Translational Research in Stroke

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Accession Site Does Not Influence the Risk of Stroke after Diagnostic Coronary Angiography or Intervention: Results from a Large Prospective Registry

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Keywords

 $\label{eq:stroke} Stroke \cdot Transient \ is chemic \ attack \cdot Cardiac \ catheterization \cdot Femoral \ access \cdot Radial \ access$

Abstract

Introduction: Periprocedural stroke represents a rare but serious complication of cardiac catheterization. Pooled data from randomized trials evaluating the risk of stroke following cardiac catheterization via transradial versus transfemoral access showed no difference. On the other hand, a significant difference in stroke rates favoring transradial access was found in a recent meta-analysis of observational studies. Our aim was to determine if there is a difference in stroke risk after transradial versus transfemoral catheterization within a contemporary real-world registry. **Methods:** Data from 14,139 patients included in a single-center prospective reg-

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Introduction

Stroke represents a major and potentially devastating complication of cardiac diagnostic and interventional catheterization procedures. Meta-analyses evaluating the risk of stroke following cardiac catheterization via transradial access (TRA) versus transfemoral access (TFA) showed no difference in pooled data from randomized trials (RT) [1–5]. A debate has continued for over 13 years on whether the choice of accession site increases the risk of periprocedural stroke [6–9]. The debate seemed settled until recently when a significantly lower risk was reported for radial catheterization in a Japanese registry [5]. However, such conclusions are not in line with observations from the European and American cohorts [6–9].

Our aim was to determine the odds of periprocedural transient ischemic attack (TIA)/stroke between patients undergoing cardiac catheterization via transradial versus transfemoral approach. The primary hypothesis was tested in the sample of consecutive patients undergoing cardiac catheterization in Pardubice Hospital between 2009 and 2016.

Materials and Methods

Database Description

In our database, the demographic, anthropometric, clinical, and procedural data of all consecutive patients undergoing elective cardiac catheterization were collected on a daily basis by the treating physicians. Data regarding procedural complications were cross-checked annually with our CathLab internal database. Records were matched with the National Health Information System (NZIS) database administered by the Institute of Health Information and Statistics of the Czech Republic (ÚZIS) using a unique patient identifier and date of procedure to provide long-term follow-up, notably 1-year mortality and 1-year revascularization.

Inclusion Criteria/Study Population

All elective invasive cardiac procedures performed at our institution between January 2009 and January 2016 were assessed for analysis, including diagnostic and/or interventional catheterization, first procedure or repeated procedure, and elective or acute catheterization. Records indicating ulnar, brachial, combined, or unspecified accession site were excluded.

Endpoint Definition

The principal endpoint was the occurrence of clinically overt stroke or TIA after cardiac catheterization within index hospitalization. All patients with suspected neurological complications were referred for clinical examination and computed tomography or magnetic resonance imaging scan. Final diagnosis and confirmation or exclusion of stroke/TIA was made by a neurological consultant. Stroke and TIA were defined as acute onset of a focal neurological deficit. Patients with transient focal neurological def-

Stroke after Transradial or Transfemoral Cardiac Catheterization icit lasting <24 h without acute ischemic lesions on magnetic resonance imaging were considered to have TIA. Patients with focal neurological deficit lasting >24 h and/or positive findings on brain imaging were considered to have stroke. Ischemic stroke, intracerebral hemorrhage, and subarachnoidal hemorrhage were considered for analysis. Modified Rankin score (mRS) at 3 months after hospital discharge was used to assess the functional outcome of patients affected [10]. Cases of delirium, contrast-induced neurotoxicity, and other transient neurological symptoms not fulfilling the criteria for stroke were not included [11].

Neurological complications following subsequent urgent cardiac surgery procedures within index hospitalization were excluded.

Cardiac Procedures

Techniques of diagnostic coronary angiography, percutaneous coronary intervention (PCI), other interventions, concomitant medication, sheath removal, and vascular access closure management were left to the discretion of individual operators. Our institution's protocol for periprocedural antithrombotic therapy did not change during the study period. Unfractionated heparin at doses of 5,000 IU for transradial and 3,000 IU for transfemoral diagnostic procedures was used. Unfractionated heparin at doses 70–100 IU/kg according to generally accepted recommendations was used for PCI [12].

Statistical Analysis

The normality of baseline covariates was checked using the Shapiro-Wilk test. Differences between the transradial and transfemoral groups were tested at $\alpha = 0.05$ using the *t* test or 2-sided exact significance test. In the following models, we included first-order covariates that (a) significantly differed between the groups or (b) were considered clinically relevant, such as age, gender, and calendar year of the intervention.

In the first step, we tested the impact of individual baseline parameters on the development of periprocedural stroke using multivariate logistic regression. Then, we calculated propensity score (PS) as the probability of being chosen for transradial catheterization based on the selected baseline parameters. The model specification was checked using the adjusted coefficient of determination, likelihood-ratio test, and plots showing PS distribution in each group. The primary hypothesis was tested using PS-adjusted logistic regression with Firth's correction for rare outcomes [13, 14]. To cross-check the hypothesis, we used PS-matching with 0.1 caliper width. Robust errors were used to correct for heteroscedasticity.

All analyses were performed in STATA 15.0 software, Stata-Corp LP, College Station, TX, USA. We report in line with the STROBE statement [15].

Results

Of the 14,302 patients entered into our database, 14,139 were selected for the analysis of whom 10,931 underwent transradial and 3,208 transfemoral catheterization (Fig. 1).

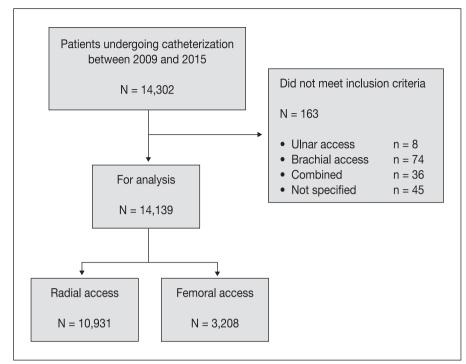


Fig. 1. Patient flow (in accordance with the STROBE statement).

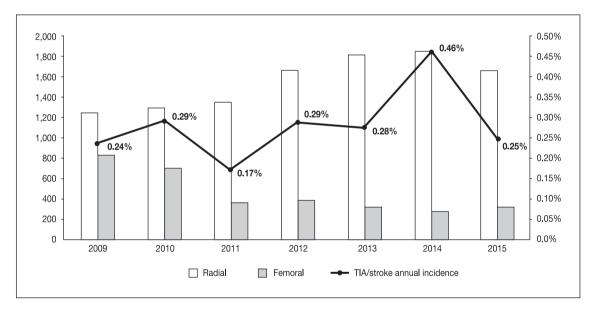


Fig. 2. Proportion of radial and femoral access procedures and annual incidence of TIA/stroke over the study period. Left vertical axis represents numbers of patients; right vertical axis represents the annual incidence of TIA/stroke.

TIA/stroke occurred in 41 (0.29%) patients, of which 40 events were ischemic and 1 hemorrhagic. The median time from catheterization procedure to TIA/stroke development was 40 min with an interquartile range of 90 min. All the patients with neurological complications underwent computed tomography scan immediately. The clinical outcome of these patients was as follows: mRS 5, severe disability in 1 patient; mRS 4, moderately severe disability in 2 patients; and mRS 0–2, no symptoms or slight disability in 37 patients. The 30-day mortality of patients

	Transradial group mean (±SD)/ <i>n</i> (%)	Transfemoral group mean (±SD)/ <i>n</i> (%)	<i>p</i> value
Number	10,931 (76.5)	3,208 (22.4)	
Reason for admission: ACS	1,906 (17.4)	646 (20.1)	0.002
Age	66.8 (±10.5)	67.3 (±11.2)	0.016
Male	6,888 (63.0)	2,011 (62.7)	0.839
BMI	29.6 (±5.1)	28.3 (±10.9)	0.000
Comorbidity			
Hypertension	9,363 (85.7)	2,725 (85.0)	0.703
Diabetes	3,564 (32.6)	1,082 (33.7)	0.329
Type 2	3,411 (31.2)	1,022 (31.9)	0.560
Type 2 on insulin	934 (8.5)	339 (10.6)	0.001
Dyslipidemia	8,072 (73.8)	2,484 (77.4)	0.039
Smoking (current)	1,926 (17.6)	489 (15.2)	0.004
Ex-smoker	2,771 (25.3)	829 (25.8)	0.626
COPD	1,433 (13.1)	387 (12.1)	0.145
CKD	910 (8.3)	400 (12.5)	0.000
Peptic ulcer disease	1,108 (10.1)	369 (11.5)	0.037
Previous cardiovascular disease			
Any previous form of CHD	3,138 (28.7)	1,525 (47.5)	0.000
ACS	1,992 (18.2)	963 (30.0)	0.000
Stable angina	1,146 (10.5)	562 (17.5)	0.000
Previous revascularization	2,270 (20.8)	1,286 (40.1)	0.000
Previous PCI	1,975 (18.1)	530 (16.5)	0.066
Previous PCI + CABG	109 (1.0)	185 (5.8)	0.000
Previous CABG	175 (1.6)	565 (17.6)	0.000
Valvular disease	999 (9.1)	384 (12.0)	0.000
Aortal stenosis	402 (3.7)	132 (4.1)	0.264
Mitral regurgitation	383 (3.5)	144 (4.5)	0.013
History of TIA/stroke/carotid artery stenosis	987 (9.0)	424 (13.2)	0.000
Ischemic stroke/TIA	876 (8.0)	372 (11.6)	0.000
Hemorrhagic stroke	28 (0.3)	8 (0.2)	0.976
Asymptomatic carotid artery stenosis	80 (0.7)	43 (1.3)	0.002
Antiplatelet medication			
ÁSA	8,627 (78.9)	2,663 (83.0)	0.023
Inhibitors P2Y12	4,382 (40.1)	1,440 (44.9)	0.000
Clopidogrel	3,718 (34.0)	1,179 (36.8)	0.021
Ticlopidine	570 (5.2)	245 (7.6)	0.000
Other	94 (0.9)	16 (0.5)	0.035
Anticoagulation			
LMWH	1,677 (15.3)	446 (13.9)	0.063
Warfarin	479 (4.4)	107 (3.3)	0.009
NOAC	97 (0.9)	26 (0.8)	0.695

Table 1. Differences between baseline characteristics in patients catheterized via radial and femoral accession site

There were 3.6% and 10.9% missing values of the BMI in the transradial and transfemoral groups, respectively. In the transfemoral group, 2% patients did not have information available about the history of TIA/stroke. All remaining data were complete or missed <0.5% values. Differences between the transradial and transfemoral groups were tested at $\alpha = 0.05$ using the *t* test or 2-sided exact significance test. ACS, acute coronary syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ASA, acetylsalicylic acid; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulants; TIA, transient ischemic attack; CKD, chronic kidney disease.

	Transradial group mean (±SD)/ <i>n</i> (%)	Transfemoral group mean (±SD)/ <i>n</i> (%)	<i>p</i> value
Periprocedural TIA/stroke	31 (0.28)	10 (0.31)	0.775
Skiascopic time, min	5.0 (±11.3)	5.8 (±4.8)	0.000
TIMI major or minor bleeding	2 (0.02)	15 (0.47)	0.000
30-day mortality	64 (0.59)	36 (1.12)	0.003
1-year mortality	512 (4.68)	204 (6.36)	0.003
1-year revascularization	1,718 (15.72)	399 (12.44)	0.000
1-year myocardial infarction	258 (2.36)	91 (2.84)	0.135

Table 2. Differences in outcomes of the catheterization performed via radial and femoral accession site

There were 3.2% and 13.5% missing values of the sciascopic time in the transradial and transfemoral groups, respectively. Differences between the transradial and transfemoral groups were tested at $\alpha = 0.05$ using the *t* test or 2-sided exact significance test. TIA, transient ischemic attack; TIMI major bleeding, any intracranial bleeding, clinically overt bleeding with a drop in hemoglobin of ≥ 5 g/dL; TIMI minor bleeding, clinically overt bleeding resulting in hemoglobin drop of 3 to < 5 g/day.

with periprocedural TIA/stroke (1/41 - 2.44%) and without TIA/stroke (102/14,261 - 0.72%) did not differ significantly (p = 0.192).

There has been a significant change from predominantly TFA to predominantly radial access during our study with trend analysis showing a significant decrease in the number of transfemoral procedures performed (p = 0.027) and increase in transradial procedures (p =0.038), while periprocedural stroke annual incidence remained practically constant (p = 0.484) (Fig. 2).

Patients were divided into TFA and TRA groups depending on the final vascular access utilized. Demographic, clinical, and procedural characteristics of both groups are presented in Table 1. Periprocedural TIA/stroke occurred in 31/10,931 (0.28%) patients in the TRA group and 10/3,208 (0.31%) in the TFA group, and the difference was not statistically significant. Transradial procedures were less frequently accompanied by bleeding (0.02% vs. 0.47%, p < 0.000), and the 30-day mortality was also lower (0.59% vs. 1.12%, p = 0.003) (Table 2).

To eliminate potential confounding, we chose covariates with significant baseline differences between groups and previously known risk factors for periprocedural stroke to predict the occurrence of the periprocedural TIA/stroke using multivariate logistic regression. Age remained the only significant predictor, with each additional year representing an odds ratio (OR) = 1.09 (CI 1.05–1.13, p < 0.000). In the multivariate regression, the choice of accession site had no impact on periprocedural TIA/stroke OR = 0.81 (0.38–1.75, p = 0.592) (Fig. 3A).

The same parameters were used to calculate PS as the probability of being catheterized via the radial artery

(Fig. 3B). We also tested the impact of the second-order terms and interactions, but these were not included in the final model. The impact of accession site on the risk of periprocedural stroke was tested using PS-adjusted logistic regression with Firth's correction for rare outcomes, yielding a statistically insignificant estimate OR = 0.81 (0.38–1.72, p = 0.577).

To cross-validate our result, we employed PS matching using a caliper width of 0.1. An average treatment effect resulting from 13,338 matches showed no difference in the risk of periprocedural stroke and the accession site (p = 0.664, details not presented).

Discussion/Conclusion

Taken together, in our registry cohort of 14,139 catheterizations, we show that the choice of accession site had no impact on the risk of periprocedural TIA/stroke. The result was confirmed in the multivariate regression analysis, PS-adjusted regression analysis, and via PS matching.

While rates of other catheterization complications have declined over the last decade, the periprocedural stroke rate ranges between 0.09% and 0.3% and remains constant despite important technical advancement in the field [6]. Thus, periprocedural stroke complicating cardiac catheterization is a very rare event, so absolute differences in their frequency in RT are small and analyses may be underpowered to detect statistically significant differences between TRA and TFA.

The selection of patients to be enrolled in our prospective registry reflects real-life daily practice including diag-

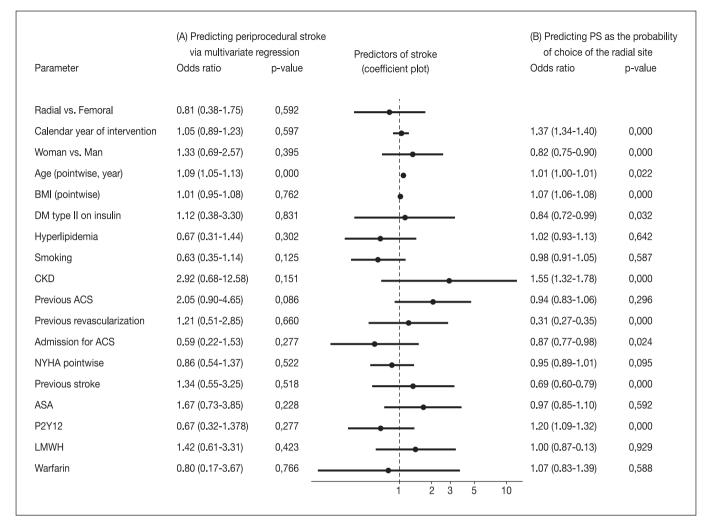


Fig. 3. (**A**) Coefficients for parameters used to predict stroke. (**B**) Coefficients for parameters used to predict the propensity score (defined as the probability to be catheterized via radial access). PS, propensity score; BMI, body mass index; DM, diabetes; CKD,

chronic kidney disease; ACS, acute coronary syndrome; NYHA, New York Heart Association class; ASA, acetylsalicylic acid; P2Y12, P2Y12 inhibitor use; LMWH, low-molecular-weight heparin use; OR, odds ratio.

nostic catheterization and intervention, and patients with acute and stable coronary heart disease, chest pain, valvular disease, heart failure with reduced ejection fraction, and structural heart disease. Sample size, prospective data collection, and validation allowed us to analyze a very rare event (stroke) in relation to the accession site used.

The TIA/stroke rate in our registry was higher than that in the articles published by the British, Portuguese, and Italian groups, and similar to Japanese data [5–8]. Inhospital mortality due to stroke was low and did not differ significantly from groups of patients without stroke.

TFA and TRA groups were balanced at baseline except for body mass index, presence of dyslipidemia, chronic

kidney disease, peptic ulcer disease, history of acute coronary syndrome (ACS), previous revascularization, valvular disease, stroke, antithrombotic medication used, and the proportion of active smokers and diabetics on insulin. The operators tended to choose the radial approach in obese patients probably due to concerns of bleeding complications. The femoral approach was preferred in different subgroups of patients: those with chronic kidney disease, where peripheral vascular disease and potential future need for arteriovenous fistula creation could come into consideration; those with previous ACS and revascularization, where a nonpalpable radial artery after a previous procedure and easier bypass graft engagement via a femoral approach could play a role; and those with previous stroke, where concerns about higher stroke risk in radial access according to pathophysiologic assumptions and limited evidence then available were raised.

Similar to all reviewed studies, there has been a significant change from predominantly TFA to predominantly radial access during our study. The transition period was long enough to witness experienced transfemoral operators becoming experienced transradial operators.

Age remained the only significant predictor of TIA/ stroke after cardiac catheterization according to the analysis of our registry. This reminds us that cardiac catheterization (even diagnostic) should be planned after thorough risk-benefit assessment in elderly patients.

Results of our robust analysis revealed different results from other observational data focused on the topic. Moreover, inspection of the primary reports of previous trials showed that periprocedural stroke is severely underreported in the primary RT, with only 3 articles presenting the periprocedural events separately [16–18]. The key meta-analysis by Sirker et al. [2] in 2016 included only 2 observational studies and 3 RT reporting neurological complications separately.

In summary, radial access for cardiac catheterization is associated with a significantly lower risk of bleeding, vascular complications, and possibly mortality, mainly in patients with ACSs [19]. The situation is different with regard to periprocedural TIA/stroke, where both accession sites confer similar risk. Despite the increasing use of transradial procedures, large-bore TFA will always be necessary in structural heart interventions, extracorporeal membrane oxygenation support, and complex PCI procedures. Transfemoral way remains the predominant access for diagnostic and interventional procedures in the Unites States [20]. Continuous reexamination of the association between accession site and stroke in more recent observational studies is necessary [21]. Our updated evidence represents important information applicable to common clinical practice and source of data for possible future meta-analyses.

Limitations

A few limitations of our study should be mentioned. Albeit prospective, the study design was observational with all known general limitations, including unbalanced baseline characteristics of transradial and transfemoral groups and possible confounding related to accession site choice by individual operators. We controlled for all (to us) known confounders using a proper adjustment by both the multivariate analysis and PS. After all, there remains a risk of unmeasured confounding – an inherent trait of nonrandomized studies. The single-center pattern of an albeit robust sample limited size and power of the estimate.

ACS patients represented approximately one-fifth of our entire cohort. The study sample represented real-life patients admitted or transferred to hospital in stabilized conditions. Patients with non-ST-elevation myocardial infarction with ongoing ischemia, ST-elevation myocardial infarction, or cardiogenic shock were not included in the analysis. Results must be generalized with caution to the entire spectrum of invasive procedures. Some studies have shown that ACS represents an independent predictor of stroke and/or favored transradial approach [5, 7]. In other studies, such a trend was not detected [8]. There was no significant interaction between subgroups of ACS patients and access site in our data.

The timeframe for identifying periprocedural TIA/ stroke was defined as the time between procedure and hospital discharge. This represents a possible bias in patients who develop TIA/stroke later during hospital course without any casual relation to the catheterization procedure. Regarding a very short time interval between catheterization procedure and TIA/stroke development in our sample, such a bias is less probable. Meanwhile, it is possible that some TIA/strokes with transient symptoms can be missed in sedated patients early after the catheterization procedure.

From the clinician's point of view, we analyzed several potential risk factors for periprocedural TIA/stroke, and age remained the only significant predictor of this complication. Other potentially important factors including burden of atherosclerotic disease in the aorta, experience of the operators, and complexity of procedures may play a significant role. These factors pose challenges for quantification and they are beyond the scope of our analysis.

Our observational estimate compared procedural complications of experienced transfemoral and transradial operators. Contemporary ways of fellow training in interventional cardiology favoring a radial-first approach can lead to low transfemoral expertise and subsequently a higher complication rate already mentioned in the literature [22, 23].

Conclusion

Observational data from a large prospective registry cohort indicate that accession site has no influence on the risk of periprocedural TIA/stroke after cardiac catheterization.

Acknowledgment

The authors appreciate the contribution of the Institute of Health Information and Statistics of the Czech Republic (UZIS) to long-term follow-up data collection.

Statement of Ethics

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Review Board of the Hospital of Pardubice (Etická komise Pardubické nemocnice) (reference number 626/B/19.6.2020). Each participant provided informed consent to the procedure and data collection.

Conflict of Interest Statement

J.M. received speaker honoraria from Servier, Novartis, and AstraZeneca. I.V. received speaker honoraria from AstraZeneca, Bayer, Pfizer, Eli Lilly, and Chiesi. V.N. received speaker honoraria from Terumo and Teleflex. M.P. received speaker honoraria from Servier. The other authors have no conflict of interests to declare.

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Author Contributions

J.M. designed the study, gathered data, and wrote the draft of the manuscript; I.V. gathered data and revised the manuscript for important intellectual content; J.T. wrote the draft of the manuscript and performed the statistical analyses; T.D. performed the statistical analyses and revised the manuscript for important intellectual content; M.B. designed the study and revised the manuscript for important intellectual content; J.P. gathered data; P.G. gathered data and revised the manuscript for important intellectual content; J.V., K.B., J.M., A.S., J.B., V.R., V.N., T.L., and M.P. gathered data; and J.V. and P.V. gathered data and revised the manuscript for important intellectual content.

Data Availability Statement

The data that support the findings of this study are available in a public repository [24].

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