



Percutaneous coronary intervention in patients hospitalized for non-ST-elevation myocardial infarction and the risk of postdischarge ischemic stroke at 6-month, 1-year, and 3-year follow-ups

Chao-Feng Lin^{1,2,3} · Ya-Hui Chang⁴ · Nai-Fang Chi⁵ · I.-M.ing Chen⁶ · Hung-Yi Liu⁷ · Li-Nien Chien⁸

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Abstract

Percutaneous coronary intervention (PCI) is suggested for treating patients with non-ST-elevation myocardial infarction (NSTEMI) to reduce adverse cardiovascular events. However, the short- and long-term effects of PCI on the risk of postdischarge ischemic stroke (IS) in patients hospitalized for NSTEMI remain unclear. This study investigated the association of PCI on the risk of postdischarge IS in patients hospitalized for NSTEMI at different period follow-ups. A population-based cohort study was conducted using data from Taiwan's National Health Insurance Research Database. Propensity score matching (PSM) was used to select 6079 pairs of the patients with NSTEMI treated invasively by PCI (received PCI during hospitalization) and initial conservative strategy (did not receive PCI during hospitalization) with similar baseline characteristics for evaluation. After adjustment for patients' clinical variables and the duration of dual antiplatelet therapy, PCI was associated with a decreased risk of postdischarge IS at 6-month, 1-year, and 3-year follow-ups [adjusted hazard ratio (aHR) = 0.41, 95% confidence interval (CI) = 0.26–0.67, $p < 0.001$; aHR = 0.61, 95% CI 0.43–0.86, $p = 0.004$; and aHR = 0.69, 95% CI 0.54–0.89, $p = 0.005$ respectively]. In the patients who had a CHA₂DS₂-VASc score of ≥ 2 , PCI was also associated with a decreased risk of postdischarge IS at 6-month, 1-year, and 3-year follow-ups (aHR = 0.54, 95% CI 0.36–0.83, $p = 0.005$; aHR = 0.72, 95% CI 0.52–1.00, $p = 0.048$; and aHR = 0.73, 95% CI 0.58–0.91, $p = 0.005$, respectively). These findings suggested that PCI might reduce the risk of postdischarge IS in patients hospitalized for NSTEMI.

Keywords Non-ST-elevation myocardial infarction · Ischemic stroke · Percutaneous coronary intervention

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✉ Li-Nien Chien
lnchien@tmu.edu.tw

¹ Department of Medicine, MacKay Medical College, New Taipei City, Taiwan

² Division of Cardiology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan

³ Ph.D. Program for Cancer Molecular Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University and Academia Sinica, Taipei, Taiwan

Introduction

Ischemic stroke (IS) is one of the serious complications leading to increased mortality in patients with acute myocardial infarction (AMI) [1–5]. In a meta-analysis conducted by Witt et al., the incidence rate of IS was determined to be 11.1

⁴ Department of Pharmacy, MacKay Memorial Hospital, Taipei, Taiwan

⁵ Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

⁶ Department of Medicine, School of Medicine, National Yang Ming University, Taipei, Taiwan

⁷ Health and Clinical Research Data Center, School of public health, Taipei Medical University, Taipei, Taiwan

⁸ School of Health Care Administration, College of Management, Taipei Medical University, Taipei, Taiwan

[95% confidence interval (CI) 10.7–11.5] per 1000 patients during hospitalization for AMI, 12.2 (95% CI 10.4–14.0) at 30 days after AMI, and 21.4 (95% CI 14.1–28.7) at 1 year [4]. Compared with patients with ST-elevation myocardial infarction (STEMI), patients with non-ST-elevation myocardial infarction (NSTEMI) typically have more comorbidities and worse clinical outcomes after discharge [6–9]. The invasive strategy with percutaneous coronary intervention (PCI), rather than conservative treatment, is recommended for patients with NSTEMI to reduce the incidence of angina, rehospitalization, and adverse cardiovascular events, particularly for patients with NSTEMI who have a high cardiovascular risk [6, 10, 11]. Although PCI has been suggested for treating patients with NSTEMI [6, 10, 11], the results of our previous study showed that only approximately half of the patients with NSTEMI received PCI during hospitalization [12]. Moreover, the short- and long-term effects of PCI on the risk of postdischarge IS in patients hospitalized for NSTEMI remain unknown.

In the present retrospective cohort study, we investigated the association between invasive strategy with PCI and the risk of postdischarge IS in patients hospitalized for NSTEMI at 6-month, 1-year, and 3-year follow-ups using data from Taiwan's National Health Insurance Research Database (NHIRD).

Materials and methods

This study was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201607039). In this study, we used the NHIRD, a claim-based database that covers 99% of residents in Taiwan under the legislation of the National Health Insurance (NHI) program. Because individual identifiers cannot be recognized in the NHIRD after the data released to researchers, informed consent was waived under the review process of the TMU-JIRB.

The NHIRD includes inpatient, outpatient, and prescription drug claims. Prescribed medications can be classified according to the Anatomical Therapeutic Chemical (ATC) system, and the disease diagnosis is coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The death record from the National Death Registry can also be linked to the NHIRD based on patients' encrypted identifiers [13].

Within the retrospective cohort, we included patients who had received a primary diagnosis of AMI (ICD-9-CM code 410) based on the discharge claim between 2001 and 2013. The date of admission for AMI was considered the index date of AMI. We excluded patients who were < 20 years, were not citizen in Taiwan, had a history of cerebrovascular diseases before the index date, and had died at AMI

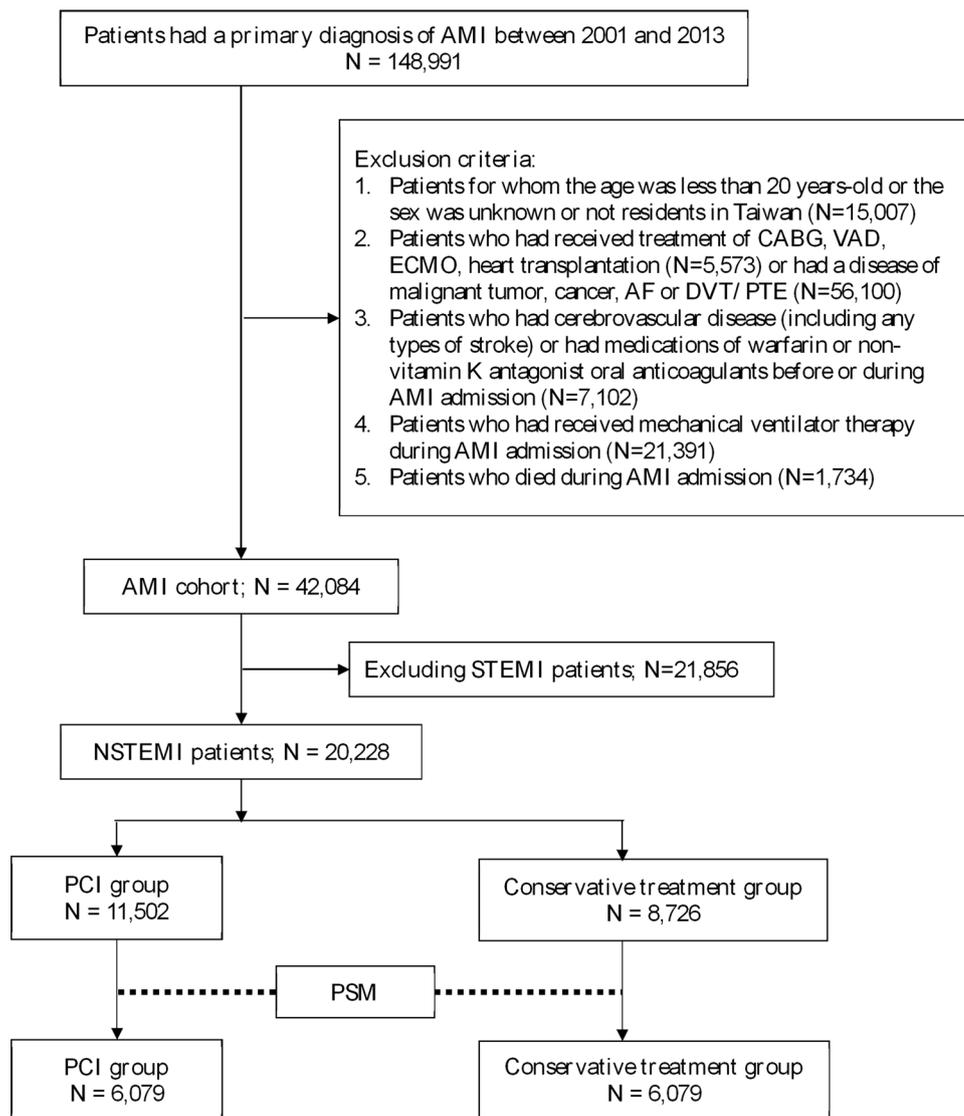
admission. Patients with AMI are at a high risk to develop IS during hospitalization irrespective of receiving PCI or not [1–5]. To avoid the bias caused by AMI itself, we excluded any type of concomitant stroke during hospitalization for AMI. We also excluded patients who were at a high risk of stroke, including those who had received a diagnosis of a malignant tumor or cancer [14], atrial fibrillation (AF) [15], or venous thromboembolism (e.g., deep vein thrombosis [16] and pulmonary thromboembolism [17]); had received warfarin or non-vitamin K antagonist oral anticoagulants; or had received mechanical ventilation therapy during hospitalization for AMI [18], coronary artery bypass grafting [19], ventricular assist device support [20], extracorporeal membrane oxygenation [21], or heart transplantation [22] during the study period. Finally, we excluded patients who had received a diagnosis of STEMI. Figure 1 presents the patient selection process. Patients who had and had not received PCI during their index AMI admission were comprised the PCI and conservative treatment groups, respectively.

To reduce the selection bias when estimating the effect of PCI on the occurrence of postdischarge IS, we used propensity score matching (PSM) to select a pair of patients from the PCI and conservative treatment groups who had similar baseline characteristics but different PCI statuses. PSM is increasingly being used to estimate the effects of exposure using observational data [23–25]. In this study, we applied the most common PSM implementation: a pair of patients was matched on the logit of the propensity score using calipers of a width equal to 0.2 of the standard deviation. Covariates used to calculate the propensity score included age, sex, the year of NSTEMI diagnosis, previous or coexisting medical conditions, and drug prescriptions (Table 1).

Previous or coexisting medical conditions, including diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, congestive heart failure (CHF), chronic obstructive pulmonary disease or asthma, chronic liver disease, dementia, Parkinson disease, osteoarthritis, rheumatoid arthritis, and rheumatism, were defined if patients had ≥ 2 diagnostic claims in the 1 year prior to the index date of NSTEMI hospitalization. Moreover, we calculated the CHA₂DS₂-VASC score, which is the sum of risk factors for CHF, hypertension, age ≥ 75 years, diabetes, stroke, vascular disease, age of 65–74 years, and sex category of female, and used it for patient matching [26]. The CHA₂DS₂-VASC score is widely used to stratify the risk of stroke in patients with or without AF following AMI [26, 27]. Because this study focused on newly developed IS, the CHA₂DS₂-VASC score did not consider the risk factor for previous stroke.

Medication prescriptions included angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs), antiplatelets, nitrates, statins, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, steroids, and beta-blockers. The ICD-9-CM codes for disease diagnosis

Fig. 1 Patient selection diagram. PCI group: who had received PCI treatment during AMI hospitalization. Conservative treatment PCI group: who did not received PCI treatment during AMI hospitalization



and the ATC codes for medication are listed in Supplementary Tables A and B, respectively.

The principal outcome in the present study was the occurrences of postdischarge IS (ICD-9-CM codes 433, 434, and 436). The patients were followed-up with at 6 months, 1 year, and 3 years, and those who died or did not have the events of interest during the follow-up periods were treated as censored cases.

A primary analysis was performed to examine the association between PCI during hospitalization and the risk of postdischarge IS. A subgroup analysis of patients with more cardiovascular risk factors (age ≥ 75 years and $\text{CHA}_2\text{DS}_2\text{-VASc}$ score ≥ 2) was also performed. A multivariable Cox proportional hazard regression model was used to compare the risk of principal outcomes between the PCI and conservative treatment groups after PSM. The assumption of proportional hazards was also evaluated. In

this present study, we reported the adjusted hazard ratio (adjusted HR). Variables used in the models were baseline covariates listed in Table 1, including age, sex, the year of NSTEMI diagnosis, previous or coexisting medical conditions, and prescribed medications. To assess the effect of dual antiplatelet therapy (DAPT), we calculated medication possession ratio (MPR) which was defined as total number of days covered by filled prescriptions divided by a pre-defined period (i.e., 6 months) [28, 29]. An MPR of DAPT < 0.4 , 0.4 to < 0.8 , and ≥ 0.8 was classified as low, intermediate, and high adherence, respectively and included in the regression models [28, 29]. All were performed using SAS/STAT 9.2 software (SAS Institute Inc., Cary, NC) and STATA 12 software (Stata Corp LP, College Station, TX). A value of $p < 0.05$ was considered significant.

Table 1 Baseline characteristics of patients with NSTEMI before and after PSM

	Before PSM				SMD ^a	After PSM				
	Conservative		PCI			Conservative		PCI		SMD ^a
	N	(%)	N	(%)		N	(%)	N	(%)	
Sample size	8726		11,502			6,079		6,079		
Men	5883	(67.4)	9,355	(81.3)		4,431	(72.9)	4,431	(72.9)	
Age, years										
Mean (\pm SD)	66.0	(\pm 15.3)	60.2	(\pm 13.3)		63.7	(\pm 13.9)	63.7	(\pm 13.8)	
20–44	792	(9.1)	1,358	(11.8)	0.09	545	(9.0)	547	(9.0)	0.00
45–64	3097	(35.5)	5,946	(51.7)	0.33	2,562	(42.1)	2,561	(42.1)	0.00
65–74	1872	(21.5)	2,192	(19.1)	0.06	1,384	(22.8)	1,373	(22.8)	0.00
\geq 75	2965	(34.0)	2,006	(17.4)	0.39	1,588	(26.1)	1,598	(26.1)	0.00
Diagnosis year										
2001–2005	2910	(33.3)	1,530	(13.3)	0.49	1,538	(25.3)	1,310	(21.5)	0.09
2006–2009	2841	(32.6)	3,754	(32.6)	0.00	2,013	(33.1)	2,243	(36.9)	0.08
2010–2013	2975	(34.1)	6,218	(54.1)	0.41	2,528	(41.6)	2,526	(41.6)	0.00
Comorbidities										
Diabetes	2019	(23.1)	2,232	(19.4)	0.09	1,401	(23.0)	1,421	(23.4)	0.01
Hypertension	2637	(30.2)	3,194	(27.8)	0.05	1,746	(28.7)	1,886	(31.0)	0.05
Hyperlipidemia	240	(2.8)	487	(4.2)	0.08	204	(3.4)	183	(3.0)	0.02
CKD	648	(7.4)	507	(4.4)	0.13	405	(6.7)	391	(6.4)	0.01
CHF	556	(6.4)	267	(2.3)	0.20	216	(3.6)	239	(3.9)	0.02
COPD or Asthma	458	(5.2)	365	(3.2)	0.10	233	(3.8)	253	(4.2)	0.02
CLD	179	(2.1)	153	(1.3)	0.06	103	(1.7)	99	(1.6)	0.01
Dementia or Parkinson disease	325	(3.7)	113	(1.0)	0.18	75	(1.2)	108	(1.8)	0.05
OA, RA or Rheumatism	1068	(12.2)	1,088	(9.5)	0.09	652	(10.7)	716	(11.8)	0.03
CHA ₂ DS ₂ -VAsC Score										
0–1	1066	(12.2)	2,354	(20.5)	0.23	865	(14.2)	865	(14.2)	0.00
\geq 2	7660	(87.8)	9,148	(79.5)	0.23	5,214	(85.8)	5,214	(85.8)	0.00
Medication prescription										
ACEI/ARB	6180	(70.8)	9,417	(81.9)	0.26	4,706	(77.4)	4,814	(79.2)	0.04
Antiplatelets	8268	(94.8)	11,494	(99.9)	0.33	6,070	(99.9)	6,073	(99.9)	0.01
Nitrates	7862	(90.1)	11,090	(96.4)	0.25	5,765	(94.8)	5,781	(95.1)	0.01
Statins	3644	(41.8)	8,091	(70.3)	0.60	3,301	(54.3)	3,315	(54.5)	0.01
PPIs	1041	(11.9)	896	(7.8)	0.14	630	(10.4)	632	(10.4)	0.00
NSAIDs	3501	(40.1)	4,063	(35.3)	0.10	2,290	(37.7)	2,334	(38.4)	0.02
Steroids	1349	(15.5)	1,286	(11.2)	0.13	827	(13.6)	855	(14.1)	0.01
Beta-blockers	5266	(60.3)	8,464	(73.6)	0.28	4,163	(68.5)	4,136	(68.0)	0.01

^aSMD = difference in means or proportions divided by the standard error and imbalance defined as an absolute value greater than 0.1

ACEI/ARB angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, CHA₂DS₂-VAsC Score congestive heart failure, hypertension, age \geq 75 years, diabetes, stroke, vascular disease, age of 65–74 years, and sex category of female, CHF congestive heart failure, CKD chronic kidney disease, CLD chronic liver disease, COPD chronic obstructive pulmonary disease, CVD cerebrovascular disease, NSAIDs non-steroidal anti-inflammatory drugs, NSTEMI non-ST-elevation myocardial infarction, OA osteoarthritis, PCI percutaneous coronary intervention, PPIs proton pump inhibitors, PM person-month, PSM propensity score matching, RA rheumatoid arthritis, Ref reference, SD standard deviation, SMD standardized mean difference

Results

Of the 20,228 patients hospitalized for NSTEMI who were examined in this study, 11,502 (56.9%) received PCI during hospitalization. Patients in the PCI group were younger and

had fewer comorbidities and lower CHA₂DS₂-VAsC scores than did those in the conservative treatment group. Compared with the patients in the conservative treatment group, those in the PCI group more frequently used ACEIs/ARBs, antiplatelets, nitrates, statins, and beta-blockers (Table 1).

Additionally, patients in the PCI group had a better adherence of DAPT than did those in the conservative treatment group (Supplementary Table C). After PSM, 6079 patient pairs were selected from the PCI and conservative treatment groups. The baseline characteristics were markedly similar in the PCI and conservative treatment groups after PSM (Table 1).

The cumulative incidence rate of postdischarge IS was lower in the PCI group than in the conservative treatment group at 6-month (Fig. 2a), 1-year (Fig. 2b), and 3-year (Fig. 2c) follow-ups. In addition, the incidence rates (per 100 person-months) of postdischarge IS at 6-month, 1-year, and 3-year follow-ups were higher in the conservative treatment group (1.97, 95% confidence interval [CI]=1.55–2.50; 1.45, 95% CI 1.19–1.77; and 1.06, 95% CI 0.92–1.23, respectively) than in the PCI group (0.96, 95% CI 0.68–1.34; 0.94, 95% CI 0.74–1.19; and 0.79, 95% CI 0.67–0.93, respectively) (Table 2).

After adjustment for potential risk factors and the use of DAPT, PCI during hospitalization in the patients with NSTEMI was associated with a decreased risk of postdischarge IS at 6-month, 1-year, and 3-year follow-ups compared with conservative treatment, with adjusted hazard ratios (aHRs) of 0.41 (95% CI 0.26–0.67, $p < 0.001$), 0.61 (95% CI 0.43–0.86, $p = 0.004$), and 0.69 (95% CI 0.54–0.89, $p = 0.005$), respectively (Table 2). Among the patients aged ≥ 75 years, PCI during hospitalization was not associated with a decreased risk of postdischarge IS (Table 2). However, among the patients who had a CHA₂DS₂-VASc score of ≥ 2 , PCI during hospitalization was associated with a decreased risk of postdischarge IS at 6-month, 1-year, and 3-year follow-ups (aHR = 0.54, 95% CI 0.36–0.83, $p = 0.005$; aHR = 0.72, 95% CI 0.52–1.00, $p = 0.048$; and aHR = 0.73, 95% CI 0.58–0.91, $p = 0.005$ respectively) (Table 2).

Of the patients with conservative treatment, we observed that patients who received PCI after discharge had a similar incidence of IS to those who eventually did not receive PCI (Supplementary Table D). To further investigate the cutoff

at which it was safe to defer PCI, the NSTEMI patients who had received conservative treatment during hospitalization were classified into subgroups according to the timing of PCI performed after discharge. We observed no significant difference in the 1-year risk of IS among the subgroups (Supplementary Table E).

Discussion

The results of the current study revealed an association of PCI with a decreased risk of postdischarge IS in the patients hospitalized for NSTEMI. The NHIRD includes information not only from medical centers but also from non-PCI-capable hospitals in Taiwan. Thus, our findings likely represented the real-world data. Additionally, there are few structural differences in Taiwan because NHI program covers 99% of residents and necessary invasive cardiac procedures for AMI. In the present study, the patients with NSTEMI who did not undergo PCI during hospitalization were older and had more comorbidities and cardiovascular risk factors than did those who received PCI; this finding is in accordance with those reported previously [12, 30, 31]. This may be because the risk profiles of such patients are perceived to increase the risks and complications associated with invasive procedures [31, 32]. In addition, patients of an older age and with more severe comorbidities who develop NSTEMI are more likely to present with atypical symptoms rather than typical chest pain [6, 11]. Therefore, aggressive treatment with PCI following an accurate diagnosis and risk stratification in such patients is usually postponed. Other possible reasons included a lack of adherence to guidelines, lack of implementation of quality improvement programs, or suboptimal awareness of invasive cardiac procedures [5, 11, 33].

The mortality rate was higher in patients who experienced IS following AMI than in patients who did not experience IS [2, 3]. Predictors for IS following AMI include advanced age, hypertension, heart failure, renal

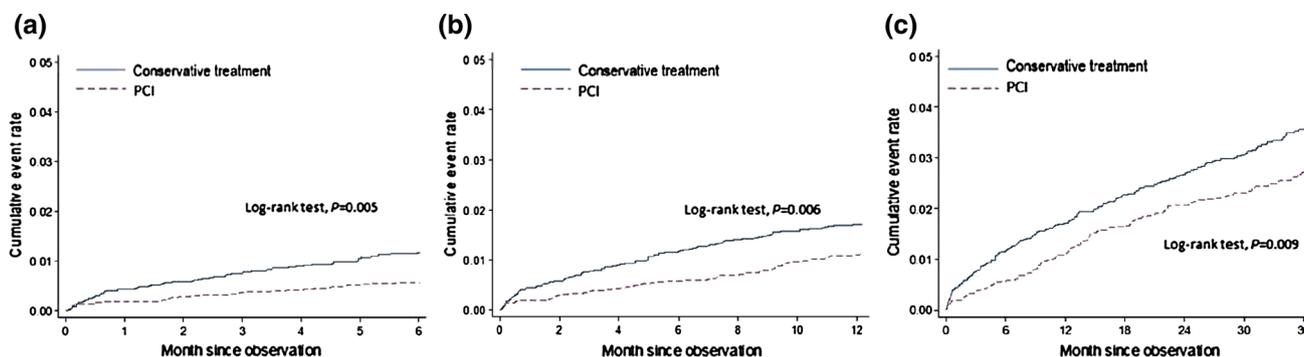


Fig. 2 Kaplan–Meier curves and log-rank tests for postdischarge IS in patients hospitalized for NSTEMI who had received conservative treatment versus PCI after PSM **a** at 6-month follow-up; **b** at 1-year follow-up; **c** at 3-year follow-up

Table 2 Incidence (per 100 person-months) and the adjusted hazard ratio of postdischarge IS of patients hospitalized for NSTEMI who had received PCI compared with those who had received conservative treatment

Whole NSTEMI cohort	Follow-up period	Treatment strategy during hospitalization	No. of Events	Incidence (95% CI)	Adjusted ^a HR (95% CI)	<i>p</i> value	
Whole NSTEMI cohort	6month	PCI	34	0.96 (0.68–1.34)	0.41 (0.26–0.67)	<0.001	
		Conservative	68	1.97 (1.55–2.50)	1.00 (Ref.)		
	1year	PCI	66	0.94 (0.74–1.19)	0.61 (0.43–0.86)		0.004
		Conservative	98	1.45 (1.19–1.77)	1.00 (Ref.)		
	3year	PCI	145	0.79 (0.67–0.93)	0.69 (0.54–0.89)		0.005
		Conservative	182	1.06 (0.92–1.23)	1.00 (Ref.)		
Subgroup							
Age ≥75 years	6month	PCI	18	1.98 (1.25–3.14)	0.81 (0.43–1.52)	0.514	
		Conservative	23	2.74 (1.82–4.12)	1.00 (Ref.)		
	1year	PCI	28	1.58 (1.09–2.29)	0.80 (0.49–1.32)		0.389
		Conservative	35	2.21 (1.59–3.08)	1.00 (Ref.)		
	3year	PCI	58	1.33 (1.03–1.73)	0.76 (0.54–1.08)		0.129
		Conservative	68	1.89 (1.49–2.40)	1.00 (Ref.)		
CHA ₂ DS ₂ -VASc ≥ 2	6month	PCI	33	1.09 (0.77–1.53)	0.54 (0.36–0.83)	0.005	
		Conservative	68	2.32 (1.83–2.94)	1.00 (Ref.)		
	1year	PCI	64	1.07 (0.83–1.36)	0.72 (0.52–1.00)		0.048
		Conservative	98	1.72 (1.14–2.09)	1.00 (Ref.)		
	3year	PCI	139	0.90 (0.76–1.06)	0.73 (0.58–0.91)		0.005
		Conservative	179	1.25 (1.08–1.45)	1.00 (Ref.)		

^aThe adjusted hazard ratio was calculated using a multivariable Cox proportional hazard model adjusted for sex, age, the year of admission for AMI, comorbidities, prescribed medications (all variables used for adjustment are listed in Table 1) and duration of dual antiplatelet therapy (DAPT) measured by medication possession ratio (MPR)

Abbreviations are listed in Table 1

disease, peripheral arterial disease, and diabetes mellitus [1, 5, 34]. These risk factors are particularly critical for patients with NSTEMI because they frequently develop the aforementioned comorbidities, as also observed in the present study. Invasive treatment with PCI is suggested to reduce the risk of adverse cardiovascular events; it might also reduce the risk of postdischarge IS in patients with NSTEMI, as noted herein. More importantly, no obvious cutoff was determined to be safe for deferring PCI according to our analysis. Previous studies reported that prescription of antiplatelet agents was associated with a reduced risk of IS following AMI [5, 34]. In this current study, we used the MPR as a proxy to control the effect of DAPT use and found that the benefit of PCI could be still observed among patients with NSTEMI after adjustment for the duration of DAPT. Aggressive treatment by PCI might be thus recommended for patients hospitalized for NSTEMI when fully evaluating the risk of the intervention. In addition to provide detailed information about the extent of atherosclerotic obstruction, PCI might facilitate more optimal revascularization of coronary arteries, less recurrent ischemia, and fewer reinfarction compared to conservative treatment [6].

In the present study, the effect of PCI on the risk of postdischarge IS in the patients aged ≥ 75 years was not significant. This might be due to the relatively low number of patients in this age group. In contrast to the elderly patients, PCI was beneficial for the patients who had a CHA₂DS₂-VASc score of ≥ 2. Our findings, as well as those of previous studies [26, 27], indicate that the CHA₂DS₂-VASc score might assist physicians in identifying high-risk patients with NSTEMI who could obtain benefits from PCI to prevent the occurrence of IS following NSTEMI. We also examined whether PCI was associated with a low risk of IS-related death (Supplementary Table F) and found that the benefit of PCI could be observed only among a specific group of patients with NSTEMI who were followed for a specific period.

Several mechanisms might explain our findings. Myocardial ischemia results in the release of inflammatory cytokines and the activation of inflammation [35, 36]. These might trigger the destabilization and rupture of plaques in cerebral circulation and result in subsequent thrombosis and IS [35–37]. Restoration of coronary flow by PCI might reduce the extent of myocardial inflammation, thereby reducing these cytokine-mediated processes and the risk of IS following NSTEMI [35,

36]. In addition, PCI has the potential to maintain cardiac function, reduce the extent of atrial or ventricular ischemia and fibrosis, thereby reduce the risk of formation of atrial arrhythmia, cardiac thrombus and subsequent long-term risk of IS [5, 34, 35].

The present study was subjected to limitations. First, the NHIRD does not provide information on patients' risk behaviors, such as tobacco use, which might be associated with an increased risk of IS. Second, the NHIRD does not provide some clinical information, such as the angiographic findings of PCI, extent of a patient's coronary artery disease, and severity of IS. Third, PSM considered only the observed variables; therefore, a hidden bias introduced by unobserved variables, such as frailty of patients, is possible. Although the NHIRD could not provide patients' information of frailty, we still noticed and reported that before PSM patients in the PCI group had a better health status compared to those in the conservative treatment group. In addition, PSM undoubtedly reduced the external validity of our study because only a subset of the treated patients was analyzed. However, despite its limitations, PSM is an acceptable approach because the findings of observational studies using PSM are moderately consistent with those of randomized clinical trials [24, 38]. Fourth, we did not consider the occurrences of IS immediately caused by PCI because we aimed to investigate the risk of postdischarge IS. Finally, a cohort of Taiwanese patients was included in this study; therefore, the results might not be generalizable to other populations. Future prospective, randomized studies are warranted to confirm our findings.

Conclusions

The patients with NSTEMI who had received invasive treatment with PCI during hospitalization had a lower risk of postdischarge IS than did those who had received conservative treatment at 6-month, 1-year, and 3-year follow-ups; these results are consistent with those for patients who had a CHA₂DS₂-VAsC score of ≥ 2 . Overall, our findings suggest that PCI significantly prevents IS following NSTEMI.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

References

- Kajermo U, Ulvenstam A, Modica A, Jernberg T, Mooe T (2014) Incidence, trends, and predictors of ischemic stroke 30 days after an acute myocardial infarction. *Stroke* 45:1324–1330
- Mooe T, Olofsson BO, Stegmayr B, Eriksson P (1999) Ischemic stroke. Impact of a recent myocardial infarction. *Stroke* 30:997–1001
- Brammas A, Jakobsson S, Ulvenstam A, Mooe T (2013) Mortality after ischemic stroke in patients with acute myocardial infarction: predictors and trends over time in Sweden. *Stroke* 44:3050–3055
- Witt BJ, Ballman KV, Brown RD Jr, Meverden RA, Jacobsen SJ, Roger VL (2006) The incidence of stroke after myocardial infarction: a meta-analysis. *Am J Med* 119:354.e1–e9
- Hachet O, Guenancia C, Stamboul K, Daubail B, Richard C, Béjot Y, Yameogo V, Gudjoncik A, Cottin Y, Giroud M, Lorgis L (2014) Frequency and predictors of stroke after acute myocardial infarction: specific aspects of in-hospital and postdischarge events. *Stroke* 45:3514–3520
- Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ, ACC/AHA Task Force Members (2014) 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 130:e344–e426
- Pilgrim T, Vranckx P, Valgimigli M, Stefanini GG, Piccolo R, Rat J, Rothenbühler M, Stortecky S, Räber L, Blöchlinger S, Hunziker L, Silber S, Jüni P, Serruys PW, Windecker S (2016) Risk and timing of recurrent ischemic events among patients with stable ischemic heart disease, non–ST-segment elevation acute coronary syndrome, and ST-segment elevation myocardial infarction. *Am Heart J* 175:56–65
- Daida H, Miyauchi K, Ogawa H, Yokoi H, Matsumoto M, Kitakaze M, Kimura T, Matsubara T, Ikari Y, Kimura K, Tsukahara K, Origasa H, Morino Y, Tsutsui H, Kobayashi M, Isshiki T (2013) Management and two-year long-term clinical outcome of acute coronary syndrome in Japan: prevention of atherothrombotic incidents following ischemic coronary attack (PACIFIC) registry. *Circ J* 77:934–943
- Fox KA, Anderson FA Jr, Goodman SG, Steg PG, Pieper K, Quill A, Gore JM, GRACE Investigators (2008) Time course of events in acute coronary syndromes: implications for clinical practice from the GRACE registry. *Nat Clin Pract Cardiovasc Med* 5:580–589
- Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JG, Lagerqvist B, Wallentin L, FIR Collaboration (2010) Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol* 55:2435–2445
- Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, ESC Scientific Document Group (2016) 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 37:267–315
- Lin CF, Chang YH, Chi NF, Chuang MT, Chien LN (2018) Effect of early percutaneous coronary intervention on one-year risk of pneumonia and pneumonia-related adverse outcomes in patients with acute myocardial infarction. *EuroIntervention* 13:1705–1713
- National Health Insurance: Review Legislations of Medical Institutes, update 2013/04/09. https://www.nhi.gov.tw/English/webdata/webdata.aspx?menu=11&menu_id=295&WD_ID=295&webdata_id=2440. Accessed 5 June 2016
- Bang OY, Seok JM, Kim SG, Hong JM, Kim HY, Lee J, Chung PW, Park KY, Kim GM, Chung CS, Lee KH (2011) Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. *J Clin Neurol* 7:53–59

15. Wolf PA, Abbott RD, Kannel WB (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 22:983–988
16. Sørensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P (2007) Venous thromboembolism and subsequent hospitalization due to acute arterial cardiovascular events: a 20-year cohort study. *Lancet* 370:1773–1779
17. Goliszek S, Wiśniewska M, Kurnicka K, Lichodziejewska B, Czurzyński M, Kostrubiec M, Gołębiowski M, Babiuch M, Paczynska M, Koć M, Palczewski P, Wyzgał A, Pruszczyk P (2014) Patent foramen ovale increases the risk of acute ischemic stroke in patients with acute pulmonary embolism leading to right ventricular dysfunction. *Thromb Res* 134:1052–1056
18. Kouraki K, Schneider S, Uebis R, Tebbe U, Klein HH, Janssens U, Zahn R, Senges J, Zeymer U (2011) Characteristics and clinical outcome of 458 patients with acute myocardial infarction requiring mechanical ventilation. Results of the BEAT registry of the ALKK-study group. *Clin Res Cardiol* 100:235–239
19. Hedberg M, Boivie P, Engström KG (2011) Early and delayed stroke after coronary surgery—an analysis of risk factors and the impact on short- and long-term survival. *Eur J Cardiothorac Surg* 40:379–387
20. Stulak JM, Davis ME, Haglund N, Dunlay S, Cowger J, Shah P, Pagani FD, Aaronson KD, Maltais S (2016) Adverse events in contemporary continuous-flow left ventricular assist devices: A multi-institutional comparison shows significant differences. *J Thorac Cardiovasc Surg* 151:177–189
21. Omar HR, Mirsaeidi M, Shumac J, Enten G, Mangar D, Camporesi EM (2016) Incidence and predictors of ischemic cerebrovascular stroke among patients on extracorporeal membrane oxygenation support. *J Crit Care* 32:48–51
22. Acampa M, Lazzerini PE, Guideri F, Tassi R, Martini G (2016) Ischemic stroke after heart transplantation. *J Stroke* 18:157–168
23. Dehejia RH, Wahba S (2002) Propensity score-matching methods for nonexperimental causal studies. *Rev Econ Stat* 84:151–161
24. D'Agostino RB Jr (2007) Propensity scores in cardiovascular research. *Circulation* 115:2340–2343
25. Kosanke J, Bergstrahl E. Gmatch. 2004 04/07/2004 16:32. <https://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros>. Accessed 4 Apr 2016
26. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 137:263–272
27. Podolecki T, Lenarczyk R, Kowalczyk J, Swierad M, Swiatkowski A, Jędrzejczyk E, Chodor P, Zielinska T, Kalarus Z (2015) Stroke and death prediction with CHA₂DS₂-VASc score after myocardial infarction in patients without atrial fibrillation. *J Cardiovasc Med (Hagerstown)* 16:497–502
28. Beyer-Westendorf J, Ehlken B, Evers T (2016) Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. *Europace* 18:1150–1157
29. Lin YC, Chien SC, Hsieh YC, Shih CM, Lin FY, Tsao NW, Chen CW, Kao YT, Chiang KH, Chen WT, Chien LN, Huang CY (2018) Effectiveness and safety of standard- and low-dose rivaroxaban in Asians with atrial fibrillation. *J Am Coll Cardiol* 72:477–485
30. Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Maya J, Husted S, Steg PG, Cornel JH, Storey RF, Stevens SR, Wallentin L, James SK (2014) Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. *Eur Heart J* 35:2083–2093
31. Polonski L, Gasior M, Gierlotka M, Osadnik T, Kalarus Z, Trusz-Gluza M, Zembala M, Wilczek K, Lekston A, Zdrojewski T, Tendera M, PL-ACS Registry Pilot Group (2011) A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: are non-ST myocardial infarctions associated with worse long-term prognoses? *Int J Cardiol* 152:70–77
32. Erne P, Radovanovic D, Seifert B, Bertel O, Urban P, AMIS Plus Investigators (2015) Outcome of patients admitted with acute coronary syndrome on palliative treatment: insights from the nationwide AMIS Plus Registry 1997–2014. *BMJ Open* 5:e006218
33. Asia-Pacific ACS Medical Management Working Group, Huo Y, Thompson P, Buddhari W, Ge J, Harding S, Ramanathan L, Reyes E, Santoso A, Tam LW, Vijayaraghavan G, Yeh HI (2015) Challenges and solutions in medically managed ACS in the Asia-Pacific region: Expert recommendations from the Asia-Pacific ACS Medical Management Working Group. *Int J Cardiol* 183:63–75
34. Ulvenstam A, Kajermo U, Modica A, Jernberg T, Söderström L, Moee T (2014) Incidence, trends, and predictors of ischemic stroke 1 year after an acute myocardial infarction. *Stroke* 45:3263–3268
35. Hornung M, Franke J, Gafoor S, Sievert H (2016) Cardioembolic stroke and postmyocardial infarction stroke. *Cardiol Clin* 34:207–214
36. Neumann FJ, Ott I, Gawaz M, Richardt G, Holzapfel H, Jochum M, Schömig A (1995) Cardiac release of cytokines and inflammatory responses in acute myocardial infarction. *Circulation* 92:748–755
37. Lindsberg PJ, Grau AJ (2003) Inflammation and infections as risk factors for ischemic stroke. *Stroke* 34:2518–2532
38. Austin PC (2014) The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 33:1242–1258

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