Nationwide Experience of Cardio- and Cerebrovascular Complications During Infrainguinal Endovascular Intervention for Peripheral Arterial Disease and Acute Limb Ischaemia

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WHAT THIS PAPER ADDS

This study supplies data on the present risks for cardio- and cerebrovascular complications during infrainguinal endovascular intervention and discusses important predictors for suffering from such complications in a population-based setting. Specifically, this article analyses major treatment complications in important subgroups with peripheral arterial disease, highlighting risks during catheter-directed thrombolytic therapy.

Objectives: Endovascular treatment for peripheral arterial disease (PAD) is increasingly used and also continuously applied to more severe vascular pathology. Only few studies report on systemic complications during these procedures, but it is important to address these risks. We report the results of a recent national audit on cardio- and cerebrovascular complications after endovascular procedures for PAD.

Methods: Data from the Swedish Vascular Registry (Swedvasc) were retrieved on all infrainguinal endovascular procedures performed between May 2008 and December 2011. A total of 9187 cases were analysed regarding the prevalence of myocardial infarction and major stroke within 30 days post-intervention.
A literature review in PubMed and Cochrane databases was conducted.

Results: The risk of myocardial infarction was 0.3% in intermittent claudication, 1.2% in critical limb ischaemia and 1% in acute limb ischaemia. Corresponding risk of major stroke was 0.4%, 0.3% and 1.4%. Thrombolytic therapy was associated with a threefold risk of major stroke.
Only a few studies relevant to the subject were found during the literature review.

Conclusions: In this population-based study we found a low risk of cardiac complications, but catheter-administered thrombolytic therapy entailed a non-negligible risk of major stroke.

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Peripheral arterial disease (PAD) is a major health problem, affecting about 18% of all individuals over the age of 60 years in Sweden.[1] Patients with PAD have a high risk for associated ischaemic heart disease[2] and other manifestations of atherosclerosis. Considering the increasing life expectancy in the western world[3] and the continuous medical improvements in cardiac disease[4] and stroke[5] prevention and management, it could be anticipated that PAD would affect even more patients in the near future.

In symptomatic PAD vascular surgical procedures are often considered, aiming at limb-salvage or improvement of symptoms. With the on-going and rapid developments in endovascular techniques, a majority of these patients are nowadays treated endovascularly.[6] Endovascular treatment offers a minimally invasive, and thereby a probably more tolerable procedure, even in patients with high age and/or with severe comorbidity. These techniques are continuously applied to more severe vascular pathology, making the procedures more complex and time-consuming; thus, there could be a significant risk for systemic complications even with the use of these less invasive techniques.

There is an abundance of papers dealing with local, procedure-related complications in association with endovascular therapy.[7–9] There are also many previous publications exploring the risk for systemic (cardiac and cerebrovascular) complications during open surgical procedures in PAD.[10,11]

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However, there are surprisingly few studies to be found that examine the risk of cardio- and cerebrovascular complications in association with endovascular procedures for PAD. The main aim of this study was to assess the concurrent nationwide prevalence of systemic complications during infrainguinal endovascular revascularisation in Sweden and also to investigate the importance of different risk factors for the treatment outcome in routine clinical practice.

METHODS

Literature review

The PubMed and the Cochrane Clinical trials databases were searched during a time period ranging from January 2002 to August 2012, using the following terms: 'heart attack' OR 'myocardial infarction' OR 'stroke' OR 'cerebrovascular accident' OR 'cerebrovascular event' AND 'Endovascular' OR 'Atherectomy' OR 'Angioplasty' OR 'Angioplasty', 'balloon [MeSH]' OR 'stent' OR 'stents' OR 'Stenting' OR 'Stent graft' OR 'Endovascular Procedures'[Mesh] AND 'PAD' OR 'intermittent claudication' OR 'critical limb ischaemia'. The search was limited to English or Swedish language, and excluded editorials, letters, comments and animal studies.

The Swedvasc

The National Swedish Vascular Registry (Swedvasc) is the oldest national vascular registry in the world, collecting prospective data from all vascular surgical procedures performed in Sweden since 1994. The registry has several times been validated regarding the accuracy of data.[12–14] In 2008, the registry was thoroughly updated (Swedvasc 2.0)[6] and the infrainguinal vascular procedures were separated in a specific module, allowing for detailed data collection of risk factors, performed procedures, complications and outcomes during invasive treatment for PAD. Follow-up visits according to the registry protocol are scheduled 1 month and 1 year after the procedure. Mortality data in Swedvasc are retrieved by automatic cross-matching with the Swedish National Cause of Death Registry, that contains robust and accurate data regarding time and cause of death for all diseased individuals in Sweden.

The definition of 30-day complications in the registry includes all events during the procedure and under the follow-up period of 30 days. Cerebrovascular complication is defined as major stroke (persistent neurological deficit) and cardiovascular complication as myocardial infarction.

Study population

In a data set ranging from May 2008 (the launch of Swedvasc 2.0) to December 2011, 15,403 infrainguinal procedures were registered. Of these, 9802 were endovascular treatments and included in this study. Eighty-one per cent of the endovascular procedures were done for chronic PAD, 13% were performed for acute limb ischaemia and 1.5% ($n = 147$) were done for popliteal artery aneurysms. The procedures for popliteal artery aneurysms were excluded from further analysis, as were a remaining 4.9% ($n = 477$) because of missing data regarding the indication for surgery. The subsequent analysed data set contained 9178 procedures, of which 86% ($n = 7923$) were for chronic limb ischaemia and 14% ($n = 1255$) for acute limb ischaemia.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using χ^2 test significance analysis. Multivariate associations were assessed by a logistic regression analysis and the results are presented as odds ratios (ORs). The number of predictors used in the multivariate regression analysis was adjusted according to the number of events, as it has been recommended when using logistic or Cox regression analysis.[15] Significance was assumed at $p < 0.05$.

Ethical considerations

Ethical approval was obtained from the Regional Ethical Review Board at the University of Uppsala, D-nr 2012/282. The data set from the Swedvasc was received after a formal consent from the National Steering Committee of the Swedvasc, according to the requirements from the registry.

RESULTS

Literature review

A total of 319 studies were found during the literature search and the abstracts were reviewed. Only papers reporting on either cardio- and/or cerebrovascular complications in association with endovascular procedures were considered relevant and these are summarised in Table 1.

Study population

Demographic data for the studied population are given in Table 2. Mean age was 77 ± 14 years in the subjects with chronic disease, and 77 ± 12 years in the subjects with acute limb ischaemia. There were 52% male with chronic disease and 54% with acute limb ischaemia. Among the subjects with chronic disease, 24.4% ($n = 1937$) of the procedures were performed for intermittent claudication and 75.5% ($n = 5981$) for critical limb ischaemia. A total of 0.1% ($n = 5$) lacked data regarding disease severity in chronic disease.

In the subjects with acute limb ischaemia, according to the TransAtlantic Inter-Society Consensus for Management of PAD (TASC II) classification of degree of ischaemia: 17.3% ($n = 217$) of the extremities were viable (TASC I), 48% ($n = 603$) were marginally treated (TASC IIa) and 31% ($n = 388$) were immediately treated (TASC IIb). A total of 3.7% ($n = 47$) lacked data of degree of ischaemia.

Interventions

The performed endovascular procedures are given in Table 3.

Table 1. Summary of the results of the literature review.

Year	Author	Type of study	Participants	Procedure-related cardiovascular complication	Procedure-related cerebrovascular complication
2002	Berridge DC	Cochrane review	Acute limb ischaemia, catether-directed thrombolysis, $n = 1283$	Not reported	1.3%
2006	Nowygrod R	Registry study	PAD, lower extremity revascularisation, $n = 17,193$	0.86%	0.19%
2008	Kashyap VS	Observational, retrospective	PAD, endovascular treatment of, extensive aortoiliac disease, $n = 83$	1.2%	Not reported
2011	Vogel TR	Registry study	PAD, tibioperoneal intervention, $n = 13,258$	3.2%	Not reported
2011	Scali ST	Observational, retrospective	PAD, revascularisation of the superficial femoral artery, $n = 204$	Not reported	0%

Cardiovascular complications

In intermittent claudication, 0.3% of the subjects developed a myocardial infarction within 30 days after the procedure and for critical limb ischaemia the corresponding figure was 1.2%. In acute limb ischaemia, 1% of the subjects suffered from a myocardial infarction and this number increased to 2% for those with TASC IIb.

In the univariate analysis, the risk of myocardial infarction within 30 days after the procedure was associated with cardiovascular disease ($p < 0.001$) and diabetes ($p < 0.01$). Among the subjects suffering from a myocardial infarction, 17% died within 30 days and 36% within 90 days after the procedure.

Cerebrovascular complications

In intermittent claudication, 0.4% developed a major stroke within 30 days after the procedure and for critical limb ischaemia the risk was 0.3%. In acute limb ischaemia, 1.4% of the subjects suffered from a major stroke and this number increased to 1.6% when only subjects with acute limb ischaemia treated with catheter-directed thrombolysis ($n = 924$) were analysed.

In univariate analysis, performed on the complete data set, catheter-administered thrombolytic therapy was associated with a significantly increased risk for major stroke within 30 days after the procedure ($p < 0.001$). Among the subjects suffering from a major stroke, 30% died within 30 days and 40% within 90 days after the procedure.

Table 2. Demographics and risk factors in the studied population.

	Chronic peripheral arterial disease	Acute limb ischaemia
Age (mean + SD, years)	77 ± 14	77 ± 12
Gender (male/female), %	52/48	54/46
Previous or current smoking, %	49	41
Hypertension, %	72	65
Diabetes, %	42	22
Coronary disease/ heart failure, %	39	38
Previous TIA/stroke, %	14	15
Pulmonary disease, %	12	12
Dialysis, %	5	2
S-creatinine (mean + SD, mmol l/l)	114 ± 100	101 ± 67

Multivariate predictors of procedure-related cardio- and cerebrovascular complications

In multivariate analysis, controlled for demographics and other risk factors, diabetes and cardiovascular disease were independent predictors of risk for myocardial infarction within 30 days after the endovascular procedure (Table 4). Thrombolytic therapy imposed a threefold increased risk of suffering from a major stroke within 30 days (Table 5). Adding the performed procedure (femoropopliteal vs. crural) did not change findings.

DISCUSSION

In this large, nationwide audit of infrainguinal endovascular procedures for PAD and acute limb ischaemia, we found that the risk of adverse cardiac outcome within 30 days following the procedure was generally low and associated to the severity of the peripheral vascular disease. In this

Table 3. Actual numbers of performed endovascular procedures. Several of the subjects received more than one of the defined interventions.

	Chronic peripheral arterial disease ($n = 7923$)	Acute limb ischaemia ($n = 1255$)
PTA	7114	607
Subintimal angioplasty	2370	95
Stent implantation	2157	174
Stent graft implantation	325	63
Catheter-directed thrombolysis	340	924
Percutaneous mechanical thrombectomy	12	12
Percutaneous aspiration thrombectomy	34	25
Other endovascular procedures	480	142

Table 4. Multivariate analysis of the risk for myocardial infarction within 30 days following endovascular intervention, $n = 9178$.

	p value	OR	95% C.I. for EXP (B)	
			Lower	Upper
Males	.174	1.359	.873	2.116
Diabetes	<0.001	2.164	1.404	3.336
s-creatinine	.810	1.000	.998	1.003
Dialysis	.389	1.689	.512	5.568
Pulmonary disease	.874	1.049	.578	1.906
Cerebrovascular disease	.979	.992	.566	1.739
Cardiac disease	<0.001	2.310	1.487	3.587
Age	<0.001	.958	.935	.981

respect, we confirmed previously reported cardiac risks by Nowygrod et al.[16] from 2006. Diabetes and cardiovascular disease were independent predictors of adverse cardiac outcome. A peri-interventional myocardial infarction confers a high risk for subsequent death with a 90-day mortality rate of 36%. Other authors have done similar observations regarding the influence of a peri-procedural myocardial infarction on long-term survival[17,18] among vascular surgery patients. However, previous reports[16] have not specifically addressed the risk of suffering from these major complications among subjects treated for intermittent claudication. A major complication risk approaching 1%, taken into account the risk of underreporting, is a worrying finding. This is also highlighted by the fact that not all claudicants are offered a formalised supervised exercise program in Sweden before intervention, which could effectively reduce the numbers at risk.

Regarding adverse cerebrovascular outcome, we found similar risks as reported by previous authors.[16] Catheter-administered thrombolytic therapy was a significant and important risk factor for suffering from a major stroke within 30 days of the procedure. There may be several explanations for this increased stroke risk, with an OR of 3.5 (1.8—6.5). Firstly, as thrombolytics are most frequently used for acute arterial ischaemia that may have embolic origin, synchronous emboli to the cerebrovascular bed could be an explanation. These intracranial emboli may be clinically silent (or transient events unreported by the patient in a situation with severe acute limb ischaemia), but with the administration of thrombolytic drugs even a small cerebral ischaemic lesion could be a nidus for haemorrhagic transformation. This explanation is supported by the findings by Berridge et al. (2002) who, in a large Cochrane report,[19] reported a risk of haemorrhagic stroke of 1.3% when catheter-administered thrombolytic therapy was used in the initial management of acute limb ischaemia. However, in our data set we cannot differentiate between ischaemic and haemorrhagic stroke, and therefore our higher stroke rate may partly be due to synchronous cerebral (non-haemorrhagic) embolic events. Another mechanism may be dislodgement of new emboli from a cardiac origin, due to the systemic effect during the thrombolytic infusion. This advocates caution to use catheter-administered thrombolytic therapy in cases with possible cerebral ischaemic lesions, taken into account the risk of haemorrhagic transformation. A thorough neurological clinical evaluation, and perhaps also the use of additional brain imaging techniques (such as diffusion-weighted magnetic resonance imaging), could allow for accurate diagnosis of these cases before initiating thrombolytic therapy, and thereby improving patient selection. Both open (i.e., embolectomy) and endovascular (i.e., percutaneous mechanical thrombectomy and/or aspiration thrombectomy) techniques might be preferred in cases with diagnosed synchronous cerebral ischaemic lesions. Improvements could also be made in the peri-interventional care during catheter-based thrombolytic therapy. In 2010, Agle et al. reported a strong association between haemorrhagic stroke and poor hypertension control during the procedure.[20] As for the cardiovascular complication, the mortality rate after a cerebrovascular complication is similarly high with 40% after 90 days.

Table 5. Multivariate analysis of the risk for major stroke within 30 days following endovascular intervention, $n = 9178$. Adding more predictors did not change findings.

	p value	OR	95% C.I. for EXP (B)	
			Lower	Upper
Male gender	.296	.715	.381	1.341
Diabetes	.786	.914	.478	1.748
Cardiovascular disease	.292	1.388	.754	2.554
Cerebrovascular disease	.308	1.471	.701	3.088
Thrombolytic therapy	<0.001	3.466	1.849	6.500
Age	.322	.985	.955	1.015

This study has both strengths and limitations. Strength is the prospectively collected and populations-based data, which reflects concurrent clinical practise. Limitations include the problem with registry data, with risk of data collection inaccuracy and underreporting of cases with bad outcomes. However, taken into account these shortcomings, we think it is fair to say that the reported complication rates in our study represent 'at least' the true rate, as only major cardiac and cerebrovascular events are reported to the registry.

In conclusion, there are quite scarce data in the literature regarding cardio- and cerebrovascular complications in association with endovascular procedures for PAD. In this national audit based on Swedvasc data for infrainguinal endovascular interventions, we found a generally low risk for myocardial infarction and major stroke. However, the mortality rate is high after both these peri-procedural complications and for the subgroup with intermittent claudication, these observed risks advocate caution with the use of infrainguinal endovascular procedures.

Catheter-administered thrombolytic therapy imposes a significant risk of major stroke. A clinical implication, to improve patient selection for thrombolytic therapy, may include a careful pre-procedural neurological clinical evaluation and, if indicated, the use of appropriate brain

imaging in selected cases. However, there is a need for a more available and widespread access to these imaging techniques also in the acute setting if this is to become a reality.

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