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ORIGINAL RESEARCH

Intracranial Bleeding After Percutaneous Coronary Intervention: Time-Dependent Incidence, Predictors, and Impact on Mortality

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BACKGROUND: Limited data are available on intracranial hemorrhage (ICH) in patients undergoing antithrombotic therapy after percutaneous coronary intervention (PCI).

METHODS AND RESULTS: Using the Korean National Health Insurance Service database, we identified 219 274 patients without prior ICH and who underwent a first PCI procedure between 2007 and 2016 and analyzed nontraumatic ICH and all-cause mortality. ICH after PCI occurred in 4171 patients during a median follow-up of 5.6 years (overall incidence rate: 3.32 cases per 1000 person-years). The incidence rate of ICH showed an early peak of 21.66 cases per 1000 person-years within the first 30 days, followed by a sharp decrease to 3.68 cases per 1000 person-years between 30 days and 1 year, and to <1 case per 1000 patient-years from the second year until 10 years after PCI. The 1-year mortality rate was 38.2% after ICH, with most deaths occurring within 30 days (n=999, mortality rate: 24.2%). No significant difference in mortality risk was observed between patients who had ICH within and after 1 year following PCI (adjusted hazard ratio, 1.04; 95% CI, 0.95–1.14; *P*=0.43). The predictors of post-PCI ICH were age ≥75 years, hypertension, atrial fibrillation, end-stage renal disease, history of stroke or transient ischemic attack, dementia, and use of vitamin K antagonists.

CONCLUSIONS: New ICH most frequently occurs in the early period after PCI and is associated with a high risk of early death, regardless of the occurrence time of ICH. Careful implementation of antithrombotic strategies is needed in patients at an increased risk for ICH, particularly in the peri-PCI period.

Key Words: intracranial hemorrhage ■ mortality ■ percutaneous coronary intervention

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Antithrombotic strategies and percutaneous coronary intervention (PCI) have continuously evolved together during the past 2 decades, and its application has been extended to high-risk patients.[1] However, the risk of thrombotic complications remains the major limitation of PCI with drug-eluting stents.[2] Although periprocedural anticoagulation and dual antiplatelet therapy with aspirin and a P_2Y_{12} receptor blocker after PCI lower the risk of stent- or non–stent-related ischemic events, they increase the bleeding rate.[3] Because major bleeding is associated with a substantial risk of death,[4–6] therapeutic strategies that mitigate the risks of bleeding without ischemic harm have been developed in various patient populations and clinical settings.[7–9]

Intracranial hemorrhage (ICH) is the most feared bleeding complication and has been evaluated as an essential safety end point in trials of antithrombotic therapy. ICH after PCI is reported to be relatively rare but may result in life-changing disabilities or even death.[10–12] Because ICH is difficult to manage once it occurs,

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Nonstandard Abbreviations and Acronyms

DOAC	direct oral anticoagulant
ICH	intracranial hemorrhage
NHIS	National Health Insurance Service
VKA	vitamin K antagonist

prevention is definitely the best approach. However, little is known about the true incidence and risk factors of ICH after PCI in the real-world setting, mainly because of the incompleteness of data because of the fatal nature of the event and the subsequent loss of follow-up in prospective registries. Furthermore, the available ICH data are mostly from studies focusing on selected clinical settings with a limited duration of follow-up.[13–15] A nationwide cohort database makes it possible to capture every ICH and death event after PCI in unselected real-world settings during a long-term follow-up period and would help shed light on these questions.

In the present study, we investigated the time-dependent incidence, predictors, and impact on mortality of ICH in a large population of patients who underwent antithrombotic therapy after contemporary PCI.

METHODS

Data Sources
The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was based on claim data from the National Health Insurance Service (NHIS) of South Korea. The Korean NHIS is a single, compulsory social insurance service that provides comprehensive health coverage for the entire Korean population. All healthcare providers are obligated to join the NHIS system on a fee-for-service basis. NHIS claims are reviewed by an independent quasigovernmental organization, which evaluates the medical expenses reported by healthcare providers to minimize the risk of redundant and unnecessary medical services. As a result, all NHIS claims are systematically classified and recorded in an independent computerized database. From this database, a complete follow-up for an individual is possible regardless of the region or hospital from which the medical service is provided. The database comprises a complete set of medical claims and health information, including demographic findings, diagnoses, prescriptions, medical devices, and procedure records. Individual diagnoses in the database are coded according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*). All prescribed medications were exclusively recorded with high accuracy and classified according to the chemical composition and dose of the drug. Specific information about the devices and procedures were identified using self-developed codes.

The study flow is presented in Figure S1. We included patients aged ≥18 years who had undergone PCI for the treatment of coronary artery disease between January 2007 and December 2016. The study period was set considering the date of widespread use of second-generation drug-eluting stents. Patients were excluded if the database indicated a history of previous coronary artery disease or a revascularization therapy within 12 months of the index day (washout period), to ensure that the study included only those who underwent a first PCI procedure. Patients who died on the day of PCI without ICH or those who had experienced any type of ICH before the index procedure were excluded to create a more homogeneous risk population. A total of 219 274 patients were included in the final study population. The study protocol was approved by the local institutional review board of Asan Medical Center, Seoul, Korea. Because the database consisted of anonymous and deidentified information, the requirement for informed consent was waived.

Comorbidities and Outcomes
Patients' demographic data, comorbid conditions, and medications were ascertained from the database. The clinical presentation at the index PCI was categorized into acute myocardial infarction or others, and comorbid conditions, including hypertension, diabetes

mellitus, dyslipidemia, atrial fibrillation or flutter, peripheral artery disease, end-stage renal disease requiring dialysis, history of congestive heart failure, and prior ischemic stroke or transient ischemic attack, were evaluated. The definitions of comorbidities are summarized in Table S1. The Charlson Comorbidity Index was calculated to measure the patients' comprehensive life expectancy.[16] A wide range of antithrombotic medications, such as aspirin, P_2Y_{12} inhibitors, vitamin K antagonists (VKAs), and direct oral anticoagulants (DOACs), were evaluated for the study purpose.

The end point of the study was the occurrence of nontraumatic ICH after the index PCI. The rationale for selecting ICH as the end point was that antithrombotic therapy is associated with ICH regardless of the subtype, and bleeding definitions or consensus on high bleeding risk for patients undergoing PCI include ICH as the component for major bleeding.[17,18] The *ICD-10* system classifies nontraumatic ICH into categories as follows: I60 for subarachnoid hemorrhage, I61 for intraparenchymal hemorrhage, I62.0 for subdural hemorrhage, I62.1 for epidural hemorrhage, and I62.9 for unspecified ICH. To further ensure the diagnostic accuracy and that the event is a new one, nontraumatic ICH was qualified as the records of both *ICD-10* codes and brain imaging scans, either magnetic resonance imaging or computed tomography, during the same hospitalization. To evaluate the association between medications and ICH occurrence, the last prescription of antiplatelets or anticoagulants before ICH were identified for all patients who reached the end point. All-cause death was determined using all inpatient and outpatient claim records that indicated death. The direct impact of ICH on mortality was assessed by examining the 30-day and 6-month mortality after the ICH event. The study population was followed from the index PCI until censoring by death or December 31, 2018, whichever came first. Thus, at least 2 years of clinical follow-up was ensured for all study patients.

Statistical Analysis

Statistical analysis included the entire data set without any missing values. Summary statistics for continuous variables are presented as mean±standard deviation and categorical variables as percentages. We compared the variables between patients with and without ICH using the Student t test or the χ^2 test for continuous and categorical variables, respectively. Rates of ICH and its subtypes were reported as cumulative incidence function as well as incidence rates. Cumulative incidence rates were computed by the product limit estimator, and incidence rates were calculated by the number of cases divided by 1000 person-years based on the Wilson method. Kaplan-Meier survival analysis

was developed to compare mortality between patients with and without ICH, and between patients who had ICH in the early period and those who had ICH in the late period after PCI, and were tested by the log-rank test. The time point distinguishing the early and late period was set to 1 year, considering that a significant de-escalation of the antithrombotic strategy is usual after 1-year following PCI.

To identify the predictors of ICH after PCI, we fit a multivariable Cox model using clinical and drug-related parameters of potential importance.[18] Candidate variables included age ≥75 years, sex, clinical presentation of acute myocardial infarction, hypertension, diabetes mellitus, prior heart failure, valvular heart disease, atrial fibrillation, liver cirrhosis, chronic lung disease, end-stage renal disease, peripheral arterial disease, history of ischemic stroke or transient ischemic attack, dementia, cancer, use of potent P_2Y_{12} inhibitors, use of VKAs, use of DOACs, and use of statins. Variables with a P value ≤ 0.05 in univariate analyses were included in the multivariable model. There was no relevant multicollinearity between variables assessed by the variance inflation factor values. The model included the main effect of the predictors, without any interaction term. The impact of ICH on mortality was examined using Cox's proportional hazard models, with ICH added as a time-dependent covariate with the abovementioned covariates. We verified that the predictors satisfied the proportionality assumptions. The P values were 2-sided, and $P<0.05$ was considered significant. Data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

The cohort comprised 219 274 patients who met the eligibility criteria during the study period. The overall baseline patient characteristics are presented in Table 1. The mean age of the patients was 65.0±11.5 years, 67.9% were men, and 35.3% were diagnosed with acute myocardial infarction. In regard to cardiovascular risk factors, 30.4% of the patients had diabetes mellitus, 69.4% were treated for hypertension, and 41.6% had dyslipidemia. Other comorbid conditions included atrial fibrillation in 4.1% of the patients, history of ischemic stroke in 10.3%, and end-stage renal disease requiring dialysis in 2.2%. Most of the study patients were treated with drug-eluting stents (92.3%). Overall, 93.3% of the patients were discharged with dual antiplatelet therapy, 11.7% of whom received potent P_2Y_{12} inhibitors including ticagrelor or prasugrel. Patients who experienced an ICH were generally older, were more likely to be women, and had a higher frequency of comorbidities than

Table 1. Characteristics of Patients With or Without ICH

	Total, N=219 274	No ICH, n=215 103	ICH, n=4171	*P* Value
Age, y	65.0±11.5	64.9±11.5	68.1±10.3	<0.001
Age ≥75 y	22.2	22.1	29.3	<0.001
Male sex	67.9	68.0	62.4	<0.001
Acute myocardial infarction	35.3	35.3	32.9	0.002
Comorbidities				
Hypertension	69.4	69.2	79.8	<0.001
Diabetes mellitus	30.4	30.3	36.4	<0001
Dyslipidemia	41.6	41.6	42.0	0.59
History of heart failure	13.5	13.5	17.0	<0.001
Valvular heart disease	1.4	1.4	2.3	<0.001
Atrial fibrillation	4.1	4.0	7.7	<0.001
Liver cirrhosis	0.7	0.7	1.0	0.07
Chronic lung disease	32.6	32.5	36.7	<0.001
Renal disease	5.1	5.0	10.1	<0.001
End-stage renal disease on dialysis	2.2	2.1	5.6	<0.001
Peripheral arterial disease	20.8	20.7	23.2	<0.001
History of ischemic stroke	10.3	10.1	17.2	<0.001
History of transient ischemic attack	3.1	3.1	5.2	<0.001
Dementia	4.3	4.3	6.3	<0.001
Cancer	5.8	5.8	6.3	0.19
Charlson Comorbidity Index	2.6±2.4	2.6±2.4	3.2±2.5	<0.001
Antiplatelet therapy at discharge				
Single antiplatelet therapy	5.9	5.9	6.4	0.23
Dual antiplatelet therapy	93.3	93.4	92.5	0.04
Use of potent P_2Y_{12} inhibitors*	11.7	11.8	6.5	<0.001
Anticoagulants at discharge				
Vitamin K antagonist	2.5	2.5	6.0	<0.001
Direct oral anticoagulants†	0.3	0.3	0.4	0.91
Statin	83.5	83.6	78.6	<0.001

Data are shown as mean±standard deviation or percentage. ICH indicates intracranial hemorrhage.

*Potent P_2Y_{12} inhibitors indicate ticagrelor or prasugrel.

†Direct oral anticoagulants indicate dabigatran, rivaroxaban, apixaban, or edoxaban.

those without ICH. At discharge, patients in the ICH group were more likely to receive a VKA than those in the non-ICH group.

Incidence of ICH

During a median of 5.6 years (interquartile range, 3.2–8.3 years) of follow-up after PCI, a total of 4171 patients were newly diagnosed with ICH (overall incidence rate: 3.32 cases per 1000 person-years), with most cases being intraparenchymal (n=2556), followed by subdural hemorrhage (n=872). The cumulative incidence of ICH was 0.54% at 1 year after PCI and showed a relatively steady annual increase of 0.25% to 0.30% thereafter (Figure 1). Of note, among 1143 new ICH events at 1 year, one-fourth (n=271) occurred within 3 days and one-third (n=383) within 30 days after PCI. Accordingly, the incidence rate of ICH over time showed an early

peak of 21.66 cases per 1000 person-years within the first 30 days after PCI, followed by a sharp decrease to 3.68 cases per 1000 person-years between 30 days and 1 year, and to 1.52 cases per 1000 person-years between 1 and 2 years. Thereafter, the annual incidence rate was <1 case per 1000 person-years and showed a steady decrease, albeit to a small degree, up to 10 years (Table 2). The incidence rate trend over time was similar among different subtypes of ICH (Table S2).

Correlates of ICH

The results of the regression analysis to determine the independent predictors of ICH after PCI are shown in Table 3. Ten independent predictors were identified: age ≥75 years, hypertension, diabetes mellitus, atrial fibrillation, chronic lung disease, end-stage renal disease, history of stroke or transient ischemic attack,
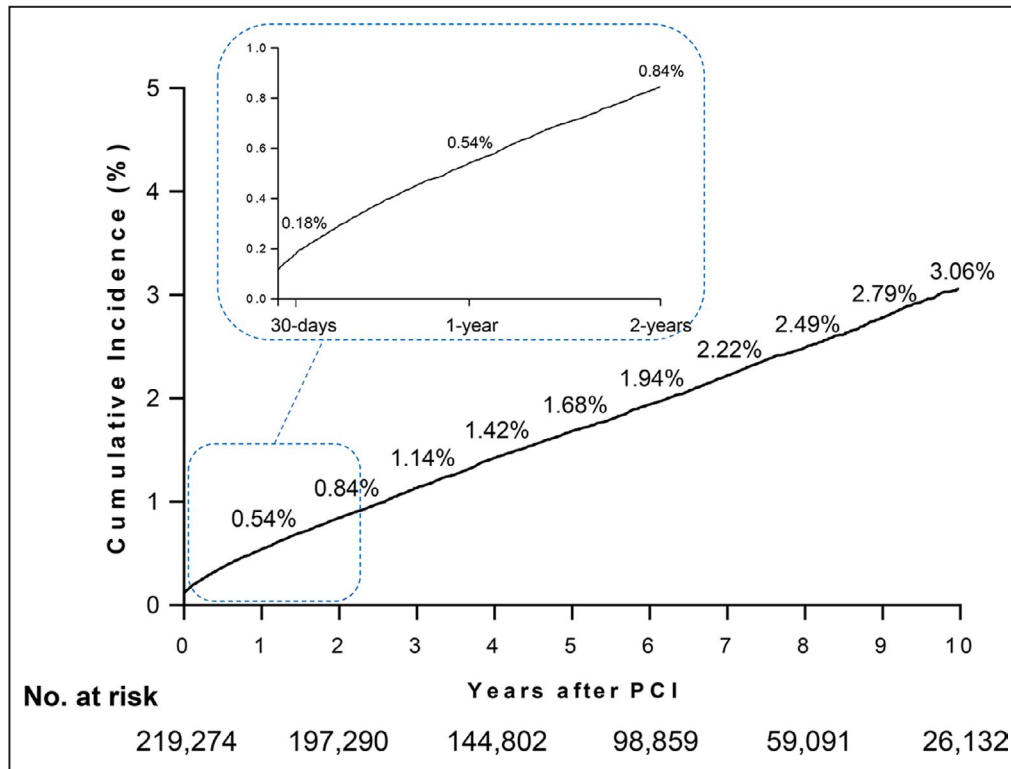
Figure 1.   Cumulative incidence of intracranial hemorrhage.
PCI indicates percutaneous coronary intervention.

dementia, use of a VKA, and statin treatment. The presence of end-stage renal disease was among the strongest predictors of ICH (hazard ratio [HR], 3.53; 95% CI, 3.08–4.05). Two drug-related parameters were identified: the use of a VKA was associated with

a 2-fold increase in the risk of ICH (HR, 2.12; 95% CI, 1.84–2.44), whereas statin treatment was associated with a 14% decrease in this risk (HR, 0.86; 95% CI, 0.80–0.93).

In terms of the last prescription of antithrombotics before the ICH event, 91.0% of 4171 patients were prescribed at least 1 drug before the event. In these patients, a combination of aspirin and clopidogrel (n=1773, 42.5%) was the most frequently prescribed antithrombotic therapy (Table S3). Of note, a substantial increase in the number of patients with ICH was observed when a VKA was combined with antiplatelet agents (VKA alone: 30 patients, VKA with antiplatelet agents: 321 patients).

Impact on Mortality

A total of 12 553 patients died during the follow-up (5-year mortality rate: 17.2%).

In the overall population, the mortality rate was 7.0% at 1 year after PCI and showed an annual increase of 2.5% to 2.7% thereafter (Figure 2A). Among them, patients with ICH had a significantly higher rate of mortality than those without (5-year incidence: 34.6% versus 16.8%, log-rank $P<0.001$; Figure 2B). The cumulative incidence curve for mortality, beginning from the time of the index ICH event in the ICH population, is shown in Figure 2C. Of note, the 1-year mortality rate was

Table 2.   Incidence Rates of ICH Over Time

Time After Index PCI	No. at Risk	No. of ICH Cases	Incidence Rate[†]
Overall	219 274	4171	3.32 (3.22–3.42)
0–30 d	219 274	380	21.66 (19.59–23.96)
30 d–1 y	211 903	763	3.68 (3.43–3.95)
1–2 y	203 339	612	1.52 (1.40–1.64)
2–3 y	197 270	540	0.92 (0.84–1.00)
3–4 y	169 519	454	0.67 (0.61–0.74)
4–5 y	144 802	348	0.48 (0.43–0.54)
5–6 y	120 717	290	0.40 (0.36–0.45)
6–7 y	98 910	250	0.36 (0.32–0.41)
7–8 y	78 235	191	0.31 (0.27–0.35)
8–9 y	59 130	151	0.28 (0.24–0.33)
9–10 y	41 735	99	0.24 (0.20–0.29)

ICH indicates intracranial hemorrhage; and PCI, percutaneous coronary intervention.

*Reported as cases per 1000 person-years (95% CI).

Table 3. Predictors of Intracranial Hemorrhage After PCI

Variables	Univariate	P Value	Multivariate	P Value
Age ≥75 y	2.00 (1.87–2.14)	<0.001	1.73 (1.61–1.86)	<0.001
Male sex	0.77 (0.72–0.82)	<0.001	0.96 (0.90–1.02)	0.19
Acute myocardial infarction*	1.01 (0.95–1.08)	0.67	NA	
Hypertension	1.78 (1.65–1.92)	<0.001	1.35 (1.25–1.47)	<0.001
Diabetes mellitus	1.42 (1.34–1.52)	<0.001	1.20 (1.12–1.28)	<0.001
History of heart failure	1.54 (1.42–1.67)	<0.001	1.04 (0.95–1.13)	0.41
Valvular heart disease	1.80 (1.47–2.21)	<0.001	1.18 (0.96–1.46)	0.12
Atrial fibrillation	2.30 (2.06–2.58)	<0.001	1.41 (1.24–1.60)	0.001
Liver cirrhosis	1.55 (1.14–2.11)	0.005	1.30 (0.96–1.77)	0.09
Chronic lung disease	1.31 (1.23–1.39)	<0.001	1.10 (1.03–1.17)	0.004
End-stage renal disease on dialysis	4.14 (3.63–4.73)	<0.001	3.53 (3.08–4.05)	<0.001
Peripheral arterial disease	1.24 (1.15–1.33)	<0.001	0.98 (0.91–1.06)	0.68
History of ischemic stroke or transient ischemic attack	1.97 (1.83–2.13)	<0.001	1.51 (1.40–1.64)	<0.001
Dementia	2.17 (1.91–2.46)	<0.001	1.32 (1.16–1.51)	<0.001
Cancer	1.25 (1.11–1.42)	<0.001	1.10 (0.97–1.24)	0.16
Use of potent P_2Y_{12} inhibitors	0.86 (0.76–0.97)	0.02	1.05 (0.92–1.19)	0.47
Use of vitamin K antagonist	2.89 (2.55–3.28)	<0.001	2.12 (1.84–2.44)	<0.001
Use of direct oral anticoagulants	2.21 (1.33–3.67)	0.002	1.21 (0.73–2.02)	0.46
Statin	0.80 (0.74–0.86)	<0.001	0.86 (0.80–0.93)	<0.001

Values are hazard ratios (95% CI). NA indicates not applicable.

*Hazard ratios are for patients with clinical presentation of acute myocardial infarction compared with those with angina.

38.2% after ICH, with most deaths occurring within 30 days (n=999, mortality rate: 24.2%). Differential mortality rate was identified according to the subtype of ICH in that the 30-day mortality rate was lower for subdural hemorrhage (17.3%) compared with intraparenchymal (27.4%) or subarachnoid hemorrhage (26.8%). The median survival time for this population was 3.5 years. Considering the usual practice of de-escalating the antithrombotic strategy over time after PCI, mortality was compared between patients who had ICH early after PCI and those who had ICH at the late period after PCI. The cumulative incidence of mortality was significantly higher in the early ICH group (≤1 year after PCI) than in the late ICH group (>1 year after PCI) (log-rank P=0.001, Figure S2). However, the mortality risk difference was no longer significant after adjusting for the patients' baseline characteristics (adjusted HR, 1.04; 95% CI, 0.95–1.14, P=0.43). In the overall population, ICH was significantly associated with an increased risk of mortality (adjusted HR, 5.24; 95% CI, 5.02–5.78, P<0.001).

DISCUSSION

This study provides the largest and most comprehensive assessment to date about the incidence, risk factors, and mortality impact of spontaneous ICH in an unbiased population of patients who underwent a first PCI procedure. We observed that new ICH most frequently occurred in the early period after PCI, with an incidence rate of 21.66 cases per 1000 person-years within the first 30 days, whereas it occurred at a relatively steady and low frequency at the late post-PCI period. ICH was associated with a high risk of early death, regardless of the occurrence time after PCI. Clinical risk factors, such as age ≥75 years, hypertension, atrial fibrillation, end-stage renal disease, and history of stroke or transient ischemic attack, were associated with an increased risk of ICH. Taken together, these results highlight the need for a careful implementation of antithrombotic strategies, particularly in the peri-PCI period in patients at an increased risk for ICH.

Antiplatelet therapy is essential in the management and prevention of thrombotic conditions during and after PCI. The increasing numbers of patients with a coexisting thrombotic condition in the heart or elsewhere and those requiring more complex PCI warrant the use of a combination regimen of antiplatelet and anticoagulant agents or a more intensified antiplatelet strategy. However, bleeding induced by the use of these drugs remains a major concern after PCI and has been recognized to be associated with a substantial risk of death.[4–6] Although ICH has been identified as the most severe form of bleeding in every bleeding definition developed for trials,[17] it has been reported to be rare and thus has often been overlooked even in
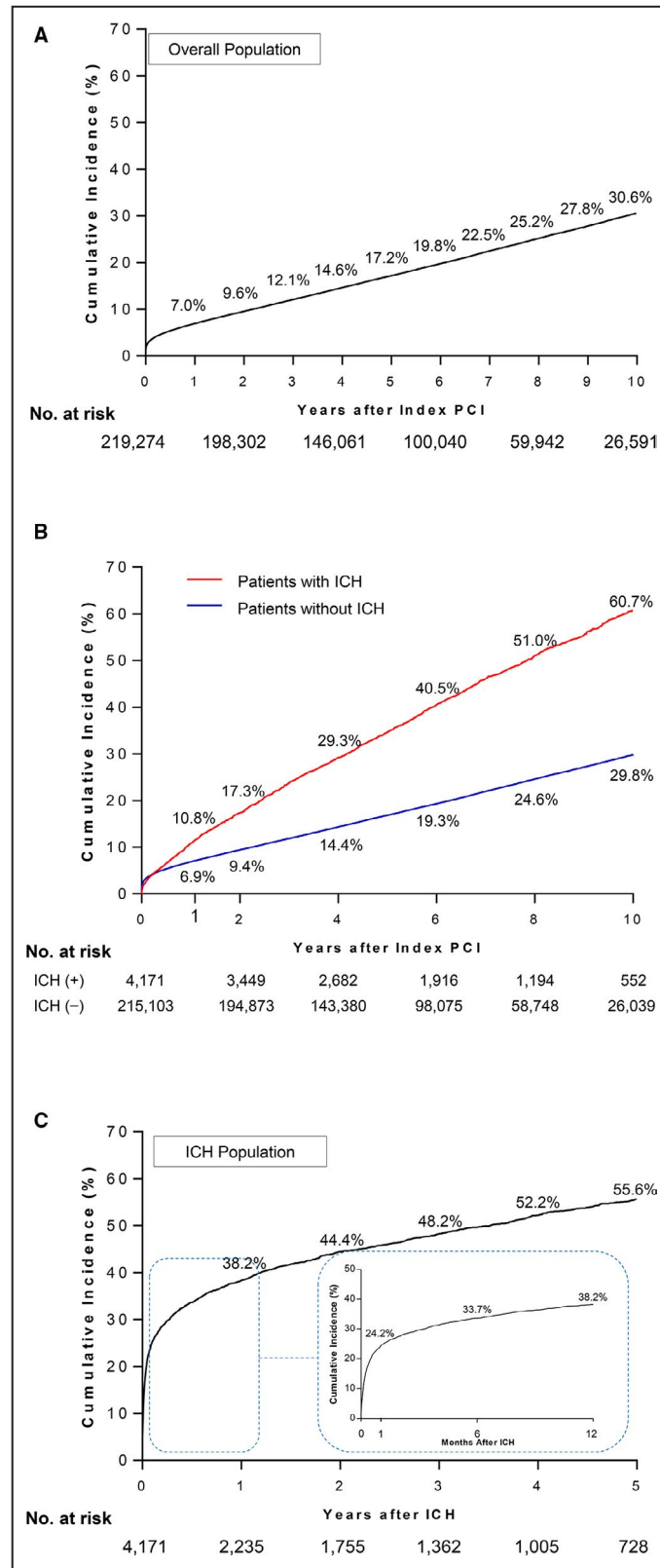
Figure 2. Cumulative incidence of mortality.
Cumulative incidence curves for mortality in the overall population (**A** and **B**) and in the ICH population (**C**). Note that (**C**) shows the cumulative incidence curve from the index ICH event. ICH indicates intracranial hemorrhage; and PCI, percutaneous coronary intervention.

representative patients that possess this risk. Accurate knowledge about PCI-related ICH would help physicians determine a balanced antithrombotic strategy. Limited studies have evaluated ICH in the era of PCI. From a multinational registry, Raposeiras-Roubín et al. reported a 0.27% 1-year rate of ICH among 11 136 patients who underwent PCI for an acute coronary syndrome. A Swedish study detected 590 cases of ICH within 1 year (0.35%) among 187 386 patients who were discharged after an acute myocardial infarction. Pooled patient-level data (n=37 815) from 4 antithrombotic therapy trials focusing on acute coronary syndrome patients reported a 0.4% rate of ICH during a median follow-up of 332 days. Advanced age and prior stroke were common predictors of ICH of the above studies. Although informative, these reports have been limited by the small number of ICH cases, selection of a population with acute coronary syndrome, and short follow-up durations, making it difficult to generalize the results to daily clinical practice.[13–15]

Our database reflects a national real-world experience that includes high-risk patients who are often excluded from randomized controlled trials. Accordingly, the incidence of ICH in our study was somewhat higher than that captured as a safety end point in drug trials (1-year rate: 0.2%–0.4%, 3-year rate: 0.5%–0.7%).[10–12,19–21] In addition to the information on the incidence at a particular time point, our data, for the first time, showed a dramatic time-dependent change in the incidence rate of ICH in an unselected population undergoing PCI. ICH, regardless of its subtype, most likely occurred immediately after the PCI, and, accordingly, the 30-day incidence rate of ICH overwhelmed the incidence rate of other post-PCI periods. This observation suggests that patients at risk are more vulnerable to ICH because of the first exposure to antiplatelet agents and the use of periprocedural anticoagulation. Thereafter, the number of new ICHs steeply decreased to <1 case per 1000 patient-years from the second year after PCI. Given that the occurrence of ICH, like other bleeding complications, is likely affected by the dose, potency, and number of associated drugs used, our study result implies that an antithrombotic strategy should be carefully applied particularly at the critical period around the index PCI in patients with a high risk for ICH. The consequence of ICH was serious. Approximately one-fourth of the patients died within 30 days, and 50% died 3.5 years after the ICH event. The mortality risk was high irrespective of the occurrence time of ICH after PCI. Considering the 1-year mortality rate of 7.0% in the overall population, the high mortality early after ICH is likely caused by the direct impact of ICH. Furthermore, because the cumulative mortality curve continued to diverge up to 10 years after PCI between patients with and without ICH, it is reasonable to speculate that the legacy effect of ICH on mortality remains for a considerable time among survivors. Thus, every effort to prevent ICH would be imperative.

The predictors of ICH identified in our analysis were generally consistent with the components of the Academic Research Consortium–defined criteria for high bleeding risk in patients undergoing PCI.[18] Because there is a progressively increased risk of both ischemia and bleeding as the number of risk factors increases, a decision to commence PCI, which is a procedure that mandates the use of antithrombotic drugs, poses a conundrum in patients with multiple risk factors. Yet, except in patients with unstable coronary disease, the threshold for undergoing PCI should remain high in stable patients who are deemed to be at a high risk for ICH, based on the negative results of a recent large-scale trial evaluating the role of PCI in patients with stable coronary disease and moderate to severe ischemia.[22,23] The association between dementia and ICH might imply the shared pathogenesis of cerebral amyloid angiopathy.[24] Cerebral amyloid angiopathy is an important cause of ICH in older patients and has been linked to cognitive impairment and dementia.[25] We also detected a differential ICH risk of anticoagulants, in that the use of a VKA was associated with a 2-fold increased risk of ICH, whereas the use of DOACs was not. These findings are compatible with previous studies demonstrating a clear advantage of DOACs over VKAs in terms of the lower risk for ICH in patients with atrial fibrillation.[26] In light of this finding, the role of DOACs or nonpharmacological treatment such as left atrial appendage occlusion as an ICH-preventive strategy should be defined in PCI-requiring high-risk patients with end-stage renal disease and atrial fibrillation.[27] Despite the proven benefits of statins, the data from the SPARCL (Stroke Prevention by Aggressive Reduction of Cholesterol Levels) trial showed a trend toward an increased rate of ICH with statin therapy.[28] However, a post hoc analysis revealed that the highest risk was linked to previous hemorrhagic stroke, and there was no relationship between ICH and low-density lipoprotein cholesterol levels.[29,30] In the present study, we found that statin therapy was associated with a lower risk of ICH. Although patients with previous ICH were excluded, our finding offers reassurance about the safety of statins in ICH.

Study Limitations

First, the observational design based on an administrative database is associated with inherent bias. Detailed results of laboratory tests, such as hemoglobin level, platelet count, or estimated glomerular filtration rate, were not available, precluding a more sophisticated classification of potential predictors of ICH. Second, because patients who underwent PCI were enrolled, those who were scheduled for PCI but failed to undergo the procedure because of ICH were not captured in our study. Thus,

the incidence rate of ICH associated with the overall PCI process may have been underestimated to some degree. Third, drugs were analyzed according to prescriptions but not actual adherence. The time in therapeutic range value of patients taking warfarin was unavailable. Potent P_2Y_{12} inhibitors and DOACs became available late in the study period, thus the prescription patterns of drugs may have changed considerably over time. Fourth, patients with a history of either spontaneous or traumatic ICH were excluded by the study design, which may have contributed to the underestimation of the ICH incidence associated with PCI. Furthermore, despite the lack of prospective data on antithrombotic therapy and bleeding risk in patients with prior ICH, it would be reasonable to consider these patients to have a high risk for recurrent ICH when considering PCI. Finally, this study included only the Asian population, potentially limiting the applicability of our findings to other racial groups with different patient and procedural characteristics.

CONCLUSIONS

Our study addresses an unmet need by providing real-world evidence for the incidence, risk factors, and impact on mortality of ICH in patients undergoing PCI. ICH most frequently occurs in the early period after PCI and is associated with a high risk of death, regardless of the occurrence time. Further effort to stratify patients with a high risk for ICH and to establish a more balanced antithrombotic strategy would be necessary.

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Supplemental Material

Table S1. Definition of covariates and study outcomes.

Diagnosis/Procedures/Drugs	Definition
Coronary artery disease	I20–I25
Revascularization procedure	
Coronary artery bypass grafting	O1640–O1642, O1647–O1649, OA640–OA642, OA647–OA649
Percutaneous coronary intervention	M6551–M6554, M6561–M6567, M6571–M6572
Intracranial hemorrhage	I60–I62 with brain imaging (CT or MRI) during the same hospitalization
Acute myocardial infarction	I21–I22
Hypertension	I10–I13, I15
Diabetes mellitus	E11–E14 and a minimum of one prescription of anti-diabetic drugs (sulfonylureas, metformin, α-glucosidase inhibitors, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitors, glucagon like peptide-1 receptor agonist, and insulin)
Dyslipidemia	E78.0–E78.5
Heart failure	I43, I50, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9
Valvular heart disease	I05–I09, I34–I39
Atrial fibrillation	I48
Liver cirrhosis	K70.3, K71.7, K74, K76.1,
Chronic lung disease	J40–J47, J60–J67, J68.4, J70.1, J70.3
Renal disease	I13.1, N03, N05, N10–N19, Z49, Z94.0, Z99.2
End-stage renal disease on dialysis	N18.5, Z49 and RID code V001, V003, V005
Peripheral arterial disease	I70-I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
History of ischemic stroke	I63, I64
History of transient ischemic attack	G45
Cancer	C00–C97 and RID code V027, V193, V194

CT=computed tomography, MRI=magnetic resonance imaging, RID=Rare Intractable Disease program

Table S2. Incidence Rates of ICH Subtypes over Time.

Time after index PCI	No. at risk	No. of ICH cases	Incidence rate[*]
Intraparenchymal hemorrhage			
Overall	219,274	2,556	2.03 (1.96 – 2.11)
0–30 days	219,274	259	14.77 (13.07 – 16.68)
30 days to 1 year	211,903	464	2.24 (2.04 – 2.45)
1–2 years	203,339	376	0.93 (0.84 – 1.03)
2–3 years	197,270	334	0.57 (0.51 – 0.63)
3–4 years	169,519	287	0.43 (0.38 – 0.48)
4–5 years	144,802	202	0.28 (0.24 – 0.32)
5–6 years	120,717	161	0.22 (0.19 – 0.26)
6–7 years	98,910	147	0.21 (0.18 – 0.25)
7–8 years	78,235	111	0.18 (0.15 – 0.21)
8–9 years	59,130	91	0.17 (0.14 – 0.21)
9–10 years	41,735	65	0.16 (0.12 – 0.2)
Subarachnoid hemorrhage			
Overall	219,274	806	0.64 (0.60 – 0.69)
0–30 days	219,274	63	3.59 (2.81 – 4.60)
30 days to 1 year	211,903	128	0.62 (0.52 – 0.73)
1–2 years	203,339	124	0.31 (0.26 – 0.37)
2–3 years	197,270	105	0.18 (0.15 – 0.22)
3–4 years	169,519	96	0.14 (0.12 – 0.17)
4–5 years	144,802	69	0.1 (0.08 – 0.12)
5–6 years	120,717	63	0.09 (0.07 – 0.11)
6–7 years	98,910	54	0.08 (0.06 – 0.1)
7–8 years	78,235	46	0.07 (0.06 – 0.1)
8–9 years	59,130	25	0.05 (0.03 – 0.07)
9–10 years	41,735	17	0.04 (0.03 – 0.07)
Other ICH			
Overall	219,274	1,160	0.92 (0.87 – 0.98)
0–30 days	219,274	80	4.56 (3.66 – 5.68)
30 days to 1 year	211,903	249	1.20 (1.06 – 1.36)
1–2 years	203,339	167	0.41 (0.36 – 0.48)
2–3 years	197,270	151	0.26 (0.22 – 0.3)
3–4 years	169,519	113	0.17 (0.14 – 0.2)
4–5 years	144,802	102	0.14 (0.12 – 0.17)
5–6 years	120,717	85	0.12 (0.1 – 0.15)
6–7 years	98,910	67	0.1 (0.08 – 0.12)
7–8 years	78,235	49	0.08 (0.06 – 0.1)
8–9 years	59,130	49	0.09 (0.07 – 0.12)
9–10 years	41,735	24	0.06 (0.04 – 0.09)

ICH=intracranial hemorrhage; PCI=percutaneous coronary intervention
[*]Reported as cases per 1000 person-years (95% confidence interval)

Table S3. Antithrombotics prescribed prior to the ICH event.

Antithrombotics92	Number (%)
None	391 (9.4)
Aspirin only	959 (23.0)
Clopidogrel only	512 (12.3)
Potent P_2Y_{12} inhibitor[*] only	6 (0.1)
Aspirin + clopidogrel	1,773 (42.5)
Aspirin + Potent P_2Y_{12} inhibitor[*]	98 (2.3)
Vitamin K antagonist only	30 (0.7)
Vitamin K antagonist + any antiplatelet agent	321 (7.7)
Direct oral anticoagulant[*] only	25 (0.6)
Direct oral anticoagulant[*] + any antiplatelet agent	56 (1.3)
Total	4,171 (100)

[*]Potent P_2Y_{12} inhibitor indicate ticagrelor or prasugrel, and direct oral anticoagulants indicate dabigatran, rivaroxaban, apixaban, or edoxaban.
ICH = intracranial hemorrhage

Figure S1. Flow Chart of the Study Population.
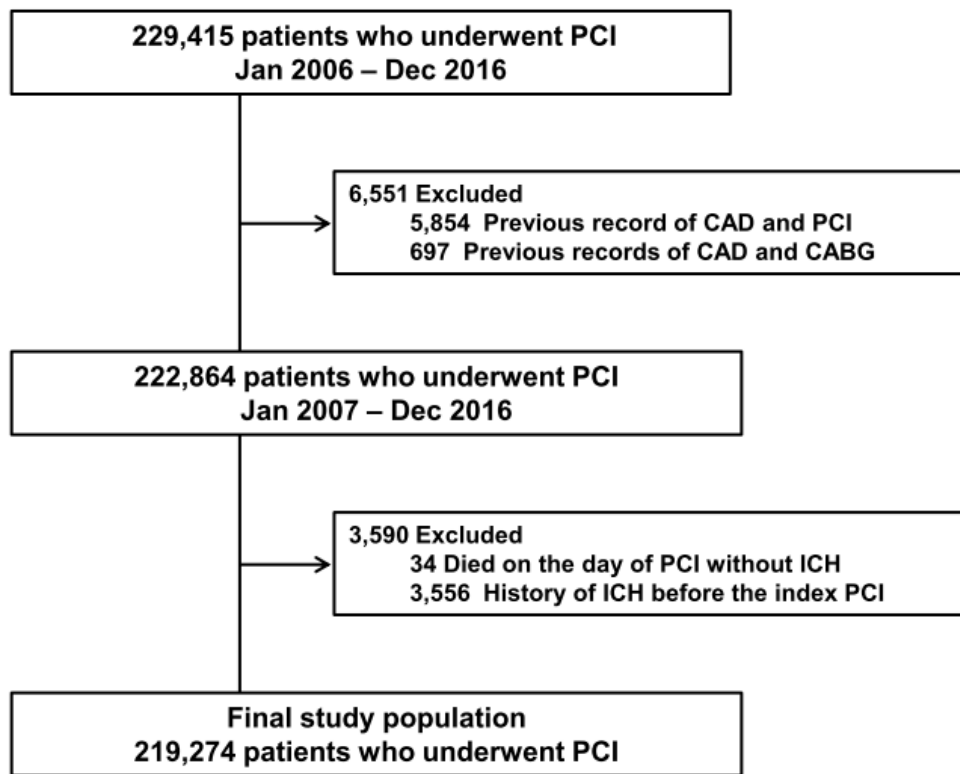
CABG=coronary artery bypass grafting; CAD=coronary artery disease; ICH=intracranial hemorrhage; PCI=percutaneous coronary intervention.

Figure S2. Cumulative Incidence of Mortality According to the ICH occurring ≤1 year and >1 year after PCI.