Percutaneous Coronary Intervention as a Trigger for Stroke

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Percutaneous coronary intervention (PCI) is a plausible triggering factor for stroke, yet the magnitude of this excess risk remains unclear. This study aimed to quantify the transient change in risk of stroke for up to 12 weeks after PCI. We applied the case-crossover method, using data from the Norwegian Patient Register on all hospitalizations in Norway in the period of 2008 to 2014. The relative risk (RR) of ischemic stroke was highest during the first 2 days after PCI (RR 17.5, 95% confidence interval [CI] 4.2 to 72.8) and decreased gradually during the following weeks. The corresponding RR was 2.0 (95% CI 1.2 to 3.3) 4 to 8 weeks after PCI. The RR for women was more than twice as high as for men during the first 4 postprocedural weeks, RR 10.5 (95% CI 3.8 to 29.3) and 4.4 (95% CI 2.7 to 7.2), respectively. Our results were compatible with an increased RR of hemorrhagic stroke 4 to 8 weeks after PCI, but the events were few and the estimates were very imprecise, RR 3.0 (95% CI 0.8 to 11.1). The present study offers new knowledge about PCI as a trigger for stroke. Our estimates indicated a substantially increased risk of ischemic stroke during the first 2 days after PCI. The RR then decreased gradually but stayed elevated for 8 weeks. Increased awareness of this vulnerable period after PCI in clinicians and patients could contribute to earlier detection and treatment for patients suffering a postprocedural stroke. **(Am J Cardiol 2017;119:35−39)**

The use of mechanical devices during PCI may dislodge atherosclerotic debris from the aorta, which subsequently may lead to a cerebral embolization and an ischemic stroke.[1,2] Transient changes in blood pressure, new-onset arrhythmias, and the use of anticoagulant and antiplatelet drugs during PCI may also trigger a stroke. The incidence of stroke shortly after PCI is reported to range from 0.1% to 0.4%.[3−10] The RR of stroke in association with PCI has, to our knowledge, not been studied before. In the present study, we applied the case-crossover design[11,12] to quantify the RR of stroke after PCI and to study the duration of the excess risk and potential differences in gender and age strata. The case-crossover design is particularly useful for studying the impact of transient risk factors on outcomes of sudden onset, and the design inherently controls for time-invariant unmeasured confounders, such as genetic factors, socioeconomic status, and many lifestyle factors.

Methods

The case-crossover design was developed by Malcom Maclure[11] and has become a widely used method for studying triggers for acute cardiovascular events.[13,14] The traditional case-control method relies on between-person comparisons, comparing exposures between cases and controls. The case-crossover method, however, relies on within-person comparisons. Only cases are included in the study, comparing exposures between one or several hazard periods and corresponding control periods for the same subjects.

The Norwegian Patient Register (NPR) is a national, administrative register containing person-identifiable information on all hospitalizations and outpatient visits in Norway. From the NPR, we identified patients with one or several PCI procedures (NCSP codes FNG02 or FNG05) and at least one main diagnosis of stroke (*International Classification of Diseases, Tenth Revision*, codes I61, I63, or I64) during the period of 2008 to 2014. A recent validation study concluded that main diagnoses of stroke in the NPR are adequately complete and correct to be useful for epidemiologic studies, whereas secondary diagnoses of stroke were hampered with a large proportion of false-positive cases.[15] In the case-crossover design, only information from discordant pairs contributes in the final analyses; thus, patients without PCI were not included. For the stroke hospitalizations, we excluded elective hospitalizations and recurrent cerebrovascular events occurring ≤28 days after the previous event.

We sought to investigate the risk of stroke for up to 12 weeks after the exposure to PCI. To quantify the transient changes in risk, we defined several nonoverlapping hazard

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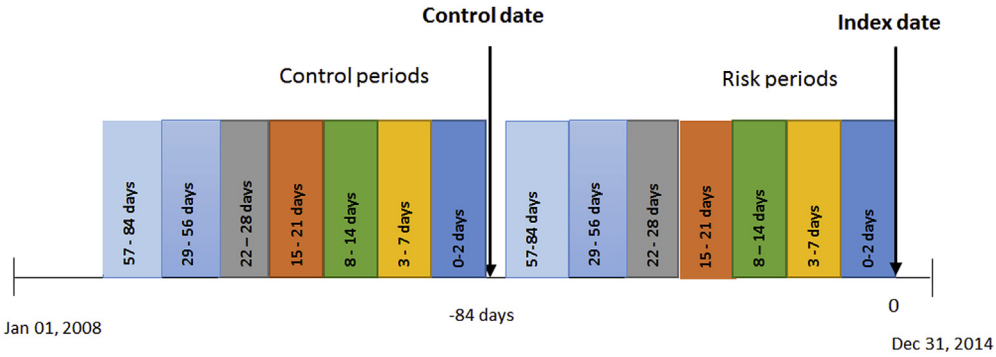

Figure 1. Case-crossover analysis, definition of hazard and control periods. Index date is the date of stroke onset. Exposure is PCI. Number of exposures during the hazard period 0 to 2 days before the index day is compared with number of exposures during the control period 0 to 2 days before the control date, etc.

periods. Counting backward from the time of stroke onset (the index date), the following hazard periods were defined: 0 to 2, 3 to 7, 8 to 14, 15 to 21, 22 to 28, 29 to 56, and 57 to 84 days. A control date was set 12 weeks (84 days) before the index date, and control periods were defined with equivalent length to the hazard periods (Figure 1). Each patient could have >1 stroke and/or >1 PCI during the study period; thus, the analysis unit was stroke events. To assess effect modification, we conducted age- and gender-specific analyses. These analyses had less statistical power and were, therefore, performed using the cumulative 0- to 28-day hazard period in addition to 29 to 56 and 57 to 84 days. Age strata were defined as <80 and ≥80 years. When analyzing hemorrhagic stroke separately, we used the same 3 hazard periods as the gender and age strata because of few events. To estimate the RR of stroke, we compared exposure to PCI in the hazard versus the control periods and calculated odds ratios with 95% confidence intervals using conditional logistic regression. We used date of hospital admission as a proxy for stroke onset and date of PCI procedure. The NPR data lacked time information on inhospital events. Thus, when the PCI procedure and the stroke occurred during the same hospitalization, we assumed that the PCI occurred first, based on the assumption that it is very unlikely that PCI would be performed immediately after a stroke. In our material, there were 15 events where PCI and stroke occurred during the same hospitalization. In these situations, time from PCI to stroke was assumed to be short (0 to 2 days).

All statistical analyses were performed using the Stata software package, version 14.0. The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway.

Results

Based on data on all hospitalizations in Norway in the period 2008 to 2014, 1,625 unique patients generating 1,811 stroke hospitalizations and 1,783 PCI procedures met our inclusion criteria. Mean age at time of stroke onset was 72.7 years (SD ± 10.5), and 70.6% of the study population were men (Table 1). The male predominance is in conformity with other large studies on PCI populations.[16,17]

We found that the risk of suffering an ischemic stroke within 2 days after PCI was >17 times higher than in the control period 12 weeks earlier (RR 17.5, 95% confidence interval 4.2 to 72.8; Figure 2). The RR declined during the following days and weeks and the estimated RR ranged from 3.5 to 5.3 during days 3 to 28 after PCI. The RR stayed elevated also 29 to 56 days after PCI, but we did not observe any considerable risk increase thereafter.

During the period 0 to 28 days after PCI, the RR of ischemic stroke for women was more than twice as high as

Table 1
Description of the sample

	Total	Women	Men
Unique patients	1625	476	1149
Stroke hospitalizations	1811	537	1274
Ischemic stroke	1600	479	1121
Haemorrhagic stroke	211	58	153
PCI hospitalizations	1783	518	1265
Male sex	70.6%		
Age at time of stroke, years, mean (SD) *	72.7 (±10.5)	75.6 (±10.7)	71.5 (±10.2)

* SD = Standard deviation.
Data from the Norwegian Patient Register 2008-2014.

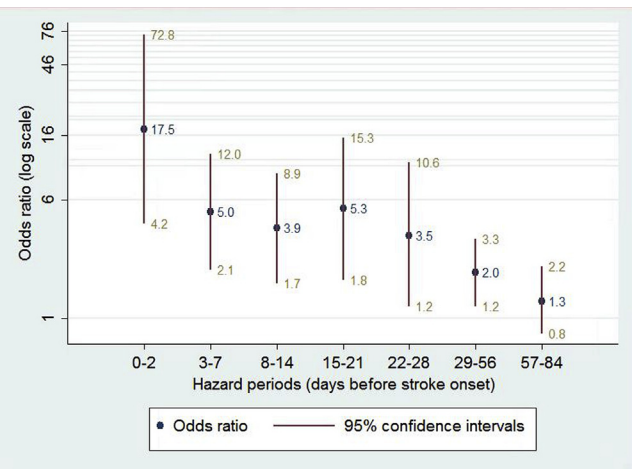

Figure 2. RR of ischemic stroke after PCI. Analyses based on the case-crossover method. Odds ratios and 95% confidence intervals for exposure to PCI in the hazard periods compared with control periods of equal length 12 weeks earlier. Data from the NPR 2008 to 2014 (see Appendix 1 for number of events).

Table 2
Relative risk of ischemic stroke after PCI. Results for women and men, and for all patients below or over the age of 80. Case-crossover analyses. Odds ratios (OR) and 95% confidence intervals (CI) for exposure to PCI in the hazard periods compared to control periods of equal length 12 weeks earlier

Hazard periods	Women, all ages			Men, all ages			All patients <80 years			All patients ≥80 years		
	N^a	N^b	OR (95% CI)	N^a	N^b	OR (95% CI)	N^a	N^b	OR (95% CI)	N^a	N^b	OR (95% CI)
0-28 days	42	4	10.5 (3.8-29.3)	83	19	4.4 (2.7-7.2)	90	14	6.4 (3.7-11.3)	35	9	3.9 (1.9-8.1)
29-56 days	14	6	2.3 (0.9-6.1)	27	15	1.8 (1.0-3.4)	27	16	1.7 (0.9-3.1)	14	5	2.8 (1.0-7.8)
57-84 days	9	7	1.3 (0.5-3.8)	21	16	1.3 (0.7-2.5)	22	17	1.3 (0.7-2.4)	8	6	1.4 (0.4-4.4)

N^a = Number of exposures in the hazard period; N^b = Number of exposures in the control period.
Data from the Norwegian Patient Register 2008-2014.

for men (Table 2). However, the gender difference was not sustained in the periods extending beyond 4 weeks after the procedure. Stratifying for age, we found that patients <80 had a sixfold increased risk for having an ischemic stroke 0 to 28 days after PCI compared with the control period 12 weeks earlier, whereas patients who were ≥80 years had approximately a fourfold increased risk in the same period. Our results were compatible with a substantial increase in RR of hemorrhagic stroke during weeks 4 to 8 after PCI, but the events were few and the estimates were very imprecise (Table 3).

We performed sensitivity analyses based on different control periods (6 and 12 months before the stroke), but these did not affect the results notably (results not shown).

Table 3
Comparison of relative risk of hemorrhagic versus ischemic stroke after PCI. Case-crossover analyses. Odds ratios (OR) and 95% confidence intervals (CI) for exposure to PCI in the hazard periods compared to control periods of equal length 12 weeks earlier

Hazard periods	Hemorrhagic stroke			Ischemic stroke		
	N^a	N^b	OR (95% CI)	N^a	N^b	OR (95% CI)
0-28 days	9	7	1.3 (0.5-3.5)	125	23	5.4 (3.5-8.5)
29-56 days	9	3	3.0 (0.8-11.1)	41	21	2.0 (1.2-3.3)
57-84 days	6	7	0.9 (0.3-2.6)	30	23	1.3 (0.8-2.3)

N^a = Number of exposures in the hazard period; N^b = Number of exposures in the control period.
Data from the Norwegian Patient Register 2008-2014.

Discussion

We found a considerable 17-fold transient increase in the risk of stroke in relation to PCI. Whereas previous studies reported the incidence of stroke after PCI, this is the first study, to our knowledge, to quantify the magnitude of the excess risk. Worldwide, several millions of patients are treated each year with PCI during hospitalizations for acute coronary syndrome or stable angina pectoris. However, dislodgement of atherosclerotic debris or other material from the aorta, the aortic valve, or from the left ventricle during the procedure may lead to an embolization, which in turn can precipitate an ischemic stroke.[18,19] In addition, air embolism, periprocedural hypotension/hypertension, new-onset arrhythmias, and arterial dissection might cause ischemic stroke during a PCI.[20,21] Furthermore, antiplatelet or anticoagulant drugs used before, during, and after PCI may lead to hemorrhagic stroke.[22,23]

Previous studies have investigated incidence, predictors, and outcome of stroke after PCI. Estimates of incidence vary from 0.1% to 1.3%.[3−10,24−27] The estimates are based on different time definitions of postprocedural stroke, ranging from 24 hours to 90 days after PCI. However, most strokes are reported to occur within 48 hours after PCI. Although rare, stroke is a serious complication to PCI. Studies have shown an association between postprocedural stroke and high morbidity and mortality rates, with inhospital mortality ranging from 22% to 37%.[5,7−9] In most studies, the vast majority of postprocedural strokes were ischemic, although 1 small, single-center study from the 1990s found that 46.5% of the strokes were hemorrhagic.[9] Many of the aforementioned studies identified diabetes mellitus, older age, female gender, hypertension, renal failure, and history of cardiovascular and cerebrovascular disease as clinical predictors of stroke after PCI.[3,7−9,24,26] Procedural risk factors included PCI in an emergency setting, use of intra-aortic balloon pump, greater contrast use, and longer catheterization time.[5,7−9] These previous studies were descriptive, and it is important to emphasize that patients who underwent a PCI are generally at an increased risk for stroke compared with the general population. Thus, the interpretation of the incidence of stroke after PCI is not straightforward.

Our estimates showed a rapid decrease in RR from day 3 after PCI and onward, confirming findings from previous descriptive studies that the first 48 hours are the most vulnerable. Furthermore, in concordance with results from other studies, we found that the RR stayed elevated for up to 8 weeks after PCI. Our estimates were not confounded by attributes stable over the investigated period, such as gender, age, genetic factors, lifestyle factors, and history of cerebrovascular events or chronic medical conditions, as the study design inherently controls for such factors. Based on clinical guidelines and experience, we know that the vast majority of Norwegian patients receive platelet aggregation inhibitors or dual antiplatelet therapy during and after PCI. Such medication is associated with reduced risk of ischemic stroke and increased risk of hemorrhagic stroke. However, our data material did not include information about medication; consequently, we were unable to separate the effect of the medication from the effect of the procedure in our risk estimates. Furthermore, we had limited ability to separate the effect of the indication to perform PCI from the effect of the procedure itself. In our data material, ~90% of the PCI hospitalizations were registered with myocardial infarction

(MI) as main diagnosis. It is known that there is an elevated risk of stroke after MI. However, the majority of strokes in relation to MI occurred later than 2 days after MI,[28] whereas we found the largest excess risk within the first 2 days after PCI. Thus, we believe the substantial elevated risk for the first 2 postprocedural days might to a large degree reflect the excess risk due to PCI itself. The approximately fourfold increased RR from days 3 to 28 is more challenging to interpret. However, regardless of the exact mechanisms, the first days and weeks after PCI must be considered a vulnerable period for ischemic stroke.

We found that women had a greater RR of ischemic stroke than men during the first 4 weeks after PCI. Recent studies have not found that female gender as such predicts adverse outcomes after PCI but rather that age and co-morbidity play an important role.[17,28] Women tend to be of older age and with more co-morbidities than men at the time of PCI.

Establishing PCI as a trigger for ischemic stroke carries implications for clinical practice. Raising awareness of the risk of stroke after PCI in patients and clinicians may lead to earlier detection of stroke and initiation of appropriate treatments at an early stage. Patients could benefit from being informed of the symptoms of stroke and from being encouraged to seek instant medical assistance if such symptoms should occur. Neurologists examining incoming patients presenting with focal symptoms consistent with stroke should explicitly look for a recently performed PCI or other angiographic intervention.

The strengths of the present study are the use of a population-based design covering a whole country and data from all hospitalizations over an 8-year period and the application of the case-crossover method, which allowed us to eliminate confounding by stable factors. However, we did not have detailed information about the type of procedure or the devices used during the PCI or of medication administered after PCI. In addition, the available information offered limited means to distinguish between the effects of the PCI procedure itself and the effects of acute clinical conditions leading to PCI. Moreover, because the majority of our PCI cases were registered with an MI diagnosis, our estimates are uncertain with regard to cases where the PCI is performed on other indications than MI.

Disclosures

The authors declare that there are no conflicts of interest.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.09.012.

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