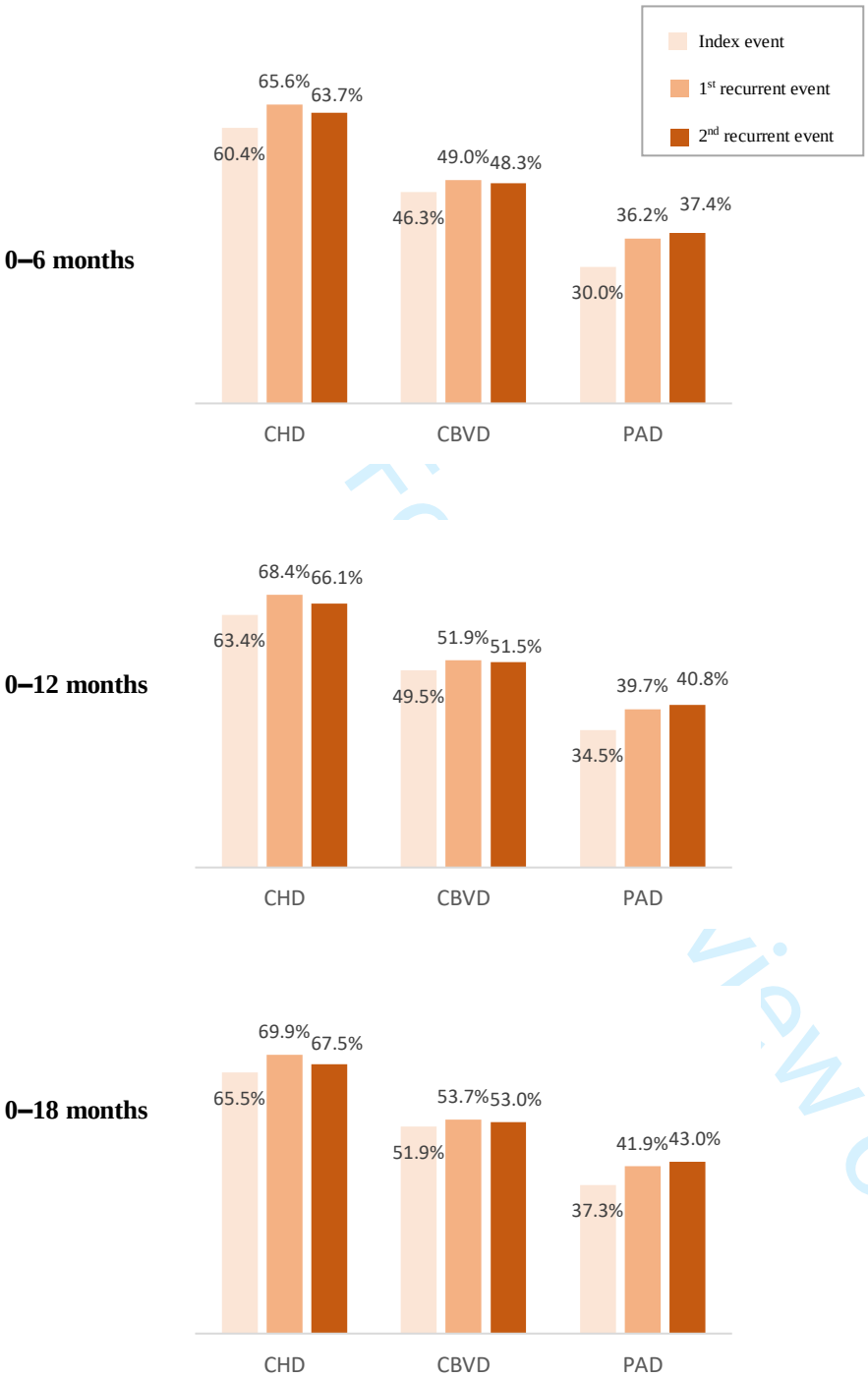
mo, months.

Supplement 6 (Figure). Percentage of patients having cardiovascular-related healthcare use following each event.



CV, cardiovascular disease; ER, emergency room OPD: outpatient department

Supplement 7 (Figure). Percentage of patients prescribed with statin following each event



CBVD: cerebrovascular disease; CHD: coronary heart disease; PAD: peripheral artery disease.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	10-11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-13
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.