Acta Cardiol Sin 2023;39:457–468
Original Article
doi: 10.6515/ACS.202305_39(3).20221021A

Epidemiology

Cardiovascular Event Recurrence and Costs after First Myocardial Infarction, Ischemic Stroke, or Intracerebral Hemorrhage in Taiwan

Fang-Ju Lin,[1,2,3] Jhih-Gang Jhang,[1] Yu-Hsuan Kuo,[1] Eric J. Yeh,[4] Lionel Pinto[4] and Chau-Chung Wu[5,6]

Background/Objectives: We aimed to assess the incidence of recurrent cardiovascular (CV) events after the first myocardial infarction (MI), ischemic stroke (IS), or intracerebral hemorrhage (ICH) and to estimate acute and follow-up medical costs.

Methods: Using Taiwan's National Health Insurance Research Database, we identified patients with their first MI, IS, or ICH between 2011 and 2017. The cumulative incidence rates of second CV events (including events of the same type [recurrent] or of the other two types) were estimated. The costs for hospitalization and all-cause follow-up were calculated for the first and recurrent CV events and are presented as median (Q1~Q3) in 2017 US dollars.

Results: We identified 70,428 patients with a first MI, 123,857 with a first IS, and 41,347 with a first ICH. The cumulative incidence rates of recurrence during the first year and after six years were 3.9% and 10.1% for MI, 5.3% and 13.8% for IS, and 3.9% and 8.9% for ICH, respectively. For first and recurrent nonfatal events, acute hospitalization costs were $4,729 (3,737~5,985) and $4,459 (2,887~6,026) for MI; $1,136 (756~2,183) and $1,224 (774~2,412) for IS; and $2,985 (1,264~8,831) and $2,170 (1,183~4,675) for ICH, respectively. Total annual costs for nonfatal first events in the first year and second year of follow-up were $2413 (1,393~6,120) and $1,293 (654~2,868) for MI, $2,174 (1,040~5,472) and $1,394 (602~3,265) for IS, and $2,963 (995~8,352) and $1,185 (405~3,937) for ICH, respectively.

Conclusion: In patients with a first MI, IS, and ICH, recurrent CV events continue to substantially impact public health and escalate the economic burden.

Key Words: Event recurrence • Intracerebral hemorrhage • Ischemic stroke • Medical costs • Myocardial infarction

Received: June 4, 2022 Accepted: October 21, 2022

[1]Graduate Institute of Clinical Pharmacy; [2]School of Pharmacy, College of Medicine, National Taiwan University; [3]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan; [4]Amgen Inc., California, United States; [5]Department of Internal Medicine (Cardiology Section), National Taiwan University Hospital; [6]Graduate Institute of Medical Education & Bioethics, College of Medicine, National Taiwan University, Taipei, Taiwan.

Corresponding author: Dr. Chau-Chung Wu, Department of Internal Medicine (Cardiology Section), National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan. Tel: 886-2-2312-3456 ext. 88560; Fax: 886-2-2321-7485; E-mail: chauchungwu@ntu.edu.tw

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Abbreviations

CV	Cardiovascular
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICH	Intracerebral hemorrhage
IS	Ischemic stroke
MI	Myocardial infarction
NHIRD	National Health Insurance Research Database
NTD	New Taiwan dollar
SD	Standard deviation
USD	United States dollar

INTRODUCTION

Cardiovascular (CV) diseases are the leading cause of death in Taiwan and worldwide.[1,2] In Taiwan, the incidence of acute myocardial infarction (MI) has increased over the past several decades[3,4] and is associated with high costs.[5] While the incidence of ischemic stroke (IS) decreased between 2001 and 2012, it nevertheless remains one of the leading causes of death.[6] IS is also a leading cause of disability in those who survive, and it is associated with a considerable healthcare burden. Intracerebral hemorrhage (ICH) accounts for 16% of strokes in Taiwan[6] and is associated with a 30-day mortality rate of 19.8% and 1-year mortality rate of 29.6% in Taiwan, along with considerable hospitalization costs.[7]

Patients who survive a first MI, IS, or ICH are at high risk of recurrence, with a further risk of mortality and healthcare expenditure.[3,5-7] In addition, event survivors may have a higher risk of other types of major CV events: for example, patients with ICH are at an appreciable risk of arterial ischemic events of the brain and heart.[8] These subsequent events, including both recurrent and other types of events, can impose an additional economic burden on society and require further exploration to understand their impact on patients and healthcare systems.

More current information on the incidence and cost burden of subsequent events after MI, IS, and ICH could inform clinical treatment or health policy decisions and highlight the potential for improvement in disease management. In addition, such an analysis can provide cost data for cost analysis during health technology assessment, as well as for consideration of reimbursement.

The 2017 Taiwan lipid guidelines recommend disease management with effective treatment strategies for the secondary prevention of CV events.[9] In addition to changes in clinical practice guidelines, changes in reimbursement criteria by Taiwan's National Health Insurance Administration may have led to different disease management and patient outcomes that were not captured in older datasets. Unit or annual costs of MI/IS/ICH events are important to calculations in health economic or cost analyses, which are a key component in reimbursement decisions.

Therefore, using Taiwan's National Health Insurance Research Database (NHIRD), we aimed to describe the cumulative incidence of second events as well as acute and follow-up costs after a first MI, IS, or ICH.

METHODS

Study design

This was a retrospective cohort study of the NHIRD spanning 2008 to 2017 (Supplementary Figure 1A). Patients with a first hospitalization for MI, IS, or ICH between 2011 and 2017 (index event) were identified. Those who survived the first MI, IS, or ICH event were then followed for up to seven years to capture the recurrence of an event (same event that occurred the second time), as well as the occurrence of the other two types of CV events. For each type of first event (MI, IS, and ICH), we captured the incidence of all three types of second event (Supplementary Figure 1B). Those who were hospitalized for one of the three types of events (both first and second event hospitalizations) were followed up for two years after discharge to obtain information on acute and follow-up costs. As shown in Supplementary Figure 1A, all-cause costs were included for the two-year follow-up period after an index event, even when the second event occurred within the index event follow-up period.

Patient eligibility

Eligible patients had at least one primary inpatient diagnosis of MI (ICD-9-CM code: 410.x; ICD-10 CM code: I21.x), IS (433.x1, 434.x1; I63.x, I64), or ICH (431; I61.x) (Supplementary Table 1A) between January 1, 2011 and December 31, 2017. The participants were adults (≥ 20 years of age) with at least three years of data available prior to the first event. Patients with a prior diagnosis of MI, IS, or hemorrhagic stroke (using a broader definition; Supplementary Table 1B) in the past three years or more before the first admission of MI, IS, or ICH were excluded. Those with missing sex data were also excluded.

Outcomes and analyses

We estimated the cumulative incidence rates of second events after the first nonfatal MI, IS, or ICH (overall and by sex); in-hospital case-fatality rates for the first (i.e., index) and second MI, IS or ICH events; acute hospitalization costs for MI, IS or ICH events (separately reported by fatal, nonfatal, first or second event); and total all-cause follow-up costs. Patient-level costs were es-

timated. The definitions and estimations of outcomes are described below.

Baseline characteristics of the included patients were collected in the year prior to their index admission. Comorbidities were determined based on the presence of at least one inpatient or two outpatient diagnoses (primary or secondary) in any claim. Medication use was defined as the presence of at least one prescription during the one-year baseline observation period. Case-fatality rates during event hospitalizations were calculated for the first (i.e., index) and second events. A second event was defined as a subsequent new hospitalization after 28 days from the first discharge of a nonfatal event.[10-12] To estimate the incidence of a particular second event, patients who survived 28 days after discharge from the index hospitalization were followed up until the date of that second event, death, or the end of the study period (31 December 2017), whichever occurred first. Cumulative incidence function, which takes into account competing risk events (i.e., death), was used to separately estimate the cumulative incidence proportion of recurrent events (of the same type) and the other two types of events over time after the first nonfatal MI, IS, and ICH.[13] When studying the incidence of a particular second event, the occurrence of the other types of second event was not considered a competing risk event; this is because these types of second events do not preclude the occurrence of one another, and the main purpose of this study was to describe the overall incidence of each type of event over time, rather than to focus on the second events that occurred first.

Acute event costs were estimated from hospitalization costs for both first and second events (including fatal and nonfatal). Direct transfer to another hospital within one day with the same primary discharge diagnosis was combined to contribute to the same index event and avoid underestimating acute hospitalization costs.

Follow-up costs after hospital discharge for the first events were analyzed only in patients who survived the event and had at least two years of follow-up. The patients included in the cost analysis were a subset of those included in the analyses of event incidence. Total all-cause follow-up costs (for inpatient, outpatient, and emergency room visits after hospital discharge) were estimated in the first and second year after the index/second event. Medication costs were included in the cost of each visit and are not reported separately. The follow-up costs included all costs incurred after the index/second event, and therefore included the costs of subsequent events if they happened within the timeframe. For example (Supplementary Figure 1A), if the second event occurred 16 months after the first event, the second event costs were included in the second-year follow-up costs after the first event, but not included in the first-year follow-up costs after the second event.

Incremental follow-up costs during the first and second year after the index nonfatal event were estimated to understand the long-term economic impact of the events. The first- and second-year incremental follow-up costs were calculated by subtracting the baseline cost (all-cause costs during the year prior to the index event) from the first- and second-year total follow-up costs of the index event, respectively.

All analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA). SAS PROC LIFETEST was used to estimate the cumulative incidence function. Costs are presented as median (Q1~Q3) and in 2017 US dollars (USD) at the currency exchange rate of 1 USD ($) = 30.28 New Taiwan dollars (NTD).

RESULTS

Study cohort

We identified 70,428 patients with a first MI, 123,857 with a first IS, and 41,347 with a first ICH (Supplementary Figure 1C). The mean age [standard deviation (SD)] was 63 (14), 68 (13), and 60 (15) years for those with a first MI, IS, and ICH, respectively, and the majority were men (76%, 60%, and 66%, respectively) (Table 1). In all three groups, the most common comorbidities were hypertension, diabetes, coronary artery disease, and renal disease. Antihypertensive drugs, platelet aggregation inhibitors, hypoglycemic drugs, and statins were the most common medications.

Rates of recurrent and other second events

The cumulative incidence rates of a recurrent or other type of second event after a first MI, IS, or ICH are shown overall and by sex in Figure 1, with exact estimates by year of follow-up presented in Supplementary Table 2. The cumulative incidence rates of recurrence at

Table 1. Demographic and baseline patient characteristics

Characteristics, n (%)	First MI (n = 70,428)	First IS (n = 123,857)	First ICH (n = 41,347)
Age (years), mean (SD)	62.9 (14.2)	67.9 (13.5)	60.4 (14.9)
Sex (men)	53,771 (76.4)	73,570 (59.4)	27,216 (65.8)
Comorbidities			
Hypertension	34,071 (48.4)	64,355 (52.0)	14,931 (36.1)
Coronary artery disease	13,326 (18.9)	15,139 (12.2)	2981 (7.2)
Peripheral artery disease	977 (1.4)	1511 (1.2)	307 (0.7)
Congestive heart failure	4628 (6.6)	7157 (5.8)	1315 (3.2)
Atrial fibrillation	1491 (2.1)	6183 (5.0)	768 (1.9)
Venous thromboembolism	375 (0.5)	691 (0.6)	220 (0.5)
Diabetes mellitus	20,866 (29.6)	35,192 (28.4)	6502 (15.7)
Liver disease	3717 (5.3)	6568 (5.3)	3197 (7.7)
Renal disease	8782 (12.5)	9678 (7.8)	3186 (7.7)
Medications			
Antihypertensive drugs	43,735 (62.1)	82,364 (66.5)	20,218 (48.9)
Hypoglycemic drugs	20,564 (29.2)	35,051 (28.3)	6284 (15.2)
Statins	17,184 (24.4)	22,789 (18.4)	4176 (10.1)
Other lipid-lowering drugs	4789 (6.8)	6564 (5.3)	1240 (3.0)
Oral anticoagulants	985 (1.4)	3715 (3.0)	578 (1.4)
Platelet aggregation inhibitors	21,480 (30.5)	30,221 (24.4)	5457 (13.2)
Antiarrhythmic drugs class I and III	2817 (4.0)	6316 (5.1)	1075 (2.6)

ICH, intracerebral hemorrhage; IS, ischemic stroke; MI, myocardial infarction; SD, standard deviation.

one year and at six years were 3.9% and 10.1% for MI, 5.3% and 13.8% for IS, and 3.9% and 8.9% for ICH, respectively. Women with a first MI had a proportionally higher cumulative incidence of MI recurrence than men (11.2% for women and 9.8% for men at six years). The incidence of post-MI IS was also proportionally higher in women than in men (5.2% and 3.5%, respectively, over six years). The rate of post-MI ICH was low for both sexes (0.8% for women and 0.6% for men during six years of follow-up). In the case of IS, recurrent or second events were slightly more frequent in men, with the six-year cumulative incidence of recurrent IS estimated at 13.1% for women and 14.4% for men; post-IS MI (2.0% in women and 2.7% in men) and post-IS ICH (1.5% in women and 2.1% in men) both occurred with a lower rate. Recurrent or second events after ICH were similarly more frequent in men: recurrent ICH had a six-year cumulative incidence of 7.8% in women and 9.4% in men; while post-ICH MI was relatively infrequent (0.7% in women and 1.2% in men) and post-ICH IS was observed in 4.8% of women and 6.1% of men.

Case-fatality rates

The in-hospital case-fatality rates were 8.2% for a first MI, 8.5% for recurrent MI, 8.4% for a post-MI IS, and 37.5% for a post-MI ICH. The case-fatality rates for IS were 4.3% and 4.6% for the first and recurrent events, respectively; however, for post-IS MI and post-IS ICH, the fatality rates were considerably higher at 14.7% and 24.0%, respectively. The highest case-fatality rates for first and recurrent events were observed for ICH, at 18.5% and 12.6%, respectively. Post-ICH MI and post-ICH IS were associated with case-fatality rates of 12.6% and 3.4%, respectively.

Costs

The acute hospitalization costs for the first and recurrent fatal and nonfatal events are shown in Table 2. The median acute costs for both first (index) and recurrent nonfatal MI were the highest of the three event types, costing $4,729 (3,737~5,985) and $4,459 (2,887~6,026) respectively, followed by $2,985 (1,264~8,831) and $2,170 (1,183~4,675) respectively for ICH, and $1,136 (756~2,183) and $1,224 (774~2,412) respectively for IS. The median costs for fatal events were generally higher than those for nonfatal events, except for ICH. The baseline one-year costs before a first event and total follow-up costs (for the first and second year) after a first or

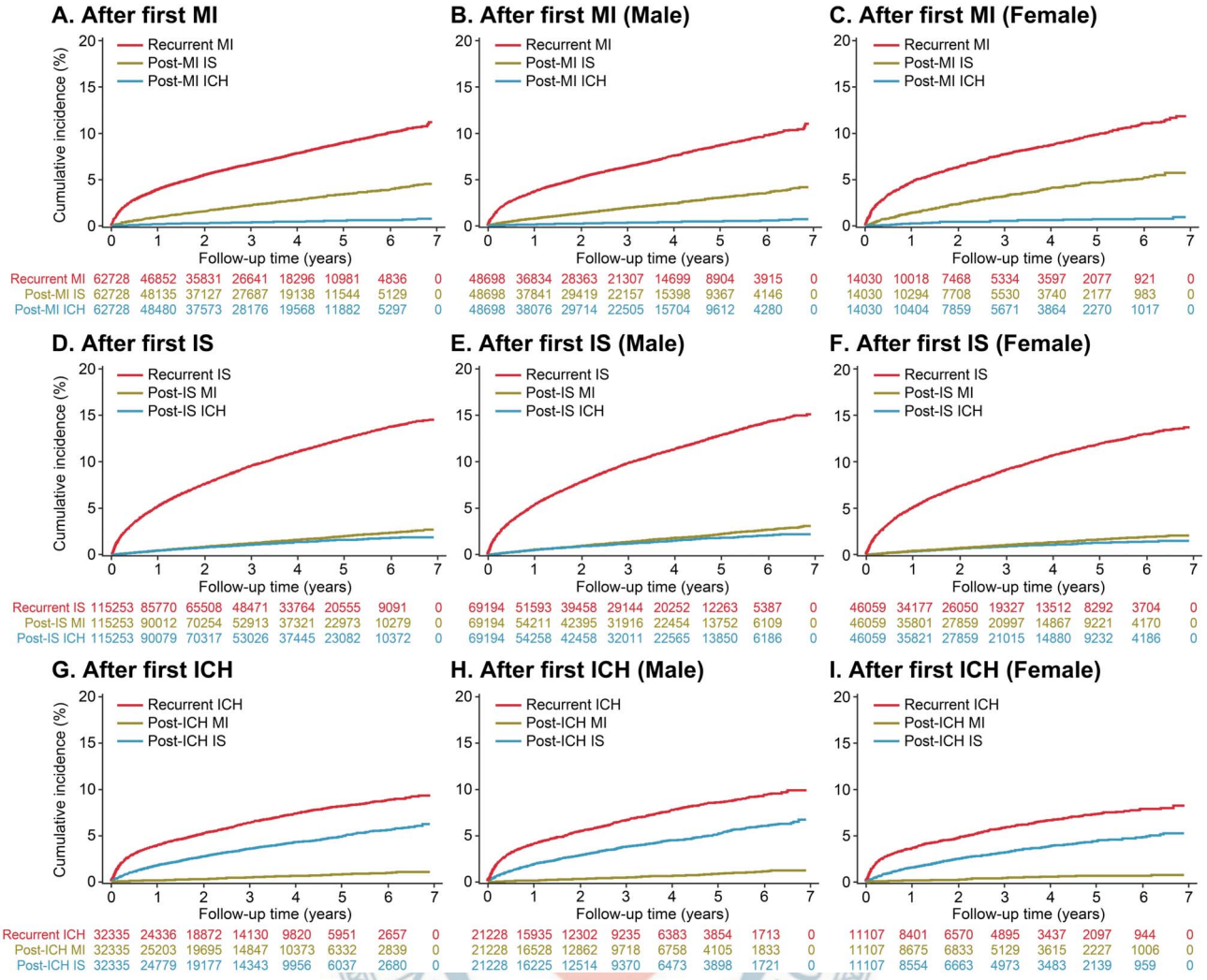


Figure 1. *Cumulative incidence of second events starting from 28 days after first MI, IS, or ICH. Subject numbers for each type of second event at each time point are presented below each graph. ICH, intracerebral hemorrhage; IS, ischemic stroke; MI, myocardial infarction.*

Table 2. Acute hospitalization costs of first (index) and recurrent events (presented in 2017 USD)

Cost	MI	IS	ICH
First event			
Fatal, n	5,747	5,321	7,644
Median (Q1~Q3)	$5,756 (1,771~11,764)	$2,677 (1,384~5,734)	$2,170 (860~5,863)
Mean (SD)	$9,876 (14,001)	$5,216 (8,396)	$4,845 (8,076)
Nonfatal, n	64,681	118,536	33,703
Median (Q1~Q3)	$4,729 (3,737~5,985)	$1,136 (756~2,183)	$2,985 (1264~8,831)
Mean (SD)	$5,554 (5,463)	$2,341 (3,863)	$6,659 (8,751)
Recurrent event			
Fatal, n	359	512	262
Median (Q1~Q3)	$5,033 (1,852~11,420)	$2,480 (1,303~5,467)	$1,816 (703~5,434)
Mean (SD)	$9,134 (13,028)	$5,478 (9,912)	$4,331 (6,123)
Nonfatal, n	3,871	10,724	1,823
Median (Q1~Q3)	$4,459 (2,887~6,026)	$1,224 (774~2,412)	$2,170 (1,183~4,675)
Mean (SD)	$5,302 (5,511)	$2,414 (4,531)	$4,842 (7,540)

ICH, intracerebral hemorrhage; IS, ischemic stroke; MI, myocardial infarction; SD, standard deviation; USD, united states dollar.

recurring event are shown in Supplementary Table 3 by cost type. The numbers of patients with a hospital stay and emergency room visit were reported and the associated costs are presented. Incremental follow-up costs (subtracting baseline costs from total costs) in the first and second years after the index events were $1,429 (633~4,506) and $591 (-35~1,541) for MI, $1,128 (286~3,861) and $591 (-84~1,984) for IS, and $2,038 (482~7,022) and $640 (0~3,036) for ICH, respectively (Table 3).

DISCUSSION

In this large retrospective cohort study of patients with a first MI, first IS, or first ICH between 2011 and 2017 in the NHIRD, we report the cumulative incidence rates of recurrence and other CV events over six years of follow-up, in-hospital case-fatality rates, and all-cause costs for both first and second events over two years of follow-up. In-hospital fatality rates of MI and IS were lower than those reported in earlier studies, although the mortality rate of ICH remained high. Not only was event recurrence common, but we also found that patients who had a first event were also at an increased risk of other types of CV events. Sex differences in the rates of recurrence were observed. Acute and all-cause follow-up costs, although substantial, were lower than those previously reported in earlier cohorts. These data offer a current view of mortality, recurrence, and costs associated with CV events in Taiwan, and show that both fatal and nonfatal MI, IS, and ICH continue to impose a substantial public health burden, as well as an economic burden, on Taiwan's healthcare system.

In-hospital case-fatality rates were highest for ICH (18.5%), followed by MI (8.2%) and IS (4.3%). Previous studies using the NHIRD have reported a trend of decreasing in-hospital mortality rates for MI, ranging from 15.9% in 1999 to 12.3% in 2008[3] and from ~13% in 2009 to under 12% in 2015.[14] The result of 8.2% in this study, which is the lowest yet reported, provides evidence of steadily decreasing mortality caused by MI. The in-hospital mortality rate of IS was reported to be approximately 6-8% in Taiwan in the 1990s.[15] The previously reported 30-day mortality for ICH in Taiwan from 2005 to 2010 was 19.8%,[7] consistent with the observation of 18.5% in the present cohort. Thus, mortality rates from MI and IS have decreased in recent years, along with advances in technology and availability of primary and secondary preventive treatments such as antiplatelets, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins, as well as procedures such as primary coronary or cerebral intervention. In contrast, mortality from ICH has remained high due to the lack of effective therapies.

After the first (index) event, we observed that recurrent events occurred continuously, with a six-year cumulative incidence of 10.1% for MI, 13.8% for IS, and 8.8% for ICH. Thus, the risk of recurrent events remained high for all three cardiovascular events investigated. Other types of second events were also observed, although at a lower frequency. In patients with a first MI during 2008-2009 in the NHIRD, Chen et al. reported a 5.3% recurrence rate of MI and a 5.0% incidence of stroke in the first three years in patients who had survived for one year without a recurrent event.[16] The rate of recurrent MI reported in the present study was slightly higher

Table 3. Incremental follow-up costs of first events (presented in 2017 USD)

Cost, median (Q1~Q3)	First MI (n = 44,212)	First IS (n = 85,223)	First ICH (n = 23,978)
First year incremental follow-up cost vs. baseline			
Total	$1,429 (633~4,506)	$1,128 (286~3,861)	$2,038 (482~7,022)
Inpatient	$0 (0~3,198)	$0 (0~1,307)	$0 (0~3,231)
Outpatient	$964 (391~1,428)	$673 (151~1,551)	$844 (230~2,397)
Emergency room	$0 (0~113)	$0 (0~110)	$0 (0~126)
Second year incremental follow-up cost vs. baseline			
Total	$591 (-35~1,541)	$591 (-84~1,984)	$640 (0~3,036)
Inpatient	$0 (0~0)	$0 (0~0)	$0 (0~0)
Outpatient	$494 (-3~981)	$450 (-52~1,159)	$484 (0~1,586)
Emergency room	$0 (-10~47)	$0 (0~33)	$0 (0~22)

ICH, intracerebral hemorrhage; IS, ischemic stroke; MI, myocardial infarction; USD, united states dollar.

than that reported by Chen et al. (6.68% during three years), although we found a lower rate of post-MI IS (2.22%); however, the difference in entry criteria complicates comparisons with the present study, as we did not require patients to be recurrence-free in the first 12 months.

We observed that women with a first MI had a higher cumulative incidence of MI recurrence than men, and that the incidence of post-MI IS was also higher in women than men. However, these differences were numerical only and not statistically significant, and therefore further investigations are needed to clarify this issue. Previous studies have shown that women are more likely to die from MI in the hospital than men[3] and are less likely than men to receive treatment.[17] Sex differences in stroke were also observed in this study. Men were more likely to have recurrence of stroke, adding to a previous report in a Taiwanese population in 2013 showing that men had higher medical costs for stroke than women.[18]

In this analysis, the costs of an acute event for both first and recurrent nonfatal MI were the highest of the three event types. For MI and IS, fatal events were associated with higher costs than nonfatal events. This may be explained by the large number of procedures performed in an attempt to save the patient's life after MI or IS. In contrast, in the case of ICH, those with nonfatal ICH might be expected to incur a higher expense to treat their complications if they survived the acute event. In a Taiwanese cohort from 2005 to 2010, the in-hospital costs were higher than those in the present study, at $7,572 for first ICH events,[7] although methodological differences may also explain this difference.

We calculated both total costs and incremental costs to achieve the most accurate cost estimates. To better measure the longer-term costs of the targeted CV events, we analyzed incremental costs in the two years after the index event, subtracting the baseline costs from the year before the index event; in this way, the incremental cost can give a better indication of the additional cost burden in the years following the index MI/IS/ICH event. Because inpatient costs of the index hospitalization were not included, most follow-up costs in all groups were from outpatient expenses. In comparison, Tang et al.[5] included acute event costs when they analyzed the costs of MI and stroke in a cohort from 2005 to 2009: the first- and second-year costs were NT$293,995 (10,150 USD in 2017) and $63,365 (2,188 USD) for MI, respectively, and NT$141,086 (4,871 USD) and NT$52,513 (1,812 USD) for stroke. Although differences in methodology make direct comparisons difficult, our results support the finding that costs in the second year of follow-up were much lower than in the first year. Our analysis adds to previously published literature by providing a more recent cost estimate, by estimating different categories of costs (acute vs. follow-up costs, fatal vs. nonfatal event costs, and first vs. second event costs), and by providing a useful estimate of incremental costs over two years, which would minimize the potential confounding of the cost of comorbid conditions from before the index event.

There were several limitations to this study. First, claims-based data have inherent limitations, such as being subject to reporting bias in which activities with high reimbursement values tend to be reported more than low-cost activities. In the present study, such bias would be expected to be minimal due to the relatively high costs associated with MI, IS, and ICH events. Claims data are also subject to possible patient misclassification due to miscoding, misdiagnosis, and underdiagnosis. In addition, we assessed only the incidence of second events after the first MI, IS, or ICH; subsequent events were not included. A 28-day lag period was set to define a new CV event; thus, there is a risk of misclassification in the case that a second event occurred within the 28-day window. Moreover, since it is very difficult to differentiate CV and non-CV related costs, we measured all-cause costs rather than CV-related costs; however, we attempted to adjust for the costs of other comorbid conditions by subtracting baseline costs in our calculation of incremental follow-up costs. The results should be interpreted with caution due to the lack of a control group. Lastly, in this study, we focused only on the costs associated with major CV events, while the economic burden of primary prevention is another important issue.

Future analyses could assess the impact of changes in reimbursement policies that can affect the clinical management of CV disease and the resulting cost estimates, such as the 2013 change in the reimbursement criteria for statins, or the 2018 change in the reimbursement of surgery costs for intra-arterial mechanical thrombectomy (for acute ischemic stroke) by Taiwan's Na-

tional Health Insurance Administration. Preventive treatment has the potential to ease the clinical and cost burden by reducing the number of CV events. Modeling using data from other populations has shown that treatment reduces MI and stroke recurrence.[19] Future studies could explore the effect of lipid-lowering treatment patterns on the incidence of first and second CV events in this more recent real-world dataset in the Taiwanese population.

CONCLUSION

In summary, MI, IS, and ICH were associated with a high likelihood of recurrent or other types of CV events, and both first and second events continue to cause a great burden on the healthcare system in Taiwan, especially in the first year after an acute event (Central Illustration).

ACKNOWLEDGMENTS

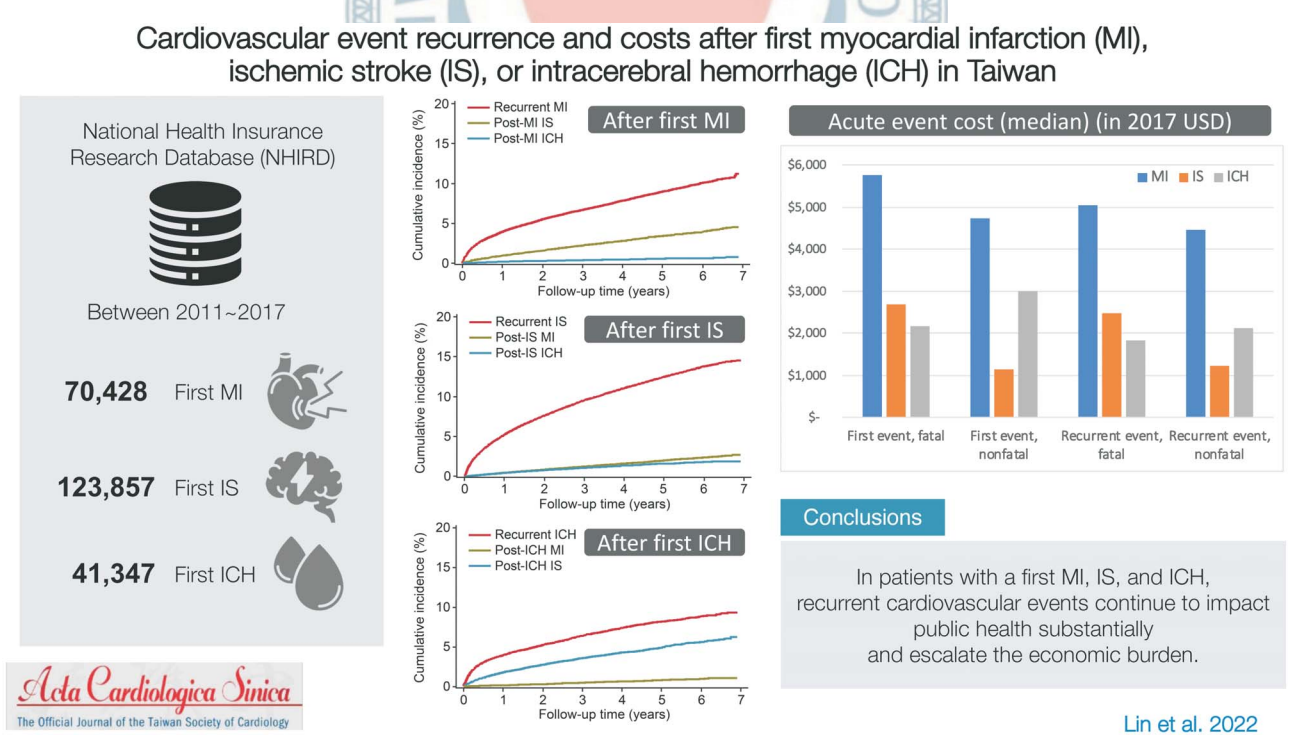
This study is based on data from the National Health Insurance Research Database provided by the National Health Insurance Administration, Taiwan's Ministry of Health and Welfare and managed by the Health and Welfare Data Science Center. The interpretation and conclusions contained herein do not represent those of the National Health Insurance Administration or the Health and Welfare Data Science Center. Wanda J Krall, Ph.D., of Wanda Krall Medical Communications, and Ellen Stoltzfus, Ph.D., of Amgen Inc., provided medical writing assistance.

PREVIOUS PRESENTATION

Part of this work was previously presented as an abstract and poster at the International Society for Pharmacoeconomics and Outcomes Research, virtual conference, May 17-20, 2021.

FINANCIAL SUPPORT

This study was sponsored by Amgen Inc. The sponsor contributed to the study design and interpretation of data and was involved in the writing of the report.



Central Illustration. *Cardiovascular event recurrence and costs after first myocardial infarction (MI), ischemic stroke (IS), or intracerebral hemorrhage (ICH) in Taiwan. USD, united states dollar.*

AUTHOR CONTRIBUTIONS

FJL, LP and CCW initiated the study concept and prepared the study protocol. JGJ and YHK performed data management and statistical analysis. EJY initiated manuscript preparation. All authors were involved in interpretations of results and manuscript review and revision.

CONFLICT OF INTEREST

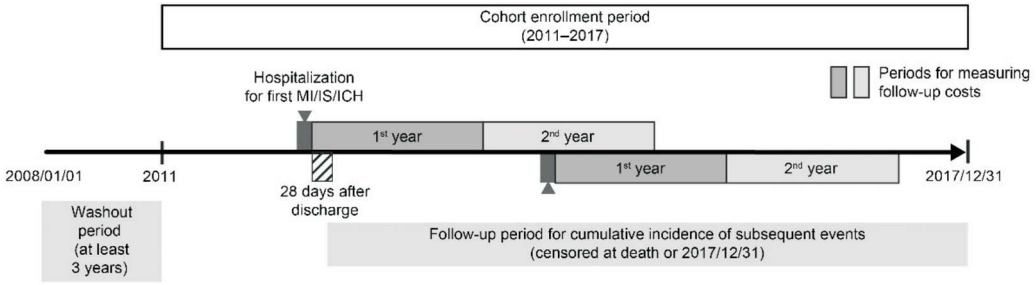
FJL and CCW received a research grant and consultation fees from Amgen Inc. FJL, JGJ, YHK, and CCW are current or former employees of National Taiwan University, which received funding from Amgen Inc. to conduct this work. LP and EJY are employees of Amgen and hold Amgen stock.

REFERENCES

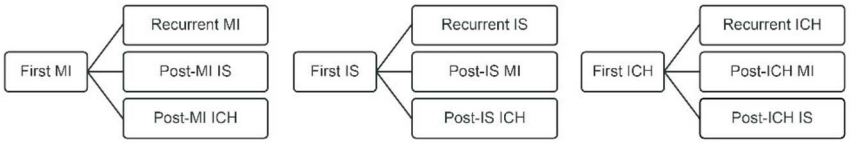
1. Ministry of Health and Welfare. 2019 cause of death statistics. 2020; https://www.mohw.gov.tw/np-128-2.html. Accessed September 22, 2021.
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204-22.
3. Lee CH, Cheng CL, Yang YH, et al. Trends in the incidence and management of acute myocardial infarction from 1999 to 2008: get with the guidelines performance measures in Taiwan. *J Am Heart Assoc* 2014;3:e001066.
4. Yin WH, Lu TH, Chen KC, et al. The temporal trends of incidence, treatment, and in-hospital mortality of acute myocardial infarction over 15 years in a Taiwanese population. *Int J Cardiol* 2016; 209:103-13.
5. Tang CH, Chuang PY, Chen CA, Fang YC. Medical costs of cardiovascular diseases in Taiwan. *Value Health* 2014;17:A759-60.
6. Hsieh FI, Chiou HY. Stroke: morbidity, risk factors, and care in Taiwan. *J Stroke* 2014;16:59-64.
7. Chan CL, Ting HW, Huang HT. The incidence, hospital expenditure, and, 30 day and 1 year mortality rates of spontaneous intracerebral hemorrhage in Taiwan. *J Clin Neurosci* 2014;21: 91-4.
8. Murthy SB, Zhang C, Diaz I, et al. Association between intracerebral hemorrhage and subsequent arterial ischemic events in participants from 4 population-based cohort studies. *JAMA Neurol* 2021;78:809-16.
9. Li YH, Ueng KC, Jeng JS, et al. 2017 Taiwan lipid guidelines for high risk patients. *J Formos Med Assoc* 2017;116:217-48.
10. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231-64.
11. Chen Y, Wright N, Guo Y, et al. Mortality and recurrent vascular events after first incident stroke: a 9-year community-based study of 0.5 million Chinese adults. *Lancet Glob Health* 2020; 8:e580-90.
12. Coull AJ, Rothwell PM. Underestimation of the early risk of recurrent stroke: evidence of the need for a standard definition. *Stroke* 2004;35:1925-29.
13. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016;133: 601-9.
14. Lee CH, Fang CC, Tsai LM, et al. Patterns of acute myocardial infarction in Taiwan from 2009 to 2015. *Am J Cardiol* 2018;122: 1996-2004.
15. Hung TP. Changes in mortality from cerebrovascular disease and clinical pattern of stroke in Taiwan. *J Formos Med Assoc* 1993; 92:687-96.
16. Chen DY, Li CY, Hsieh MJ, et al. Predictors of subsequent myocardial infarction, stroke, and death in stable post-myocardial infarction patients: a nationwide cohort study. *Eur Heart J Acute Cardiovasc Care* 2019;8:634-42.
17. Xia S, Du X, Guo L, et al. Sex differences in primary and secondary prevention of cardiovascular disease in China. *Circulation* 2020; 141:530-39.
18. Liu CT, Wu BY, Hu WL, Hung YC. Gender-based differences in mortality and complementary therapies for patients with stroke in Taiwan. *Complement Ther Med* 2017;30:113-17.
19. Lin FJ, Shyu KG, Hsieh IC, et al. Cost-effectiveness of statin therapy for secondary prevention among patients with coronary artery disease and baseline LDL-C 70-100 mg/dL in Taiwan. *J Formos Med Assoc* 2020;119:907-16.

SUPPLEMENTARY MATERIALS

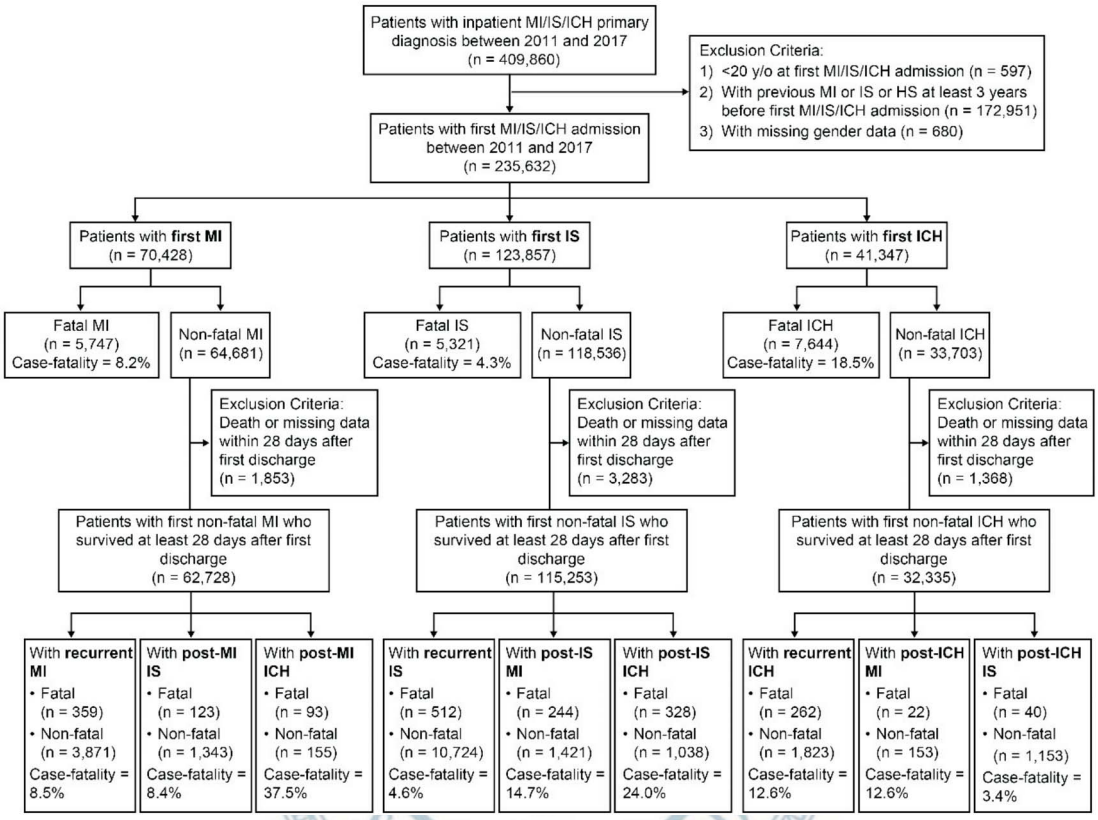
A



B



C



Supplementary Figure 1. *Illustration of study design and identification of target population: (A) Study schema, (B) Event map, (C) Study cohort flowchart. ICH, intracerebral hemorrhage; IS, ischemic stroke; MI, myocardial infarction.*

Supplementary Table 1A. Diagnosis codes for identifying first event

Event	ICD-9-CM code	ICD-10-CM code	Definition algorithm
Myocardial infarction (MI)	410.x	I21.x	1 IP, primary position
Ischemic stroke (IS)	433.x1, 434.x1	I63.x, I64.x	1 IP, primary position
Intracerebral hemorrhage (ICH)	431	I61.x	1 IP, primary position

IP, inpatient.

Supplementary Table 1B. Diagnosis codes for determining medical history

Condition	ICD-9-CM code	ICD-10-CM code	Definition algorithm
Myocardial infarction (MI)	410.x, 412.x, 429.79	I21.x, I22.x, I23.x, I25.2	1 IP or 1 OP, any position
Ischemic stroke (IS)	433.x, 434.x, 436.x, 437.x, 438.x	I63.x, I64.x, I65.x, I66.x, I67.x, I69.3x	1 IP or 1 OP, any position
Hemorrhagic stroke (HS)	430.x, 431.x, 432.x	I60.x, I61.x, I62.x, I69.0x, I69.1x, I69.2x	1 IP or 1 OP, any position

IP, inpatient; OP, outpatient.

Supplementary Table 2. Six-year cumulative incidence of the second event from 28 days after first MI, IS, or ICH

First event	Second event	Cumulative incidence of second event					
		1 year	2 years	3 years	4 years	5 years	6 years
MI	Recurrent MI						
	All	3.93%	5.49%	6.68%	7.84%	8.99%	10.09%
	Men	3.70%	5.26%	6.38%	7.60%	8.73%	9.79%
	Women	4.74%	6.34%	7.74%	8.72%	9.88%	11.16%
	Post-MI IS						
	All	0.94%	1.59%	2.22%	2.81%	3.42%	3.90%
	Men	0.80%	1.35%	1.93%	2.44%	3.05%	3.53%
	Women	1.44%	2.41%	3.20%	4.09%	4.72%	5.22%
	Post-MI ICH						
	All	0.19%	0.29%	0.39%	0.47%	0.57%	0.65%
	Men	0.16%	0.25%	0.35%	0.42%	0.52%	0.62%
	Women	0.28%	0.44%	0.52%	0.65%	0.71%	0.76%
IS	Recurrent IS						
	All	5.29%	7.67%	9.59%	11.12%	12.54%	13.82%
	Men	5.41%	7.86%	9.87%	11.40%	12.91%	14.36%
	Women	5.11%	7.39%	9.18%	10.72%	11.99%	13.05%
	Post-IS MI						
	All	0.50%	0.88%	1.27%	1.65%	2.03%	2.40%
	Men	0.55%	0.97%	1.41%	1.84%	2.26%	2.72%
	Women	0.43%	0.74%	1.07%	1.37%	1.69%	1.95%
	Post-IS ICH						
	All	0.47%	0.82%	1.10%	1.38%	1.64%	1.86%
	Men	0.53%	0.91%	1.22%	1.56%	1.85%	2.14%
	Women	0.38%	0.69%	0.94%	1.11%	1.34%	1.46%
ICH	Recurrent ICH						
	All	3.94%	5.21%	6.37%	7.37%	8.16%	8.85%
	Men	4.10%	5.47%	6.67%	7.75%	8.61%	9.39%
	Women	3.65%	4.72%	5.82%	6.66%	7.33%	7.83%
	Post-ICH MI						
	All	0.15%	0.28%	0.46%	0.63%	0.80%	0.98%
	Men	0.16%	0.32%	0.48%	0.67%	0.89%	1.17%
	Women	0.14%	0.22%	0.44%	0.58%	0.63%	0.72%
	Post-ICH IS						
	All	1.76%	2.73%	3.56%	4.26%	4.87%	5.60%
	Men	1.87%	2.87%	3.77%	4.49%	5.15%	6.06%
	Women	1.55%	2.47%	3.17%	3.84%	4.38%	4.82%

ICH, intracerebral hemorrhage; IS, ischemic stroke; MI, myocardial infarction.

Supplementary Table 3. Total follow-up cost of first and recurrent events (presented in 2017 USD)

Cost, median (Q1~Q3)	First MI (n = 44,212)	First IS (n = 85,223)	First ICH (n = 23,978)	Recurrent MI (n = 2,225)	Recurrent IS (n = 6,504)	Recurrent ICH (n = 1,020)
Baseline cost over one year prior to the index event						
Total	651 (174~1,683)	668 (208~1,545)	286 (39~976)			
Inpatient	0 (0~0)	0 (0~0)	0 (0~0)			
No. of patients with hospital stay	7,871	14,859	3,146			
Cost among patients with hospital stay	1,500 (716~3,717)	1,266 (628~3,011)	1,316 (653~3,360)		Not estimated	
Outpatient	532 (133~1,254)	546 (158~1,163)	227 (29~745)			
Emergency room	0 (0~77)	0 (0~64)	0 (0~0)			
No. of patients with ER visit	14,768	27,892	5,852			
Cost among patients with ER visit	166 (77~367)	146 (67~300)	123 (58~288)			
First year follow-up cost						
Total	2,413 (1,393~6,120)	2,174 (1,040~5,472)	2,963 (995~8,352)	3,510 (1,654~11,409)	3,530 (1,591~7,580)	5,578 (1,984~12,088)
Inpatient	0 (0~3,539)	0 (0~1678)	0 (0~3,566)	760 (0~5,236)	512 (0~3,449)	1,649 (0~7,295)
No. of patients with hospital stay	20,826	34,887	11,349	1,243	3,572	659
Cost among patients with hospital stay	3,764 (1,578~6,557)	2,555 (968~6,410)	4,002 (1,466~10,101)	4,584 (1,748~9,633)	2,939 (1,157~6,975)	5,264 (1,856~10,860)
Outpatient	1,570 (1,109~2,222)	1,385 (759~2,510)	1,343 (629~3,105)	1,789 (1,166~3,018)	1,707 (932~3,068)	1,769 (781~3,898)
Emergency room	0 (0~182)	0 (0~179)	0 (0~178)	78 (0~416)	55 (0~291)	22 (0~280)
No. of patients with ER visit	19,627	38,327	10,295	1,273	3,655	519
Cost among patients with ER visit	221 (99~471)	216 (86~428)	225 (92~430)	355 (146~735)	257 (110~505)	275 (121~537)
Second year follow-up cost						
Total	1,293 (654~2,868)	1,394 (602~3,265)	1,185 (405~3,937)	1,713 (609~6,163)	1,974 (753~4,796)	2,340 (582~5,927)
Inpatient	0 (0~422)	0 (0~345)	0 (0~0)	0 (0~1,710)	0 (0~1,112)	0 (0~1,248)
No. of patients with hospital stay	11,755	22,545	5,726	800	2,330	355
Cost among patients with hospital stay	2,759 (957~5,357)	1,949 (843~4,927)	2,081 (898~5,332)	3,647 (1,315~8,245)	2,180 (934~5,423)	2,380 (1,084~5,981)
Outpatient	1,051 (573~1,774)	1,082 (499~2,012)	882 (331~2,272)	1,199 (477~2,368)	1,328 (541~2,525)	1,340 (422~3,501)
Emergency room	0 (0~79)	0 (0~79)	0 (0~51)	0 (0~197)	0 (0~165)	0 (0~128)
No. of patients with ER visit	14,277	28,096	7,001	925	2,558	371
Cost among patients with ER visit	186 (86~408)	199 (81~392)	213 (84~411)	269 (119~671)	245 (103~469)	249 (98~494)

Note: Only patients who had at least two years of follow-up after the first event were included in this analysis.

ER, emergency room; ICH, intracerebral hemorrhage; IS, ischemic stroke; MI, myocardial infarction.