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The impact of different techniques used for coronary angiography and percutaneous coronary intervention on the occurrence of procedure-related ischemic cerebral complications

by

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Wer nicht neugierig ist, erfährt nichts.

Johann Wolfgang von Goethe

To my wonderful family
Mikael, Ida and Isak

CONTENTS

Abstract

Background
Coronary angiography (CA) is the gold standard in diagnosing and determining the treatment of patients with coronary heart disease. Procedure-related neurological complications are rare; 0.1-0.4% for CA and percutaneous coronary intervention (PCI). In contrast, the incidence of procedure-related silent cerebral lesions, shown with diffusion-weighted magnetic resonance tomography, is considerably higher (2-35%). Cerebral microemboli have been observed during different vascular procedures and are related to new silent cerebral lesions but their clinical impact is debated. CA and PCI can be performed with different techniques, i.e. with the radial or the femoral access. As procedure-related stroke is associated with high mortality, considerable morbidity and suffering it is important to study which technique entails the lowest risk for patient injury.

Methods and results
Study I: Fifty-one patients with stable angina pectoris were randomised to CA with the radial or the femoral access and the number of cerebral microemboli was assessed with bilateral transcranial Doppler technique of the middle cerebral arteries (MCAs). The number of particulate cerebral microemboli was significantly higher with the radial compared to the femoral access. The number of cerebral microemboli was higher for both access sites during catheter exchanges compared with other specific procedural steps during CA, with most cerebral microemboli detected in the right MCA in the radial group. This indicates a causal anatomical link, as the catheter is advanced from the right radial artery through the brachiocephalic trunk before it bends into the ascending aorta to reach the coronary ostia.

Study II: Forty-one patients with stable angina pectoris or non-ST-segment-elevation myocardial infarction scheduled for CA were randomised to two different guidewire techniques with the femoral access involving catheter advancement with or without a leading guidewire over the aortic arch. After the CA was completed, including contrast injections, the opposite technique was used on the same patient without further contrast injections. At the same time, the number of cerebral microemboli was registered using bilateral transcranial Doppler technique. The number of cerebral microemboli was higher when the catheter was advanced with, rather than without a leading guidewire over the aortic arch, independent of whether a complete CA was performed or if a catheter was placed in the vicinity of the coronary ostia only.

Study III: All CAs and PCIs reported between 2003 and 2011, n= 336,836, to the Swedish Coronary Angiography and Angioplasty Register with information on access site were retrospectively analysed regarding the association between access site and procedure-related stroke or transient ischemic attack (TIA). After cross-checking the reported neurological complications with the corresponding medical records the incidence of procedure-related stroke or TIA was 0.16%. After multivariable adjustment, the radial access was associated with a higher risk for procedure-related stroke or TIA (risk ratio 1.30, 95% confidence interval 1.04-1.62) compared with the femoral access. Parallel to the increased use of the radial access over time, the risk for procedure-related stroke or TIA also increased, although there was no significant interaction between the different time intervals observed.

Study IV: Ninety-three patients with suspected or stable angina pectoris scheduled for CA or PCI were tested with Montreal Cognitive Assessment (MoCA) before and twice after the coronary procedure to study post-procedural cognitive impairment. A subgroup was monitored with bilateral transcranial Doppler technique to explore the relationship between cerebral microemboli and cognitive function. The patients were also randomised to radial or femoral vascular access site to study if the access site used was related to post-procedural cognitive impairment. Cognitive function assessed with the MoCA test was not impaired after the coronary procedure. There was no significant correlation between the results of the MoCA test and cerebral microemboli or vascular access site.

Conclusions
The choice of access site and guidewire technique used for CA and PCI had an impact on the occurrence of cerebral microemboli. There may be an association between the radial access and increased risk for procedure-related stroke or TIA, which should be studied further. Earlier studies have shown that cerebral microemboli are related to new silent cerebral lesions, but we found no cognitive impairment after coronary procedures using the MoCA test. Further studies are needed to explore the clinical impact of cerebral microemboli and to minimise or prevent the occurrence of procedure-related ischemic cerebral lesions in patients undergoing CA and PCI.

SAMMANFATTNING

Bakgrund
Kranskärlsröntgen är standardundersökningen för diagnostik och beslut om behandling av patienter med ischemisk hjärtsjukdom. Procedurrelaterade neurologiska komplikationer är sällsynta; 0,1-0,4% vid kranskärlsröntgen och kranskärlsinterventioner. Däremot är uppkomsten av procedurrelaterade tysta hjärninfarkter, diagnosticerade med diffusionsviktad magnetisk resonanstomografi betydligt vanligare (2–35%). Cerebrala mikroembolier har observerats under olika kärlingrepp och associerats med nytillkomna tysta hjärninfarkter, men deras kliniska betydelse är omstridda. Kranskärlsröntgen och kranskärlsinterventioner kan tekniskt utföras på olika sätt, exempelvis via radialis- eller femoralisartären. Eftersom procedurrelaterad stroke är kopplad till hög dödlighet, betydande sjuklighet och lidande är det viktigt att undersöka vilken teknik som medför lägst risk för patientskada.

Metoder och resultat
Studie I: 51 patienter med stabil kranskärlssjukdom randomiserades till kranskärlsröntgen via radialis- eller femoralisartären och antalet cerebrala mikroembolier monitorerades via transkraniell Doppler i bägge cerebrimediaartärerna. Signifikant fler solida cerebrala mikroembolier registrerades i radialisgruppen jämfört med femoralisgruppen. Antalet cerebrala mikroembolier var högre för båda kärlaccesserna vid kateterbyte jämfört med andra specifika moment under kranskärlsröntgen med flest cerebrala mikrombolier detekterade i högra cerebrimediaartären i radialisgruppen. Detta talar för ett kausalt anatomiskt samband, eftersom katetern framförs vid instick i högra radialisartären via truncus brachiocephalicus innan den böjs i aorta ascendens för att nå koronamynningarna.

Studie II: 41 patienter med stabil kranskärlssjukdom eller icke ST-höjningsinfarkt planerade för kranskärlsröntgen randomiserades till två olika kateteriseringstekniker via femoralisartären, som innebär kateterisering med eller utan ledare över aortabågen. Efter avslutad kranskärlsröntgen, med kontrastinjektioner, genomfördes den andra kateteriseringstekniken på samma patient, men utan ytterligare kontrastinjektioner. Samtidigt registrerades cerebrala mikroembolier med transkraniell Doppler bilateralt. Antalet cerebrala mikroembolier var högre när katetern fördes med ledaren över aortabågen jämfört med utan ledare, oavsett om en fullständig kranskärlsröntgen utfördes eller om katetrar enbart placerades vid kranskärlsmynningarna.

Studie III: Alla kranskärlsröntgen och kranskärlsinterventioner som rapporterats till det Svenska koronarangiografi- och angioplastikregistret med uppgift om instickställe mellan 2003 och 2011, n= 336836, analyserades retrospektivt med avseende på sambandet mellan kärlaccess och procedurrelaterad stroke eller transitorisk ischemisk attack (TIA). Efter att de rapporterade neurologiska komplikationerna hade verifierats med inhämtade journaler från respektive patient, beräknades incidensen av procedurrelaterad stroke eller TIA till 0,16%. Efter justering för flera förväxlingsfaktorer var kranskärlsröntgen eller kranskärlsintervention via radialisartären associerad med ökad risk för procedurrelaterad stroke och TIA, (risk ratio 1,30, 95% konfidensinterval 1,04-1,62) jämfört med motsvarande undersökning via femoralisartären. Under observationstiden ökade risken för procedurrelaterad stroke eller TIA parallelt med ökande antal kranskärlsröntgen och kranskärlsinterventioner via radialisartären, utan signifikant interaktion mellan observationstidens olika tidsintervaller.

Studie IV: 93 patienter med misstänkt eller stabil kranskärlssjukdom planerade för kranskärlsröntgen eller kranskärlsintervention testades med Montreal Cognitive Assessment (MoCA) före och två gånger efter kranskärlsproceduren för att undersöka om deras minnesfunktion hade försämrats efter ingreppet. I en undergrupp användes transkraniell Doppler bilateralt för att utreda ett eventuellt samband mellan cerebrala mikroembolier och minnesfunktion. Slutligen randomiserades patienterna till instickställe för att undersöka om kärlaccess hade en inverkan på minnesfunktion efter proceduren. Minnesfunktionen försämrades inte efter kranskärlsröntgen när den testades med MoCA. Det fanns ingen signifikant korrelation mellan resultaten från MoCA testen och och antalet cerebrala mikroembolier eller instickställe.

Slutsats
Val av kärlaccess och ledarteknik vid kranskärlsröntgen och kranskärlsintervention påverkade antalet cerebrala mikroembolier. Det kan finnas ett samband mellan radialisaccess och ökad risk för procedurrelaterad stroke eller TIA, vilket bör studeras vidare. Tidigare studier har visat att cerebrala mikroembolier är kopplade till nytillkomna tysta hjärninfarkter, men vi kunde inte påvisa försämrad minnesfunktion efter kranskärlsproceduren med MoCA test. Ytterligare studier krävs för att bättre kartlägga den kliniska betydelsen av cerebrala mikroembolier och för att kunna minska eller förhindra uppkomsten av procedurrelaterade ischemiska cerebrala lesioner hos patienter som genomgår kranskärlsröntgen och kranskärlsinterventioner.

List of Scientific Papers

This thesis is based on the following studies, which will be referred by their Roman numerals

I
Juliane Jurga, Jesper Nyman, Per Tornvall, Maria Nastase Mannila, Peter Svenarud, Jan van der Linden, Nondita Sarkar
Cerebral microembolism during coronary angiography
A randomised comparison between femoral and radial arterial access
Stroke. 2011;42:1475-1477.

II
Juliane Jurga, Per Tornvall, Jan van der Linden, Nondita Sarkar
Guidewire withdrawal in ascending aorta increases cerebral microembolism during coronary angiography —
A randomised comparison of two guidewire techniques
J INVASIVE CARDIOL 2014;26(1):1-6.

III
Juliane Jurga, Mihaela O. Romanitan, Mia von Euler, Lina Benson, Jan van der Linden, Bo Lagerqvist, Nondita Sarkar, Per Tornvall
Association between access site and periprocedural stroke or TIA –
A register study of 336,836 coronary angiography and PCI procedures
Submitted manuscript

IV
Juliane Jurga, Per Tornvall, Linda Dey, Jan van der Linden, Nondita Sarkar, Mia von Euler
Absence of cognitive impairment after coronary angiography and PCI-
A prospective pilot study
Submitted manuscript

List of Abbreviations

ACC/AHA	American College of Cardiology/ American Heart Association
BMI	Body mass index
CA	Coronary angiography
CAD	Coronary artery disease
CABG	Coronary artery bypass graft
CCS	Canadian Cardiovascular Society
CI	Confidence interval
CIN	Contrast-induced nephropathy
dw-MRI	Diffusion-weighted magnetic resonance imaging
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
GEE	Generalised estimating equation
h	Hour
IQR	Interquartile range
IU	International unit
MACE	Major adverse cardiac events
MACCE	Major adverse cardiac and cerebral events
MCA	Middle cerebral artery
MCI	Mild cognitive impairment
MI	Myocardial infarction
MMSE	Mini-mental state examination
NACE	Net adverse clinical event
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome
NSTEMI	Non-ST-segment elevation myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
PMD	Power motion-mode Doppler
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomised controlled trial
RR	Risk ratio
STE-ACS	ST-segment elevation acute coronary syndrome
STEMI	ST-segment elevation myocardial infarction
TCD	Transcranial Doppler
TIA	Transient ischemic attack
UAP	Unstable angina pectoris

Introduction

Historical background and technique

The first cardiac catheterisation in man is considered to have been performed by the German surgeon Werner Forssman, who in 1929, advanced a catheter for 60 cm into the right atrium via his left antecubital vein (1). For this he shared the Nobel Prize 27 years later. Sven I. Seldinger, a Swedish radiologist, contributed in 1953 to an atraumatic approach by the invention of the percutaneous technique, still the gold standard for entering blood vessels for catheterisation (2). Other milestones were the first selective coronary angiography (CA) reported by the American cardiologist Mason Sones in 1959 (3) and the first balloon angioplasty treatment, known as percutaneous transluminal coronary angioplasty (PTCA) by the German cardiologist Andreas R. Grüntzig in 1977 (4). In 1987, for the first time, the German cardiologist Ulrich Sigwart and colleagues placed a metallic scaffold, termed stent, within a diseased coronary artery segment to maintain luminal patency (5). Stents improved early and late results of balloon angioplasty. The results have been further enhanced by the release of anti-proliferative bioactive agents (drug eluting stents) (6). Since then, the broader term percutaneous coronary intervention (PCI) has been adopted which also includes the use of various devices. PCI is the most common revascularization modality practiced in patients with coronary artery disease (CAD).

During cardiac catheterisation, the Seldinger technique is applied by puncture of the vessel wall with a needle through which a flexible guidewire is advanced, remaining intravascular as the needle is withdrawn allowing a sheath to be placed upon it (Figure 1). The sheath is equipped with a back-bleed valve and a side port, supporting catheter placement and drug administration.

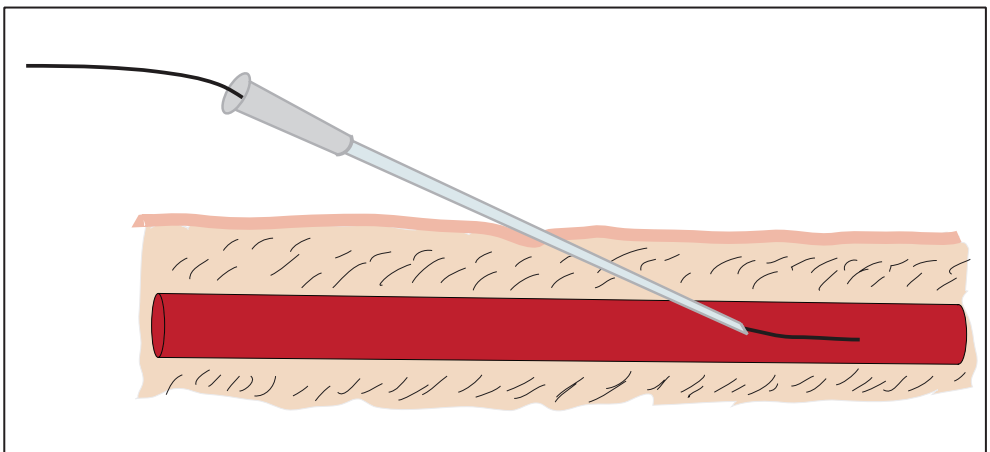


Figure 1. Seldinger technique.
The vessel is entered by a needle through which the guidewire is inserted.

Femoral Access

Since the American radiologist Melvin P. Judkins further modified selective CA in 1967, the femoral access has been the standard access for percutaneous coronary procedures, enabling the use of large sized catheters (7). The common femoral artery is punctured 1-2cm distal from the inguinal ligament (8) and a sheath is placed with the help of a guidewire. The guidewire is introduced through the sheath and advanced to the abdominal aorta followed by the insertion of a flushed catheter over the guidewire to be then advanced together with the guidewire to the thoracic aorta. Currently two catheterisation techniques exist: when applying the Judkins technique, the leading guidewire is withdrawn in the descending aorta (7), whereas catheters are advanced over the aortic arch with help of a leading guidewire using the other technique (9), (Figure 2). It is claimed that the latter technique is preferable as the risk for dislodging arteriosclerotic debris from the aortic arch is minimised (10). Operators' preference for either technique is governed by local traditions and evidence regarding the prevention of ischemic neurological complications is rare. To achieve hemostasis after the catheterisation, removal of the femoral arterial sheath is followed by either compression of the vascular entry, applied manually or by mechanical devices (FemoStop®, St. Jude Medical Inc., ST. Paul, MN, USA) or closure by vascular devices (AngioSeal®, St. Jude Medical Inc., ST. Paul, MN, USA) which reduces the time for hemostasis using a resorbing plug at the arterial puncture site (11).

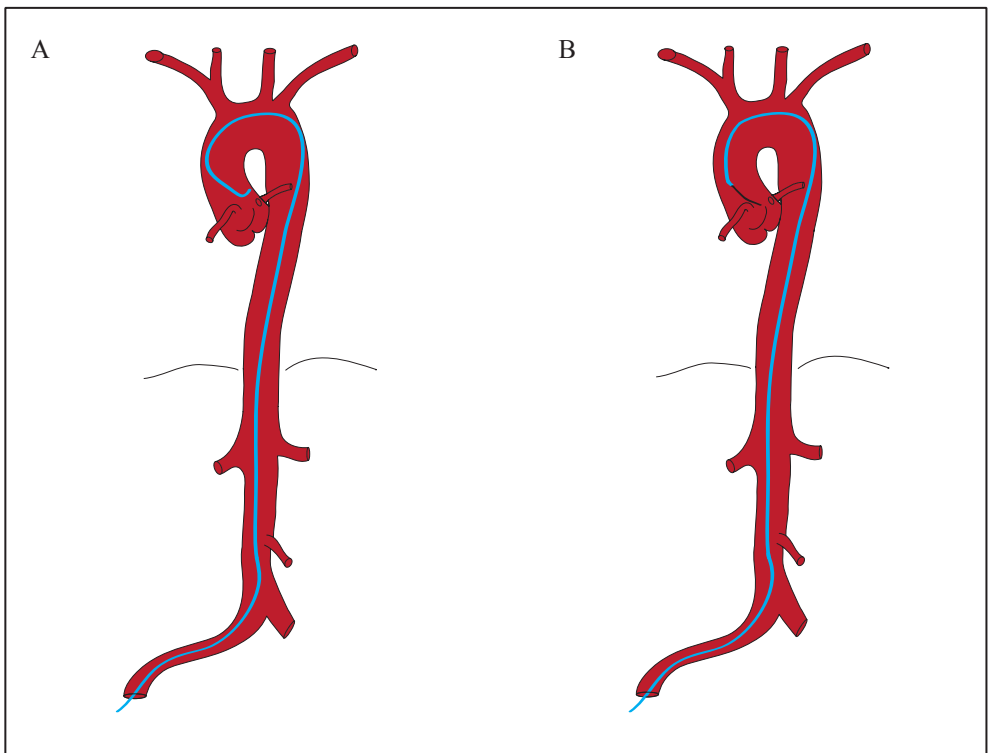


Figure 2. Catheter and guidewire techniques used with the femoral access.
Panel A shows the Judkins technique with guidewire withdrawal in the descending aorta followed by advancement of the catheter alone over the aortic arch.
Panel B shows the other technique with advancement of the catheter with help of a guidewire over the aortic arch.

Radial access

In 1989 the Canadian cardiologist Lucien Campeau reported the first transradial CA (12), further developed by Ferdinand Kiemeneij, interventional cardiologist from the Netherlands, who in 1992 performed the first transradial percutaneous coronary intervention (PCI) (13). The patency of the palmar arch should be assessed, as radial artery occlusion is reported to occur in 2-30% following transradial catheterisation (14, 15). The radial artery is punctured 1-2cm proximal of the radial styloid process and a sheath is placed with the help of a guidewire. Then 2,000-5,000 international units (IU) of heparin are administrated to avoid thrombotic radial artery occlusion (16). To prevent radial artery spasm, a "cocktail" of vasodilatators including different compositions of nitroglycerine and verapamil can be administered through the sheath (17). In comparison with the femoral access, the diagnostic catheter is advanced over a longer guidewire to the ascending aorta. As the right radial access is mainly used (18), the catheter has to be advanced from the radial, brachial and subclavian artery to the brachiocephalic trunk, where it has to bend sharply into the ascending aorta on its way to the coronary orifices. In addition to anatomical variations of the radial artery including loops and bifurcations, tortuosities at all other levels proximal from the radial artery can appear, requiring caution and readiness to change access (19). The radial sheath is directly removed after completion of the catheterisation procedure and a compression device (i.e. TR Band®, Terumo Corp., Tokyo, Japan) is placed over the puncture site to achieve hemostasis.

Although technically more demanding, recently the radial access has been increasingly used, in over 80% of all catheterisations in Sweden (20), 40% in Europe and 16% in the USA (21, 22). This is mainly explained by fewer major access site bleedings compared with the femoral access (23, 24) leading to mortality benefits for patients with STE-ACS (25) where access site bleeding represents 30-70% of total bleeding events (26). Despite this, there have been concerns about higher rates of procedure-related ischemic cerebral embolic events with the radial access (27).

Radial versus femoral access

Advantages of the radial artery access include the superficial anatomic position enabling easy compression, absence of important adjacent structures, faster time to ambulation, high patient preference and reduced periprocedural discomfort in a mixed population (28, 29). Compared to men, women are recognised as having smaller radial arteries and may be more prone to spasm, which has been shown to be a major cause of procedure failure with the radial access (30, 31). When quality-of-life and impairment of functional status were examined following CA and PCI, women, asked for repeat procedures, preferred the radial compared with the femoral access, although there was no difference in these factors between the access sites (32). Limitations of the radial access comprise small artery size restricting the use of some interventional devices for complex procedures and higher radiation exposure (19, 33).

Different studies have compared the radial and femoral access for cardiac catheterisations in terms of clinical outcome. When Agostoni and co-workers published the first meta-analysis the aim was to combine several small sized randomised controlled trials (RCT) to achieve more statistical power (34). They found a similar risk for major adverse cardiac events (MACE), but substantially fewer vascular access site complications with the radial access compared to the femoral access (34). Five years later, Jolly and co-workers published a meta-

analysis including twice as many patients and concluded that the radial access was associated with a reduction in major bleedings, but without an effect on the combined endpoint death, myocardial infarction (MI) and stroke (35). With inclusion of observational studies and RCTs in a huge meta-analysis consisting of over 750,000 patients treated with PCI, Bertrand and co-workers confirmed fewer major bleedings and demonstrated reduced mortality with the radial compared with the femoral access. The mortality benefit was mainly due to observational studies (23). More recently published studies focused on high-risk groups when comparing outcome according to access site. Both Karowni and co-workers (25) and Pancholy and co-workers (36) associated the radial access with mortality benefits in patients with ST-segment elevation myocardial infarction (STEMI), but the latter included only patients in cardiogenic shock, from cohort studies. Notwithstanding the value of combining studies to generate a large sample size, meta-analyses have several limitations: besides selection bias, heterogeneity of the studies included, different primary end-points (in hospital versus 30 day mortality), operator or centre experience, type of procedure (some studies include CA), patient cohort (proportion of ACS patients), and substantial disparities of bleeding definitions used.

The RIVAL trial, presented in 2011, the first large-scale RCT comparing outcome of the two vascular access sites, showed no difference for the composite endpoint of death, MI, stroke, and non-coronary artery bypass graft (non-CABG) related major bleeding in ACS patients undergoing CA with possible intervention, while the subgroup analysis showed benefits for STEMI patients with the radial access (37). The RIFLE-STEACS trial, published one year later, has demonstrated beneficial outcome for STE-ACS (ST-segment elevation acute coronary syndrome) patients treated via the radial compared with the femoral access in the composite of cardiac death, stroke, MI, target lesion revascularization and bleeding (38). These findings were confirmed by the STEMI-RADIAL trial (39). When the composites of the combined endpoint were analysed separately, bleeding rates and cardiac mortality were significantly lower in the radial arm of the RIFLE-STEACS trial, whereas the STEMI-RADIAL trial did not show a significant reduction in mortality despite the similarity in patient cohorts and primary endpoints (38, 39). Obviously, the latter negative finding may be explained by the smaller sample size in STEMI-RADIAL (39), but due to earlier ambulation with the radial access, in-hospital stay was 1 day shorter with the radial than with the femoral access in RIFLE-STEACS, which may be a potentially contributory factor to a reduced mortality (38). In the recently published MATRIX study, the radial access, in comparison with the femoral access, decreased the composite endpoint rate of death, MI, stroke or bleeding in ACS patients by a reduction in major bleeding and all-cause mortality (40).

Although considerably higher compared to register-based incidence (0.3-0.7%), no significant difference in stroke incidence was reported in the above mentioned RCTs including an updated meta-analysis presented with the MATRIX results (37-40). Given the low incidence of procedure-related stroke or transient ischemic attack (TIA), adequately powered RCTs are difficult to implement. Thus, these RCTs were not designed to evaluate procedure-related stroke or TIA rates. Recently published observational studies have addressed this question. In a rather small single centre study, Raposo and co-workers did not find significant differences in stroke or TIA rates between the access sites when analysing 27 patients with confirmed diagnosis of stroke and TIA (41). No association between vascular access site and neurological complications was reported by Ratib and co-workers based on data from a PCI registry including over 300,000 patients (42). However, register studies could lack accuracy regarding the reported neurological complications and are influenced by several confounders.

Table 1. Overview of studies comparing outcome according to vascular access sites for CA and PCI.

Author/ Study	Type of study	Years	Number of patients/ Number of studies	Primary endpoint R vs. F	Secondary endpoint R vs. F
Agostoni, P (34)	Meta-analysis	1994-2003	3,224 12 RCTs (7 CA studies, 5 PCI studies incl. 2 studies ACS/MI)	MACE OR 0.92 (95% CI 0.57-1.48)	Vascular access site complication OR 0.20 (95% CI 0.09-0.42)
Jolly, S (35)	Meta-analysis	1994-2006	7,020 23 RCTs (6 CA studies, 17 PCI studies incl. 6 studies STE-ACS)	Major bleeding OR 0.27 (CI 0.16-0.45) n=4,458	Composite death, MI, stroke OR 0.71 (CI 0.49-1.01) n=4,083
Bertrand, OF (23)	Meta-analysis	1995-2011	761,919 76 (15 RCT, 61 observational studies)	Major bleeding OR 0.22 (95% CrI 0.16-0.29)	Mortality OR 0.56 (95% CrI 0.45-0.67)
Pancholy, SB (36)	Meta-analysis	2012-2014	8,131 8 (1 RCT, 7 cohort studies, cardiogenic shock only)	30 day all-cause mortality RR 0.6 (95% CI 0.52-0.71)	30 day MACCE RR 0.68 (95%CI 0.63-0.73)* 6 studies
Karowni, W (25)	Meta-analysis	2003-2012	5,055 STE-ACS 12 RCTs	Mortality OR 0.55 (95% CI 0.4-0.76)	Major bleeding OR 0.51 (95%CI 0.31-0.85) Stroke OR 1.07 (95% CI 0.45-2.54)
Ratib, K (42)	Retrospective (multi-centre)	2006-2010	348,092 PCI procedures	NC OR 0.99 (95% CI 0.79-1.23)	
Raposo, L (41)	Retrospective (single centre)	2006-2012	16,710 procedures (40% PCI)	Periprocedural stroke/TIA OR 1.21 (95% CI 0.49-2.98)	
Jolly, S RIVAL (37)	RCT (158 centres)	2006-2010	7,021 ACS (7,005 CA, 4,660 PCI)	30 day composite death, MI, stroke, non-CABG bleeding HR 0.92 (95% CI 0.72-1.17)	30 day composite death, MI, stroke HR 0.98 (95% CI 0.76-1.28) 30 day non-CABG major bleeding HR 0.73 (95% CI 0.43-1.23)
Romagnoli,E RIFLE STE-ACS (38)	RCT (4 centres)	2009-2011	1,001 STE-ACS (Primary PCI)	30 day NACE HR 0.7 (95% CI 0.5-0.9)	Cardiac death 5.2% vs. 9.2% (95% CI 0.8%-7.3%) Bleeding 7.8% vs. 12.2% (95% CI 2.7%-12.0%) MI, target vessel revascularization, stroke= ns
Bernat, I STEMI -RADIAL (39)	RCT (4 centres)	2009-2012	707 STEMI	30 day bleeding and access site complication 1.4% vs.7.2%, p<0.001 30 day NACE 4.6% vs.11%, p<0.01	Composite death, MI, stroke= ns Mortality rate at 30 days and 6 month = ns
Valmigli, M MATRIX (40)	RCT (78 centres)	2011-2014	8,404 ACS	MACE RR 0.85 (95% CI 0.74-0.99) ** NACE RR 0.83 (95% CI 0.73-0.96)	Major bleeding RR 0.67 (95% CI 0.49-0.92) Mortality RR 0.72 (95% CI 0.53-0.99)

*CA= coronary angiography, CrI= credible interval, F= femoral access, OR= odds ratio, R= radial access, RCT= randomised controlled trial, RR= risk ratio, PCI= percutaneous coronary intervention, MACE=major adverse cardiac events, MACCE= major adverse cardiac and cerebral events, NACE= net adverse clinical event (composite of cardiac death, stroke, myocardial infarction, target lesion revascularization, bleeding), NC= neurological complication, ns= not significant, STE-ACS= ST-segment elevation acute coronary syndrome, **p=0.03 not significant at predefined α<0.025.*

In addition to being large-scale, high-quality register-based studies have the capability to shed light on the question of whether vascular access site has an impact on procedure-related stroke or TIA , which was the reason for designing **Study III.**
The above discussed studies are summarised in Table 1.

Indications for CA and PCI

According to European and American guidelines, noninvasive stress testing is appropriate for initial diagnosis and risk stratification for most patients with suspected ischemic heart disease (43, 44). However, CA is the gold standard in evaluating the diagnosis and determining the treatment of patients with ischemic heart disease, with annually 40,000 and 2 million procedures performed in Sweden (20) and in the United States, respectively (45). The intraluminal obstruction of a coronary artery is visualised two-dimensionally with CA, but the extension of the atheroma within the vessel wall and the functional significance of the stenosis can only be assumed. By combining CA with further invasive intravascular modalities such as intravascular ultrasound (46), optical coherence tomography (47) and fractional flow reserve (48), appropriate treatment strategies can be determined.

Depending on clinical situations, indications for CA can be separated into three main categories: (i) assessment in stable and (ii) unstable CAD and in special conditions (iii). Furthermore it should be considered whether CA is performed due to symptomatic or prognostic reasons.

Thus, patients with severe stable angina pectoris, classified as Canadian Cardiovascular Society (CCS) grade III, which is equal to marked limitation after one flight of stairs (49), despite optimal medical treatment, have a recommendation for CA followed by revascularization for symptom relief in accordance with the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines (43, 44). Mild symptoms are accepted only in patients in whom non-invasive risk stratification indicates a high-event risk, aiming for revascularization for improvement of prognosis (44).

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) as an entity of unstable CAD that should be treated invasively, which is recommended in both the ESC and ACC/AHA guidelines (50, 51) due to morbidity benefits (reduced risk for recurrent ACS episodes, rehospitalisations and revascularization) (52-54). Also a survival benefit after invasive treatment in NSTE-ACS has been suggested, but convincing evidence is lacking as different meta-analyses have shown divergent results. A Cochrane review found no improved survival (52), Fox and co-workers found a risk reduction in high-risk patients (53) whereas Bavry and co-workers reported a reduced risk for mortality following invasive compared with conservative treatment (54). The optimal timing for early invasive approach is still subject to research, although high-risk patients with NSTE-ACS should undergo CA with subsequent revascularization within 24 hours (h) from the onset of symptoms (51).

Timely invasive management with primary PCI of patients with ST-segment elevation acute coronary syndrome (STE-ACS) is superior to fibrinolysis to restore blood flow in the infarct-related artery, in terms of survival, intra-cranial haemorrhage and recurrent MI (55). This approach is therefore recommended by the ESC and ACC/AHA guidelines as first-line treatment in areas with PCI facilities available (56, 57).

Table 2. Indication for coronary angiography with number and proportion of patients in the Swedish Angiography and Angioplasty Registry (SCAAR) performed 2014 (20).

Indication	Number	Proportion (%)
NSTEMI	8 491	21.2
Stable angina pectoris	8 265	20.7
Unstable angina pectoris	6 678	16.7
STEMI	5 418	13.6
Unspecified chest pain	3 136	7.8
Investigation for congenital heart defects and valve pathologies	2 931	7.3
Investigation for congestive heart failure/cardiomyopathy	1 700	4.3
Arrhythmia investigation	945	2.4
Other	395	1.0
Cardiac arrest no STEMI	380	1.0
Silent ischaemia	335	0.8
STEMI >24h	308	0.8
Cardiac arrest with STEMI	220	0.6
Pre- or post transplant investigation	219	0.5
Aortic aneurysm/dissection	158	0.4
STEMI/Rescue PCI	136	0.3
Risk assessment after successful thrombolysis	85	0.2
Suspected complication after angiography/PCI	75	0.2
Suspected complication after CABG	54	0.1
Research and development	16	0.0
Angiography not possible to perform	11	0.0
Mechanical complication after MI	9	0.0
Total	**39 965**	**100.0**

CABG= coronary artery bypass graft, NSTEMI= non-ST-segment elevation myocardial infarction, MI= myocardial infarction, PCI= percutaneous coronary intervention, STEMI= ST-segment elevation myocardial infarction

Also, survivors of cardiac arrest should undergo CA (56), as 80% have ACS as a precipitating factor (58, 59). Special conditions for elective CA comprise heart failure, heart transplant, structural heart disease or valve disease and preoperative risk assessment for non-cardiac surgery. Table 2 summarises the indications for CA by showing the proportions of CAs performed in Sweden in 2014.

Complications of CA and PCI

The spectrum of procedure-related complications varies from minor without leaving sequelae to major complications including death. Periprocedural complications are influenced by multiple components such as patient-related factors (age, burden of other diseases), cardiac anatomy (severe CAD/left main disease, structural heart disease), the clinical situation,

Table 3. Comparison of access site complications according to puncture site.

	Radial Access	**Femoral Access**
Vascular access site complications	0.2-0.5% (24, 34, 79) Radial artery spasm (2-22%) (19) Radial artery occlusion (1.5-33%) (19) Radial artery perforation (1%) (80) Pseudoaneurysm (~1%) (81) AV fistula (0.2-0.4%) (19) Radial artery avulsion (*) (19, 82) Acute hand ischemia (*) (14)	0.5-0.7% (24, 62, 68) Femoral artery thrombosis/occlusion (0.2%) (68) Dissection (< 0.1%) (68) Pseudoaneurysm (0.3-7%) (68, 83) AV fistula (1%) (84)
Bleeding	Puncture site (0.8%) (24) Forearm haematoma (~1%) (81) Compartment syndrome (<0.5%) (85, 86)	Puncture site (1.8%) (24, 87) Retroperitoneal bleeding (0.74%) (88)
Others, very rare	Sterile granuloma (*) (19) Catheter entrapment (81) Radial nerve injury (*) (19)	

(*) case reports

type of procedure performed and also operator experience. The procedure-related mortality risk is 0.1% for cardiac catheterisation (60-62) and 1.4-2.2% for PCI procedures (63-65). Other major periprocedural complications include MI 0.1% for CA (62, 66) and 0.4-20% for PCI (63, 67), depending on the definition used for MI (Q-wave versus creatine kinase-MB fraction elevation in blood sample). Vascular complications are reported to occur equally often (0.5%) for CA and PCI (62, 68, 69). Bleeding is the most common complication, reported as major bleeding in registries at a rate between 1.7-5.4% (20, 69-72) and is associated with a significant morbidity and mortality (70). Different strategies to avoid bleeding should be considered, including the choice of access site. The radial access has been associated with less access site bleeding (23, 24). Table 3 summarises access site complications. Other procedure-related complications include allergic reactions, due to nonionic iodinate contrast media, with a rate of 0.1-0.7% (73-75) and contrast induced nephropathy (CIN). CIN, defined as a serum creatinine raise of >25% above baseline or >44μmol/L 48h after contrast administration, has an overall incidence of <2%, but has at least a 10-fold higher incidence in high-risk patients i.e. in patients with diabetes mellitus, pre-existing renal impairment or heart failure (76). Various arrhythmias may occur during CA and PCI, most likely ventricular premature beats that are related to catheter placement during ventriculography. Ventricular tachycardia or ventricular fibrillation can follow prolonged intracoronary contrast injections and are reported in 0.1% (62). Furthermore, radiation exposure entails adverse effects, partly as direct radiation-induced injuries, but also by increasing the exposed´s life-time cancer risk (77, 78). Figure 3 depicts an overview of procedure-related complications in SCAAR in 2014 (16).

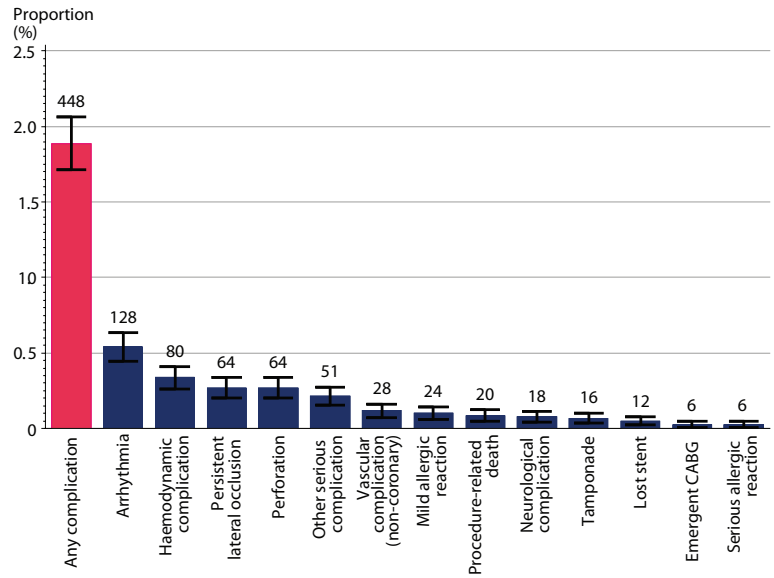


Figure 3. Overview of procedure-related complications in PCI patients, reported from the catheterisation lab in SCAAR 2014 (number of complications above the bar, 95 % CI) (20).

Procedure-related stroke or TIA in patients undergoing CA and PCI

Procedure-related neurological complications consist mainly of stroke and TIA. But also other neurological symptoms such as migraine, sedative-induced delirium (89), seizures, confusions, conditions related to cerebral hypoperfusion and peripheral nerve injury are reported to occur during coronary procedures **(Study III)**. Thus, the term neurological complications may not only comprise procedure-related stroke or TIA.

Procedure-related stroke is rare with an incidence ranging between 0.1 and 0.3 % for CA (89, 90) and 0.1-0.4% for PCI (42, 91, 92) and the rate is influenced by the definition and by the study type. Single centre studies with specific neurological assessment and comprehensive use of brain imaging techniques tend to report somewhat higher incidence (91, 93). Several factors are known to be associated with an increased risk for procedure-related stroke. Those can be categorised as patient-related (previous stroke, previous CABG, renal failure) (91, 92, 94, 95), situation-related (urgent, STE-ACS or NSTE-ACS) (92, 94, 95) and technical aspects (number and size of the catheters, fluoroscopy time) (89, 93). The impact of the vascular access site on procedure-related stroke or TIA as a primary endpoint has been assessed in register-based studies without showing significant differences between the femoral and radial access site (42). Prospective randomised trials, conducted to compare morbidity and mortality, mainly in patients with ACS, between access sites, also did not report significant differences in procedure-related stroke (37, 40). To date, no randomised controlled trial has been specifically designed to answer this question.

Clinical silent cerebral ischemic lesions and CA and PCI

In contrast to the low incidence of procedure-related stroke or TIA after CA and PCI, cerebral microemboli have frequently been observed during various cardiac procedures with transcranial Doppler technique (27, 96, 97). Cerebral microemboli can consist of air bubbles, fat emboli, atheromatous material or blood clots (98) and have been related to new ischemic lesions found on cerebral magnet resonance imaging (MRI) with diffusion-weighted imaging (dw) sequences (27, 99). Silent brain infarcts lack stroke-like symptoms but can cause subtle neurological deficits such as depressive symptoms, visual field deficits, arm and leg disturbances and frailty (100). To date no standard definition for "silent" infarction exists, thus a silent infarction might be a cerebral infarction that was unnoticed or overlooked as well as an "asymptomatic" patient who may have mild facial paresis or reflex abnormity (101). Although their clinical impact is undecided, silent ischemic lesions have been linked to cognitive impairment and to increasing the risk for dementia (27, 100).

Mild cognitive impairment

Mild cognitive impairment (MCI) is a preclinical stage of dementia on the continuum of cognitive decline from normal ageing to dementia with a prevalence of 10-20% for adults over 65 years of age (102). In contrast to dementia, activities of daily living are preserved (102). Besides increasing age and male gender, further risk factors have been identified such as low educational level, vascular risk factors (hypertension and diabetes mellitus), vitamin D deficiency, sleep apnoea and previous critical illness (102). A higher educational level has been associated with a lower prevalence of dementia perhaps through increasing the cognitive reserve (103, 104). The risk for conversion from MCI to dementia is estimated to be between 2-20% depending on the population studied (105).

Background summary

CA and PCI are commonly used for diagnosing and treatment of patients with coronary artery disease. Overall, the procedure-related complication rate is 0.1-5% (60-62, 106), with 0.1-0.4% procedure-related stroke or TIA (89, 91, 92). The occurrence of procedure-related silent ischemic cerebral lesions, associated with cognitive decline (27, 100), is significantly higher (2-35%) (107) and related to cerebral microemboli (27, 99, 108). Different techniques exist for CA and PCI including the choice of access site. The radial access, increasingly used over time, is shown to be beneficial for patients with STE-ACS, as access related bleedings are significantly reduced compared with the femoral access, resulting in lower mortality for this patient group (25). Notwithstanding those advantages, the relation between vascular access site and procedure-related stroke or TIA and silent ischemic cerebral lesions are not thoroughly studied. Furthermore, evidence regarding how to advance the guidewire when using the femoral access is lacking. With an ageing population, minimising the risk for overt and silent ischemic cerebral lesions is relevant. The choice of technique used for diagnostic and interventional procedures which carry the lowest risk for neurological complications is of importance. The purpose of this thesis was to scrutinise these gaps of knowledge.

Aims

The aim of this thesis was to investigate if different techniques used for CA and PCI influence the occurrence of procedure-related ischemic cerebral complications.

The specific aims of the studies were to investigate:

1. if the number of cerebral microemboli in the middle cerebral arteries differs when the radial and femoral access are used during CA in patients with stable angina pectoris **(Study I)**.

2. if the number of cerebral microemboli in the middle cerebral arteries differs between two techniques used for CA with the femoral access, where catheters are advanced with or without a leading guidewire over the aortic arch **(Study II)**.

3. retrospectively, if the vascular access site used for CA or PCI is associated with procedure-related stroke or TIA **(Study III)**.

4. if cognitive function is impaired after CA or PCI and to explore its possible relationship to the number of cerebral microemboli detected in the middle cerebral arteries and the vascular access site used **(Study IV)**.

METHODS

Study groups

This thesis is based on four studies which evaluate the different techniques used for CA and PCI regarding procedure-related ischemic cerebral lesions in patients with suggested or established CAD. As described in Figure 4 in **Studies I, II and IV** 185 patients were prospectively enrolled. Using a register, in **Study III** 336,836 CA and PCI procedures, corresponding to 255,609 individual patients, were assessed retrospectively.

Study I, a prospective randomised trial, included 51 patients with stable angina pectoris, who had been referred for diagnostic CA to the Karolinska University Hospital/Solna between February 2007 and June 2008. Exclusion criteria were valvular heart disease, previous CABG, a pathological Allan´s test (collateral circulation of the right radial artery (109)), advanced kidney disease with an estimated glomerular filtration (eGFR) rate below 30 ml/min (Cockroft-Gault formula), and if both middle cerebral arteries (MCAs) were not detectable with TCD. All patients were treated with aspirin prior to CA.

After randomisation to the radial or femoral access, the CA procedure was divided into 6 predefined steps reflecting catheter exchange and engagement of the coronary ostia (Table 4). CA was performed by two interventional cardiologists with one catheter for the right and one for the left coronary artery, respectively. When the radial access was used a pharmacological "cocktail" consisting of 5,000 IU heparin, 250 µg glycerylnitrate, and 2.5 mg verapamil hydrochloridium in 15 ml of saline was injected into the 6 Fr Flexor Radial sheaths (Cook Group Inc., Bloomington, IN, USA). Directly after its insertion 6 Fr JL 3.5 and JR 4 catheters

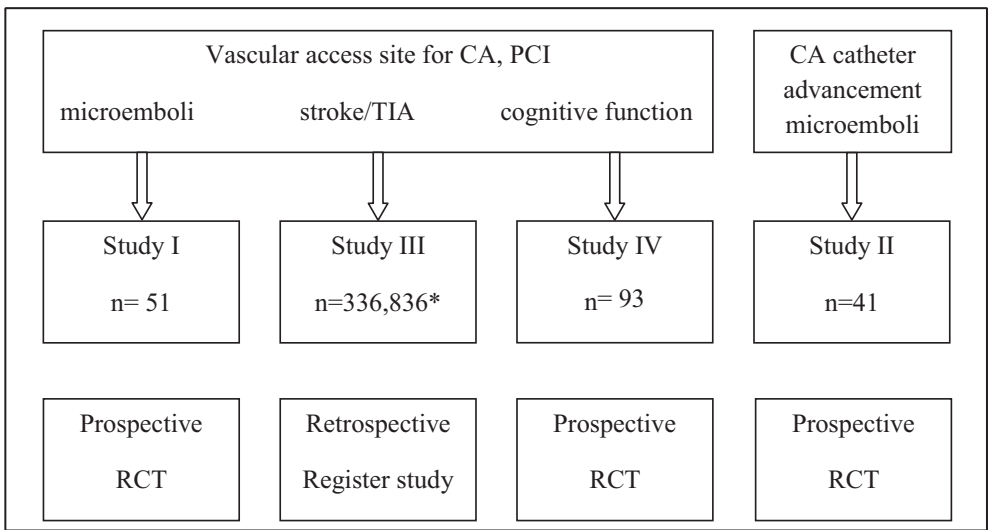


Figure 4. Studies included in this thesis.
*= procedures

(Boston Scientific Corp., Boston, MA, USA) were advanced to the valsalva sinus and exchanged over the wire using 0.035" 250 cm guidewires (Cordis Corp., Fremont, CA, USA). For the femoral access Ultimum 6 Fr sheaths (St. Jude Medical Inc., ST. Paul, MN, USA) were used, 6 Fr JL and JR 4 catheters (Boston Scientific Corp., Boston, MA, USA) and 0.035" 150 cm guidewires (Boston Scientific Corp., Boston, MA, USA) were advanced to the ascending aorta. Prior to use, all catheters and guidewires were heparinised. All patients received a standard contrast medium Visipaque 320 mg/ml® (GE Healthcare, Little Chalfont, UK). Fluoroscopy time and delivered contrast volume were recorded. Simultaneously, cerebral microemboli were measured with the transcranial Doppler (TCD) technique, whereby both the right and the left MCA were insonated. Additionally, with help of a synchronised clock, the TCD recording was correlated to the predefined stages of the CA procedure.

Study II, a prospective randomised trial, included 41 patients with stable angina pectoris or non-ST-segment elevation acute coronary syndrome (NSTE-ACS), who had been referred for CA to the Karolinska University Hospital/Huddinge. Exclusion criteria were ST-segment elevation myocardial infarction (STEMI), advanced kidney disease with eGFR below 30 ml/min (Cockroft-Gault formula) and if both MCAs were not detectable with TCD.

CA was performed with the femoral access using similar sheaths, guidewires, catheters and contrast medium as described for the femoral access in **Study I**. The study protocol comprised of two parts: part one consisted of catheter and guidewire advancement including diagnostic

Table 4. Procedural stages of the CA.

Procedural stage	**Practical implementation**
1. Arterial access	• Insertion and flushing of the introducer
2. Insertion of the first catheter	• Insertion of the guidewire* • Insertion of the catheter • Removal of the guidewire • Withdrawal of blood and flushing of the catheter
3. Coronary angiography	• Engagement of the coronary ostium • Contrast delivery
4. Exchange of the catheters	• Disengagement of the catheter • Introduction of the guidewire • Removal of the first catheter • Insertion of a new catheter • Removal of the guidewire • Withdrawal of blood and flushing of the catheter
5. Coronary angiography	• Engagement of the coronary ostium • Contrast delivery
6. Removal of the guidewire and the catheter	• Disengagement of the catheter • Introduction of the guidewire • Removal of the guidewire and the catheter

(*) with the femoral access the guidewire and the catheter were inserted together

CA followed by part two, where only catheters and guidewires were advanced as opposed to part one. In part one, patients were randomised to either catheter and guidewire advancement in the ascending aorta or to withdrawal of the guidewire in the descending aorta, and catheter advancement alone over the aortic arch. Following this protocol, both techniques were used in each patient; the randomisation was used to ensure an equal chance for either technique to start with. The study protocol is depicted in Figure 9. Independent of randomisation, more than 10 ml of blood was aspirated and discarded and all catheters were flushed with 20 ml of heparinised saline. Ventriculography, aortography, intracoronary pressure measurement or PCI were performed when indicated, but always after the study protocol was accomplished. Cerebral microemboli were detected using TCD in a similar setting as described in **Study I**.

In **Study III** all CA and PCI procedures performed between 2003 and 2011 listed in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) with information on access site were assessed retrospectively regarding the occurrence of procedure-related neurological complications. To increase the accuracy of the outcome variable, medical records of the patients, in whom a neurological complication had been reported, were collected from the treating hospitals, reviewed by two independent neurologists, and determined to be procedure-related if the onset was within 24h of the procedure in the absence of atrial fibrillation. Neurological complications were categorised as stroke or TIA (ischemic stroke and intracerebral haemorrhage but not subarachnoid haemorrhage), other neurological complications or no neurological complication. Including centre experience (with experienced centre defined as when more than 50% of the procedures were performed with the radial access per year), data on co-morbidity from SCAAR and the National Patient Register (NPR), a regression analysis was performed to determine the Risk Ratio (RR) for procedure-related stroke or TIA of the radial access compared with the femoral access.

Study IV, a prospective randomised trial, included 93 patients with stable angina pectoris who had been referred for CA or PCI at the Karolinska University Hospital between September 2011 and March 2012. Exclusion criteria were previous CABG, advanced kidney disease with an eGFR below 30 ml/min (CKD-epi formula), a pathological Allan´s test and language difficulties in Swedish.

Patients were randomised to either the radial or femoral access site and their cognitive function was assessed repeatedly with help of the Montreal Cognitive Assessment (MoCA). The baseline test was executed before the procedure, while the first and the second follow-up MoCA tests were scheduled for 3 and 30 days, respectively, after the procedure. In a subgroup of 35 patients cerebral microemboli were registered with TCD during the CA or PCI procedure in a similar setting as described in **Studies I and II**.

Transcranial Doppler and microemboli detection

The transcranial Doppler (TCD) technique is a noninvasive ultrasound method for measurement of blood flow velocity in cerebral arteries based on the principle of the Doppler effect. Introduced in 1982 by Aaslid (110) to detect intracranial vasospasm in patients with subarachnoid haemorrhage, it is still used for this purpose. Other clinical applications include diagnosis of cerebrovascular ischemia (steno-occlusive disease, acute ischemic stroke), monitoring of blood flow velocity, and assessment of intracranial arteriovenous malformations, cerebral microemboli, and cerebral circulatory arrest (111).

Ultrasound waves are emitted from the probe, transmitted through the skull and reflected by moving red blood cells within the cerebral vessels. The difference between the emitted and reflected waves is referred to as the Doppler shift frequency. For the TCD measurement, a 2 MHz frequency ultrasound probe was used (Embodop®, DWL, Singen, Germany), to allow penetration through thinner regions of the skull. The trans-temporal window enables the identification of the intracranial carotid artery bifurcation, after which the middle cerebral artery (MCA) can be insonated by a flow direction towards the probe (111, 112).

Ultrasound waves are deflected by microemboli and emerge as high-intensity transient signals (HITS). The multi-frequency technique enables automatic differentiation, as the backscatter of gaseous and particulate microemboli are different; i.e. particulate emboli reflect more ultrasound at the higher than at the lower frequency, whereas it is the opposite for gaseous microemboli, Figure 5 (113-115).

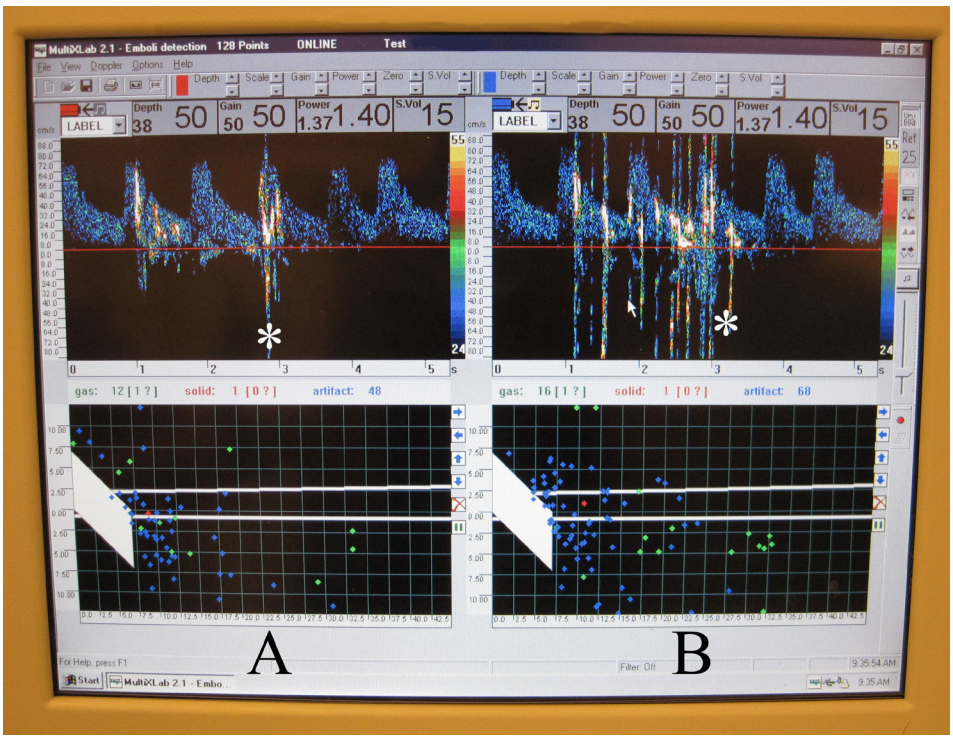


Figure 5. Display of TCD with MCA and HITS.
The upper panels on the left side show the pulse wave of the left middle cerebral artery (A) and the right middle cerebral artery (B). Occurrence of high-intensity transient signals (HITS) is shown in the upper panel, marked with asterisk (*). Their differentiation is shown in the lower panel as artefacts (blue dots), gaseous (green dots), and particulate (red dots) microemboli.

In **Studies I, II** and **IV** a multi-frequency TCD was used. The detection level for microemboli was set as a 7 dB or greater increase above background level (embolus blood ratio [dEBR]) that lasted 4 ms or longer simultaneously in both 2.0- and 2.5-MHz frequency channels. The MCAs of the patients were detected at a depth of 40 to 55 mm. The sample volume was 13 mm, no filter, a power of 200 mW, and a scale of 80 cm/s was applied. To facilitate online rejection of artefacts a reference gate was set 15 mm superficial to the MCA insonation gate. Transcranial Doppler monitoring was recorded continuously from start of sheath insertion and until the final catheter had been withdrawn, emboli were automatically counted and differentiated into particulate and gaseous and in **Studies I and II** correlated to predefined procedural steps during CA (111, 113-115).

Registers

The Swedish Coronary Angiography and Angioplasty Registry (SCAAR), established 1998 and exclusively supported by Swedish Health Authorities, is part of the nationwide internet-based Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) register. All 30 centres performing CA and PCI in Sweden report every procedure directly on-line to the register. SCAAR contains information about patient characteristics, indications for CA and PCI, procedural details, choice of intervention as well as outcome data. Since 2001 data from all hospitals are verified by comparing 50 entered variables in 20 randomly selected interventions per hospital and year with the patients' hospital records, with an overall correspondence of 95.2% (116). SCAAR was used in **Study III**, where all CA and PCI procedures performed between 2003 and 2011 were assessed and included in the analysis if their vascular access site was recorded.

The Swedish National Patient Register (NPR) has complete nationwide coverage and was used in **Study III** to acquire data on co-morbidity used in the regression analysis. By merging SCAAR data with NPR at the time of the procedure, primary and secondary International Classification of Diseases, tenth revision codes (ICD-10) were obtained from 1997 until 2010.

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) test is a screening tool with good sensitivity (80-100%) and specificity (50-76%) compared with neuropsychological tests for detection of mild cognitive impairment (117, 118). The MoCA test assesses major cognitive domains such as visuospatial / executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation in 10 to 15 minutes, is easy to administer and to interpret. To minimise the learning effect from multiple testing, we used the MoCA test in **Study IV** serially with two different versions, with permission from the author.

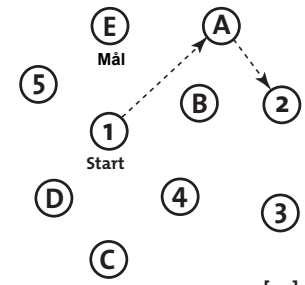
Endpoints

In **Studies I and II** the primary endpoint was the number of cerebral microemboli. The primary endpoint in **Study III** was procedure-related stroke or TIA. In **Study IV** cognitive impairment was the primary endpoint, whereas the relation to cerebral microemboli and to vascular access site were secondary and tertiary endpoints, respectively.

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Svensk version / Swedish version

NAMN :
Utbildning : Födelsedatum :
Kön : DATUM:

VISUOSPATIAL / EXEKUTIV — Poäng



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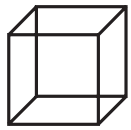

Rita av kuben [ ]

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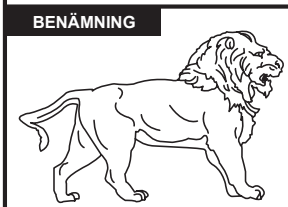

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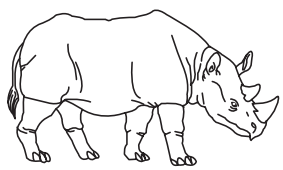

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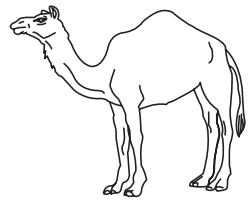

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MINNE — Läs orden, försökspersonen ska återge dem. Gör 2 försök. Prova igen efter 5 minuter.

	STOL	PLÅNBOK	TÅNG	MUNSPEL	SAX
Försök 1					
Försök 2					

Inga poäng

UPPMÄRKSAMHET — Läs en nummerlista (1 siffra/sek) Försökspersonen ska repetera i samma ordning [ ] 2 1 8 5 4
Försökspersonen ska repetera baklänges [ ] 7 4 2 __/2

Läs bokstäverna. Försökspersonen knackar i bordet var gång "A" läses. (inga poäng för mer än två fel)
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Upprepa subtraktion av 7 från 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4-5 korrekta: 3p, 2-3 korrekta: 2p, 1 korrekt: 1p, 0 korrekta: 0p __/3

SPRÅK — Upprepa: "Jag vet att det är Johan som ska få hjälp idag" [ ]
"Katten gömde sig alltid under soffan när det var hundar i rummet" [ ] __/2

Ordflöde / Ange på en minut så många ord som möjligt som börjar på bokstaven F [ ] _____ (N ≥ 11 ord) __/1

ABSTRAKTION — Likhet mellan t.ex. banan - apelsin = frukt [ ] tåg - cykel [ ] klocka - linjal __/2

FÖRDRÖJD ÅTERGIVNING

	Måste komma ihåg orden utan hjälp	STOL [ ]	PLÅNBOK [ ]	TÅNG [ ]	MUNSPEL [ ]	SAX [ ]	Poäng endast för korrekta svar utan hjälp.
Valfritt	Hjälp med kategori						
	Hjälp med alternativ						

__/5

ORIENTERING [ ] Datum [ ] Månad [ ] År [ ] Dag [ ] Plats [ ] Ort __/6

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Svensk översättning: Thomas Lindén MD

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30
Lägg till 1p om max 12 års utbildning

Administrerat av: _____

Figure 6. The MoCA test, Swedish version (118a).

Statistical methods

Numerical non-normally distributed data were presented as medians and interquartile ranges (IQR) and compared with the Mann-Whitney U-test (**Study I, II, IV**) such as the number of cerebral microemboli or the difference in MoCA test results between access site groups. More than two groups were compared with the Kruskal-Wallis test (**Study II**). Categorical data such as baseline characteristics were compared with the χ^2 test and Fisher´s exact test (**Study I**). For pairwise comparison the Wilcoxon signed-rank test was used (**Study II, IV**). Correlation analysis between the number of cerebral microemboli and difference in MoCA test results between baseline and follow up was performed with the Spearman rank test (**Study IV**). In **Study III**, associations between verified procedure-related stroke or TIA and predefined clinical variables were estimated using a generalised estimating equation (GEE) model with an autoregressive correlation matrix to allow for possible dependence in repeated procedures on the same patient. Multiple imputation using predictive mean matching was applied when data were missing. Additionally, a propensity score for vascular access site was estimated for each procedure and included in another GEE model together with access site.

All statistical tests were two-tailed with a significance level of 0.05. Statistical Package for Social Science (SPSS) version 17 (SPSS Inc., Chicago, IL, USA), versions 19 and 22 (IBM corp., Armonk, NY, USA) were used for data analysis in **Study I, II** and **IV**, respectively. For **Study III** all analyses were performed using R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical considerations

All studies were approved by the local ethics committee (Stockholm and Uppsala), conformed with the Declaration of Helsinki, and followed the principles of good clinical practice. All patients in **Studies I, II, IV** obtained more detailed information about CA techniques and risk for procedure-related complications, especially neurological complications. All patients provided written informed consent. Being a study patient implied to waive preference to vascular access site, limited head movement during the cardiac catheterisation due to TCD recordings and in **Study IV** time consuming extra hospital visits. Furthermore, in **Study II** additional catheters and guidewires were used, implying a small but potential risk for complications and prolonged catheterisation procedures compared with standard care. As in **Study I** and **IV** disadvantages for the patients mainly comprised modest discomfort and in **Study II** the additional complications risk was estimated to be low, the expected benefits outweighed the study related risk, in the light of gaps in evidence-based knowledge regarding the impact of catheter techniques on potentially harmful cerebral embolisation.

In **Study III** patients were informed about the inclusion in a register (SCAAR) and had the right to decline participation, but did not provide written informed consent. The merge of the registries used in **Study III** was approved by the National Board of Health and Welfare. In order to verify procedure-related stroke or TIA, medical records were collected and analysed by two neurologists. As further analysis was performed with anonymised data only, the possible risk of revealing confidential medical records was minimised and considered to be outweighed by the benefit of validated data.

Results and Discussion

Study I

The hypothesis in **Study I** was that the number of cerebral microemboli in the MCAs differs when the radial and the femoral access site are used for CA in patients with stable angina pectoris.

Of the 340 patients screened, 263 patients did not meet inclusion criteria and 26 patients were not included due to other reasons. Hence, a total of 51 patients were included in the study and randomised to the radial (n=28) or the femoral (n=23) access site. In the radial group 8 patients were converted to femoral access and excluded from the final analysis. Thus, the statistical analysis included 20 patients in the radial group and 23 patients in the femoral group. Baseline characteristics and results for the study cohort are shown in Table 5. Patients in the femoral access group were more likely to have diabetes mellitus and one- or two-vessel disease on CA.

Table 5. Baseline characteristics and results

	Angiography via right femoral artery n=23	Angiography via right radial artery n=20	p-value
Age	66.3±7.6	61.6±8.8	0.08
Women	4 (17)	2 (10)	0.67
Hypertension	16 (70)	12 (60)	0.51
Diabetes mellitus	12 (52)	2 (10)	0.004
Prior stroke/TIA	4 (17)	2 (10)	0.68
Prior acute myocardial infarction	3 (13)	4 (20)	0.68
Prior percutaneous coronary intervention	3 (13)	4 (20)	0.69
Number of coronary stenoses:			
No stenosis	5 (22)	12 (60)	0.03
1-VD	12 (52)	3 (15)	
2-VD	4 (17)	2 (10)	
3-VD	2 (9)	3 (15)	
Contrast volume (ml)	75 (60-100)	82.5 (50-160)	0.31
Fluoroscopy time (min)	2.5 (1-5)	6 (2-12)	<0.0001
Number of gaseous microemboli	44 (7-131)	58 (19-469)	0.08
Right MCA	19 (1-69)	32 (11-171)	0.003
Left MCA	21 (6-85)	23.5 (3-298)	0.44
Number of particulate microemboli	6 (1-19)	10 (1-120)	0.02
Right MCA	2 (0-9)	7 (1-65)	0.004
Left MCA	3 (0-15)	3 (0-55)	0.57

Values are mean±SD, numbers (%) or median (min-max range). MCA= middle cerebral artery, VD= vessel disease.

In 2 patients in the radial and femoral group, respectively, additional catheters were used to cannulate the coronary ostia. Microemboli detected during these additional procedural stages were excluded from the statistical analysis.

No vascular complications or clinical overt neurological complications were observed during hospital stay.

Cerebral microemboli occurred during all CAs without significant diversity between the operators. There were significantly more particulate cerebral microemboli detected in the radial compared with the femoral group (Table 5, Figure 7). When the right and left MCA were analysed separately, significantly more particulate cerebral microemboli passed the right MCA with the radial compared to the femoral access, whereas there was no difference between the access site groups regarding the left MCA (Table 5). Also more gaseous microemboli were observed in the right MCA with the radial access, but unlike particulate microemboli, overall their number did not differ between the access sites (Table 5).

When different angiographic procedural steps were analysed, the count of particulate cerebral microemboli in both MCAs was higher during catheter exchanges compared with examination of the coronary arteries (7 (0-51) versus 1 (0-67), $p<0.001$). When catheter exchanges were evaluated separately for left and right MCA, more cerebral microemboli were detected in the right MCA with the radial compared with the femoral access, Figure 8. Likewise, during coronary artery examination more cerebral microemboli were identified in the right MCA with the radial access, Figure 8.

Discussion

In this randomised study the number of cerebral microemboli was compared between vascular access sites. Cerebral microemboli were detected during all CA procedures, but more particulate cerebral microemboli were identified when the radial access was used. A higher count of

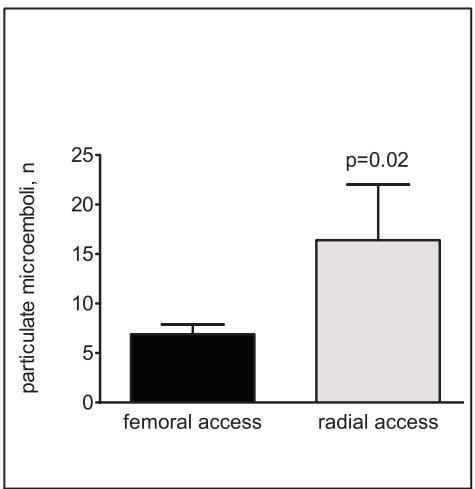

Figure 7. Number of particulate cerebral microemboli during coronary angiography for femoral and radial access site

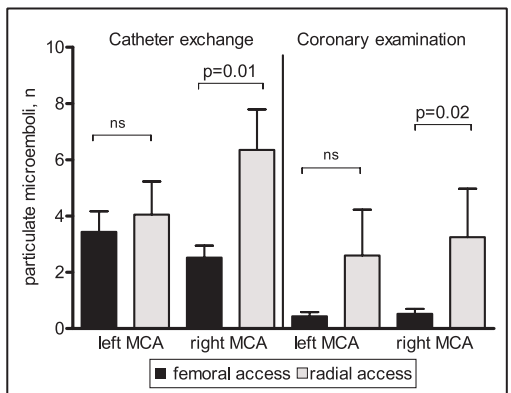

Figure 8. Number of particulate cerebral microemboli during coronary angiography divided into procedural stages of catheter exchange and coronary examination, for the right and left middle cerebral artery (MCA), respectively, for femoral and radial access site

cerebral microemboli with the radial access during CA and PCI has previously been shown in a non-randomised study (27). Lund and co-workers also linked cerebral microemboli to new ischemic lesions on diffusion-weighted MRI (27). By contrast, a randomised study including patients with aortic stenosis examined with CA did not show a significant difference in new ischemic lesions with diffusion-weighted MRI according to access site, but was underpowered as admitted by the authors (119). The comparability to our study is limited since only a subgroup of the study patients were examined with TCD (119).

Compared with other procedural steps, a higher number of cerebral microemboli were observed during catheter exchange for both access sites, but most emboli were detected in the right MCA with the radial access. The reason could be the passage of anatomical structures: catheters and guidewires need to be advanced from the right radial-, brachial- and subclavian artery via the brachiocephalic trunk and bend sharply into the ascending aorta on their way to the coronary ostia, which may disrupt atherosclerotic plaques adherent in the vessel wall. This hypothesis needs to be proven as no data on atherosclerosis of the aortic arch were available in our study cohort. However, in support of this concept Pacchioni and co-workers showed that the number of cerebral microemboli was lower when the left, compared to the right, radial access was used (120). Aiming to reduce the number of cerebral microemboli with the radial access, the use of only one diagnostic catheter for the examination of both coronary arteries should be favourable. Indeed, Pacchioni and co-workers recently showed that using two diagnostic catheters compared with a single one almost doubled the number of microemboli detected performing CA with the right radial access (121).

Our study has several limitations. The crossover rate from the radial to the femoral access was higher than expected. However, those patients were excluded from the analysis. The operators were experienced with both access sites and as the low number of additional catheters show, they changed access site rather than trying additional catheters. Moreover, as already mentioned, most cerebral microemboli were detected in operator independent stages such as catheter insertion and exchanges. The fluoroscopy time was longer in the radial access group, implying a potential confounder due to longer contact time of the catheters within the vessels. Even though the difference in fluoroscopy time has been reduced over time, the radial access is still associated with higher radiation exposure (19, 33). Despite the higher risk for stroke due to the absence of additional heparin use and the higher co-morbidity, such as diabetes mellitus and severe CAD, less cerebral microemboli were detected in the femoral group.

In summary cerebral microemboli occurred frequently during diagnostic CA. The number of particulate cerebral microemboli was higher when the radial access was used. That microemboli were mainly detected during catheter exchanges and predominantly in the right MCA with the radial access indicates a causal relationship.

Study II

The hypothesis of **Study II** was, that the number of cerebral microemboli differs according to guidewire techniques used with the femoral access: catheter advancement over the aortic arch with or without the help of a guidewire.

Of the 102 patients screened 44 were included in the study. Ultimately, 41 patients were analysed due to incomplete TCD recordings in three patients. Thus, 21 patients were randomised to initial advancement of the catheters with a guidewire over the aortic arch and flushing of catheters in the ascending aorta (group A), and 20 patients to initial guidewire withdrawal and flushing of catheters in the descending aorta (group B), Figure 9. Baseline characteristics are shown in Table 6. The majority of the patients were treated with aspirin and clopidogrel, and half of the patients with fondaparinux, due to a preliminary diagnosis of NSTE-ACS. In two cases the final diagnosis of NSTE-ACS and the treatment given were divergent due to changed diagnosis and missed administration. Patients with stable CAD did not receive heparin. No overt stroke or TIA was observed before patient discharge.

CAs were performed by six interventional cardiologist. Procedure times for part 1 and part 2 did not differ between group A and group B (Table 6). No reinsertion of the catheters due to twisting or bending was necessary.

Cerebral microemboli were detected in all patients, without significant differences dependent on operator. Their count did not differ according to whether it was the right or left MCA, extend of vessel disease or use of fondaparinux. More particulate and gaseous cerebral

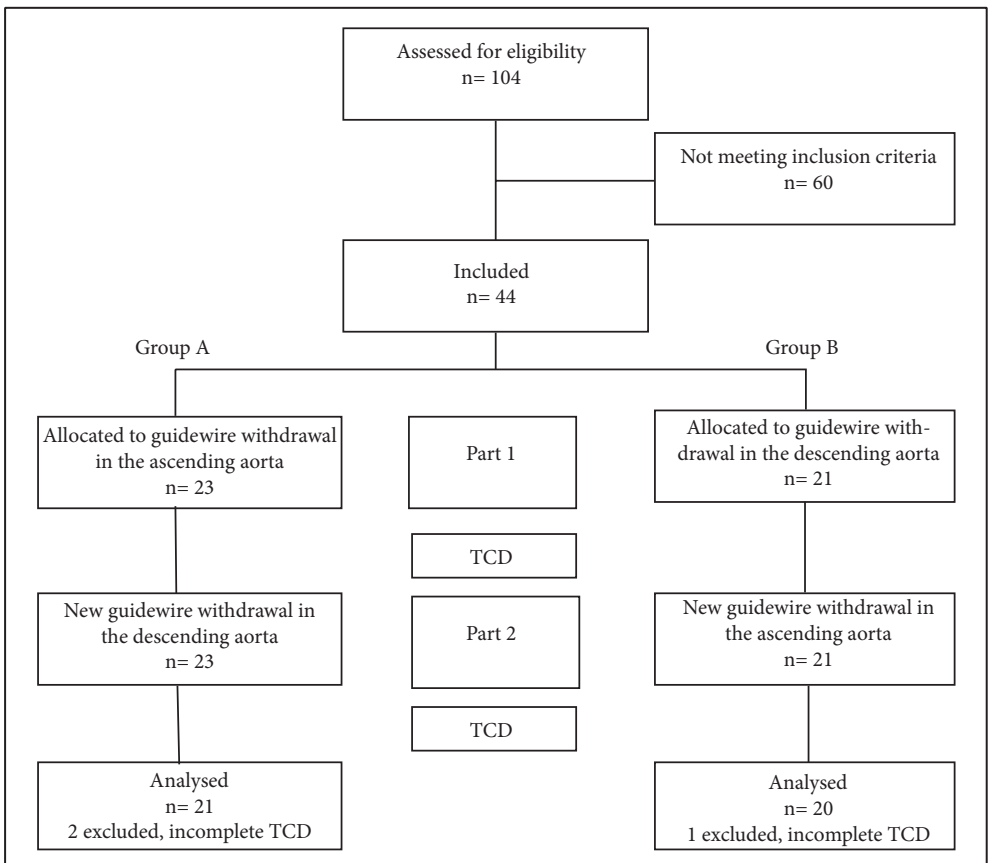

Figure 9. Study design.
TCD= transcranial Doppler

Table 6. Patient characteristics and diagnostic results.

	Group A n=21	Group B n=20
Age	62 ± 10	60 ± 7
Women	5	5
Smokers	6	1
Hypertension	10	12
Diabetes mellitus	4	5
Prior Stroke or TIA	1	2
Peripheral vascular disease	1	1
Prior MI	5	2
Prior PCI	4	2
ASA	21	18
Clopidogrel	19	18
Fondaparinux	12	10
Warfarin	0	2
Discharge diagnosis		
Stable angina pectoris	8	11
NSTE-ACS	13	9
Angiographic results		
0	8	9
1 VD	7	7
2 VD	2	2
3 VD	4	2
Procedure time		
Part 1	10:06 (06:52)	10:22 (02:59)
Part 2	03:32 (00:37)	03:21 (00:38)
Number of particulate cerebral microemboli		
Part 1	ASC 9 (9)	DESC 3 (5)
Part 2	DESC 0 (2)	ASC 2 (7)
Number of gaseous cerebral microemboli		
Part 1	ASC 48 (51)	DESC 27 (31)
Part 2	DESC 4 (12)	ASC 31 (44)

Values are presented as mean ± SD and median (IQR). Procedure time in minutes: seconds (IQR). ASC= guidewire withdrawal in ascending aorta (ASC), DESC = guidewire withdrawal in descending aorta, MI = myocardial infarction, NSTE-ACS= non-ST-segment elevation acute coronary syndrome, PCI = percutaneous coronary intervention, VD= vessel disease.

microemboli were identified when the catheters were advanced with a leading guidewire over the aortic arch compared with when the guidewire was withdrawn in the descending aorta and the catheter was advanced alone over the aortic arch, Figure 10.

As part 1 included a complete coronary examination, more cerebral microemboli were detected in part 1 compared to part 2; particulate 6 (8) versus 1 (3), ($p<0.001$) and gaseous 34 (35) versus 13 (29), ($p<0.001$), respectively.

Sub-analyses of parts 1 and 2, respectively, showed more particulate (Figure 11) and gaseous cerebral microemboli (Table 6) with the ascending technique, compared with the descending technique.

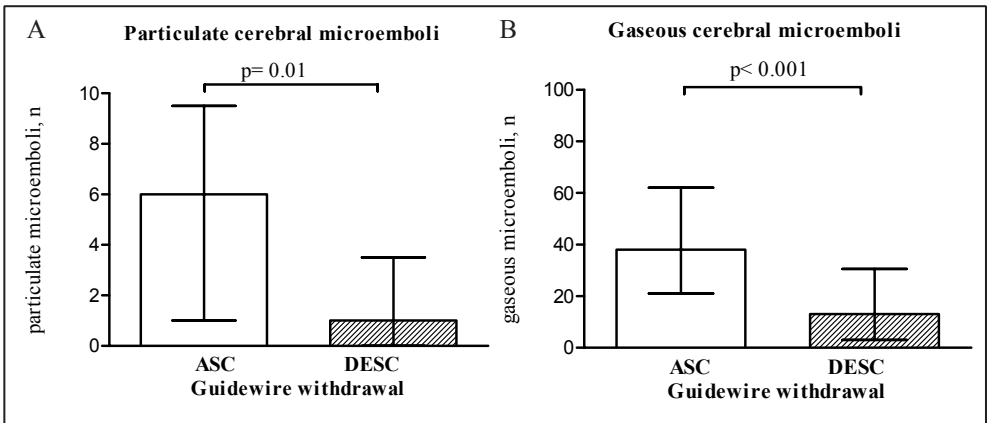

Figure 10. Total number of cerebral microemboli detected with transcranial Doppler (TCD), independent of allocation group. Guidewire withdrawal in the ascending aorta (ASC) and descending aorta (DESC) for (A) particulate cerebral microemboli and (B) gaseous cerebral microemboli. Data given as median (interquartile range).

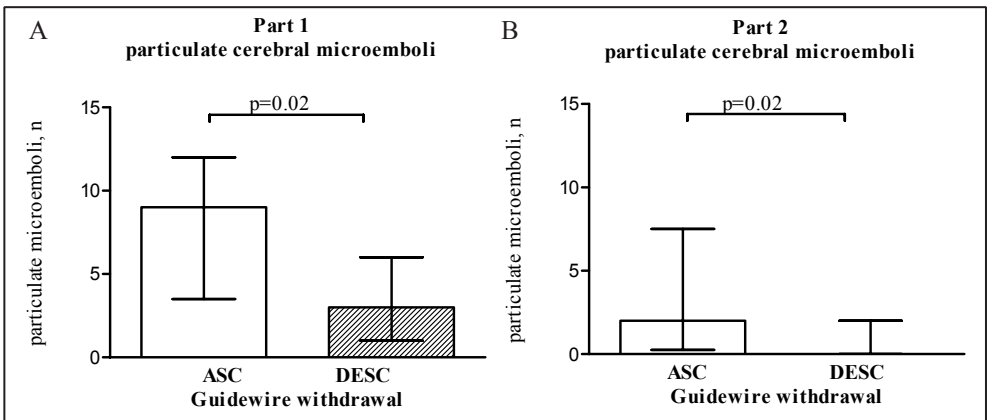

Figure 11. Number of particulate cerebral microemboli detected with transcranial Doppler (TCD) during part 1 and part 2 of the procedure. Number of particulate cerebral microemboli detected when the guidewire was withdrawn in the ascending aorta (ASC) compared with guidewire withdrawal in the descending aorta (DESC) during part 1 (A) and part 2 (B) of the study. Data given as median (interquartile range).

Discussion
By comparing two guidewire techniques this study showed that more cerebral microemboli were generated when catheters are advanced with a protruding guidewire to the ascending aorta compared with advancement of the catheter alone after withdrawal of the guidewire in the descending aorta. Our findings are in line with a previous study by Breakken and co-workers, but in their study microembolisation was assessed only on the left MCA and no differentiation into gaseous and particulate emboli was possible (122). It is reasonable that particulate cerebral microemboli have different origins. Atherosclerotic plaques in the aortic arch have been shown to be highly prevalent in a comparable patient cohort (123). To avoid contact between the edges of the catheter and the aortic wall, Judkins modified the shape of the catheter to be atraumatic by changing the catheter tip to a "bullet nose" configuration and by pointing the edge of the catheter to the rear (7). Contrary to this approach, when a catheter is straightened by a guidewire, the edge may scrape the vessel wall when advanced over the aortic arch. Indeed, the occurrence of dislodged aortic debris in catheters advanced with a guidewire has previously been reported (124, 125).

One could argue that a catheter without a leading guidewire is more difficult to engage the coronary orifices. Due to prolonged procedure durations the risk for embolisation may increase as catheters are recognised highly prothrombotic materials (9, 126). However, none of the 6 interventional cardiologists reported those difficulties, supported by equal procedure times for both techniques.

Our study has several limitations. The sample size was small, but by applying a crossover model, the sample size doubled as both techniques were used in the same patient. Due to the case-mix of stable angina and ACS patients, different atherosclerotic plaque formation may have an impact on cerebral microemboli detected. However, no difference in the number of cerebral microemboli between patients treated with and without fondaparinux was found.

No cognitive assessment was part of the study, thus leaving the clinical impact of the above findings unexamined.

In summary, more cerebral microemboli were detected when the catheter was advanced with the help of a protruding guidewire to the ascending aorta compared with catheter advancement alone and guidewire withdrawal in the descending aorta. The latter technique is easy to execute during CA and should be considered in patients at high-risk of ischemic neurological complications.

Study III

The hypothesis in **Study III** was that the occurrence of procedure-related stroke or TIA differs between the radial and the femoral access site used for CA and PCI when adjusted for confounding factors.

In this retrospective register study 336,836 procedures were included for analysis, after exclusion of 3,907 procedures with missing or unknown access site. In total, 127,746 radial and 209,090 femoral procedures were examined, whereof the majority, 255,609 (75.9%) were performed in unique patients. Over time, the radial access was increasingly used, from 20%

to 70% between 2003 and 2011. The stroke or TIA rate per year did not change significantly over time. Access site crossover was recorded in 6,430 procedures, mainly from the radial to the femoral access (94%). In the radial access group normal CA findings or 1-VD were more likely, while a higher degree of VD and other cardiovascular co-morbidities were more likely in the femoral access group. Within 24h from the procedure 2,037 patients died: 377 in the radial and 1,600 in the femoral access group, respectively.

After review, 546 reported neurological complications were verified as being procedure-related stroke or TIA, whereof 183 were considered TIA. This corresponds to an incidence of 0.16% and did not change substantially over time. Table 7 shows univariate and multivariate risk factors for procedure-related stroke or TIA. In crude analysis the radial access was not associated with a higher risk for procedure-related stroke or TIA. In contrast, after multivariable adjustment the risk ratio (RR) for procedure-related stroke or TIA was 1.30 (CI 1.04-1.62), p= 0.022 for the radial access (Table 7). Those findings were not significantly changed after exclusion of crossover procedures RR 1.27 (CI 1.01-1.60), p=0.039 or exclusion of procedures where patients died within 24h, RR 1.32 (CI 1.05-1.65), p=0.016. When adjusting for the propensity score RR was 1.23 (CI 0.99-1.53), p=0.057.

Subgroup analysis revealed a significant interaction between the group of ACS/ no ACS and access site with a higher risk for procedure-related stroke or TIA in ACS patients with the radial compared with the femoral access. Though there was an absence of significant interaction between time interval and access site, during 2009 and 2011 the procedure-related stroke or TIA risk was considerably higher with the radial access.

Discussion

In this register study the radial access was associated with a 30% higher risk for procedure-related stroke or TIA compared with the femoral access.

To our knowledge this is the first large-scale retrospective study where the reported neurological complications were verified to be procedure-related. By this, the incidence of stroke or TIA was 0.16%, which is in line with other contemporary register studies (41, 92, 94, 127). Higher incidences (0.4%) have been reported by single centre studies, possibly due to the presence of a neurologist on site and the comprehensive use of brain imaging techniques making the report of neurological complications more likely (93, 128).

Our findings are contrary to a recently published register study by Ratib and co-workers who did not find a higher risk for procedure-related neurological complication according to access site (42). There are several differences when compared with our study: Ratib and co-workers assessed PCI procedures only whereas we included CA procedures as well. This may explain the lower prevalence of patients with previous CABG in their study (42). Another difference is the definition of procedure-related: while Ratib and co-workers used neurological complication before discharge, we aimed to ensure the relation to the procedure with a 24h time frame and the exclusion of atrial fibrillation (42). Moreover, our study cohort had higher prevalence of cardiovascular co-morbidity.

In our study, patient characteristics according to access site were considerably different with a higher co-morbidity in the femoral group. We adjusted for previously known patient-related

Table 7. Association between access site and periprocedural stroke or TIA

	Crude			Adjusted		
Variable	**RR**	**95%CI**	**p-value**	**RR**	**95%CI**	**p-value**
Radial access	0.91	0.76-1.08	0.287	1.30	1.04-1.62	0.022
Age	1.05	1.04-1.06	<0.001	1.04	1.03-1.05	<0.001
Female sex	1.30	1.10-1.55	0.003	1.34	1.11-1.61	0.002
Year of procedure[§]	0.95	0.92-0.98	0.001	0.94	0.90-0.97	0.001
Current smoking	0.68	0.53-0.88	0.003	0.88	0.67-1.16	0.378
Diabetes mellitus	1.47	1.21-1.79	<0.001	1.28	1.04-1.57	0.021
Hypertension	1.10	0.92-1.30	0.292	0.89	0.74-1.08	0.238
Hyperlipidemia	1.04	0.87-1.23	0.686	0.92	0.75-1.12	0.409
Renal failure	1.58	0.99-2.52	0.057	1.36	0.84-2.20	0.209
COPD	1.10	0.81-1.50	0.542	0.94	0.69-1.29	0.715
Peripheral vascular disease	1.89	1.39-2.58	<0.001	1.29	0.94-1.78	0.112
Previous stroke	1.98	1.54-2.56	<0.001	1.45	1.12-1.88	0.005
Heart failure	1.38	1.09-1.76	0.009	0.99	0.76-1.28	0.914
Previous MI	1.28	1.06-1.55	0.009	0.99	0.79-1.23	0.928
Previous CABG	2.33	1.90-2.86	<0.001	2.23	1.75-2.85	<0.001
Previous PCI	0.82	0.66-1.02	0.076	0.79	0.62-1.00	0.052
Expert centre	0.89	0.74-1.06	0.182	0.88	0.69-1.13	0.324
Procedure						
PCI	0.31	0.16-0.60	0.001	0.25	0.13-0.49	<0.001
CA + PCI	1.14	0.97-1.35	0.121	0.88	0.72-1.09	0.258
Thrombectomy	1.33	0.90-1.97	0.157	1.24	0.82-1.86	0.306
Situation						
ACS	1.61	1.36-1.92	<0.001	1.34	1.11-1.62	0.003
Findings						
1-VD	1.69	1.29-2.21	<0.001	1.65	1.20-2.26	0.002
2-VD	2.02	1.52-2.66	<0.001	1.71	1.23-2.37	0.001
3-VD	2.57	1.99-3.31	<0.001	1.58	1.16-2.15	0.004

ACS= acute coronary syndrome, CA= coronary angiography, CABG= coronary artery bypass graft, COPD= Chronic obstructive pulmonary disease, MI= myocardial infarction, PCI= percutaneous coronary intervention, VD= vessel disease

[§] year as continuous variable between 2003-2011

risk factors for procedure-related stroke or TIA such as age, gender (94, 129), severity of CAD (89), previous stroke (91, 92, 94), previous CABG (94, 130) and procedure-related risk factors such as procedure during ACS (91, 92, 94) or thrombectomy (131). Since centre experience has been associated with patient outcome it was also included in the regression model (37, 40, 132). Besides centre experience and thrombectomy, all other known risk factors were confirmed in our analysis. That the radial access is associated with higher risk for procedure-related stroke or TIA remained significant after exclusion of crossover procedures, despite it having previously been reported that the number and size of catheters used was associated with higher procedure-related stroke risk (93). Similarly, when excluding patients dead within 24h from the procedure, the higher risk for procedure-related stroke or TIA with the radial access remained. When a propensity score was included in the main model, the point estimate supports the findings (RR 1.23), but with CI (0.99-1.53) which is strictly speaking not significant. It could be argued that the difference found in the multivariable analysis is due to chance, which is possible, but we did our best to adjust for several confounders and performed sensitivity analysis as described above.

Contrary to register studies, the incidence of periprocedural stroke in RCTs is generally higher (0.2-0.6%); partly because of stroke assessment between 48h and 30 days (37, 40), partly because the study cohort comprised patients with ACS, known to be at higher stroke risk (133). In RCTs no association between vascular access site and procedure-related stroke was reported but with respect to its the low incidence, they were not designed to answer that question either (37, 40).

The main strength of our study is that data were comprehensively assessed and that the outcome variable was verified with a clear definition of procedure-related. Notwithstanding, our study has several limitations. Neurological complications may be under-reported to the SCAAR register. Additionally, data on co-morbidity were not obtained from NPR for 2011. Data on anticoagulation treatment were not included as SCAAR do not provide those for CA procedures. Additionally we cannot exclude that unknown confounders have biased the association of procedure-related stroke and access site.

In summary, the radial access site may be associated with procedure-related stroke or TIA following CA and PCI.

Study IV

The hypothesis of **Study IV** was that procedure-related cognitive impairment occurs after CA or PCI and that the number of cerebral microemboli and vascular access site are causally related to post-procedural cognitive impairment.

Of the 586 patients screened, 97 patients were included in the study. Ultimately, the results of 93 patients were analysed including a subgroup of 35 patients with TCD recordings (Figure 12). Eighty-six and 78 patients, respectively, performed the first and second follow-up MoCA test, and 77 patients completed all three MoCA tests (Figure 12). The vascular access site for all CA or PCI procedures was evenly distributed. The patients included were on average 67 ± 8.7 years old, mainly men (20% women) with an average body mass index of 27.4 ± 4.1 and normal renal function. Co-morbidities like hypertension and hyperlipidemia were

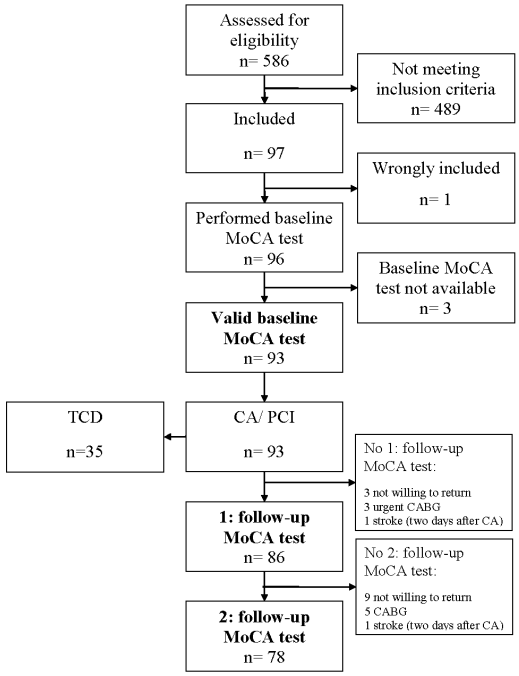

Figure 12. Study design
CA= coronary angiography, CABG= coronary artery bypass graft, MoCA= Montreal Cognitive Assessment, PCI= percutaneous coronary intervention, TCD= transcranial Doppler

common (60% respectively), 20% had diabetes mellitus, previous MI or previous PCI, 14% had previous stroke. Depression was prevalent in 14% of the patients and 57% had undergone more than 12 years of education. No stroke was observed during hospital stay, but one patient suffered a stroke two days after CA. The main reason for CA was chest pain and suspicion of angina pectoris. Normal findings on CA was found in 45% of all patients.

The median result of the baseline MoCA test was 27 (25-28) and did not change after the CA or PCI procedure (Figure 13). Subgroup analyses for women and PCI procedures showed similar MoCA test results.

Of those patients monitored with TCD during the catheterisation procedure, 33 patients completed the first follow-up MoCA test. MoCA test results were not correlated to the number of cerebral microemboli (Figure 14) or to access site.

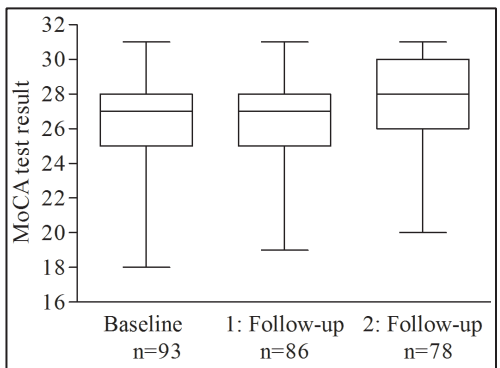

Figure 13. Results of the Montreal Cognitive Assessment (MoCA)
Boxplot with median, lower and upper quartile of MoCA test results at baseline (before the procedure), first and second follow-up (after the procedure) including whiskers from minimum to maximum MoCA test result.

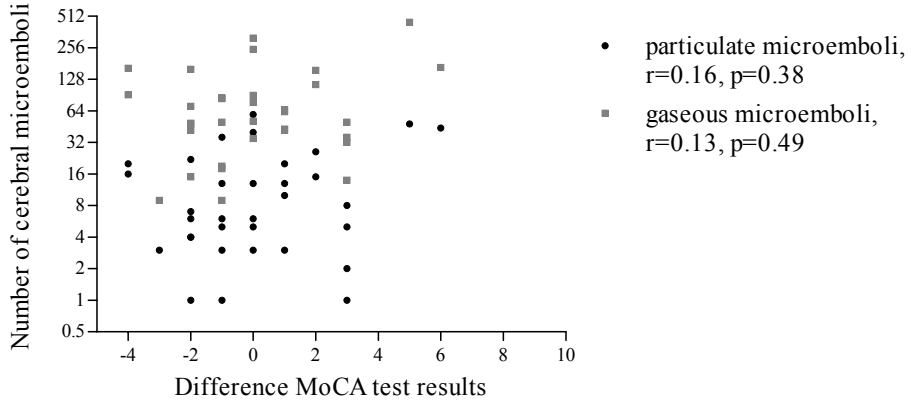

Figure 14. Correlation of cerebral microemboli and difference between baseline and first follow-up MoCA test results
Negative number indicates improvement in test results
Positive number indicates decline in test results

Of note, one third of all analysed patients (n=31) had <26 points on their baseline MoCA test, corresponding with MCI.

Discussion

In this study, no cognitive impairment following CA or PCI procedure was observed using the MoCA test. The results of the MoCA test were not correlated to the number of microemboli detected with TCD or to the access site from which the catheterisation procedure was performed.

The body of evidence regarding cognitive function in CAD patients mainly comprises studies of CABG treatment, using a battery of different neuropsychological tests and various definitions of cognitive decline. Hence, a comparison with those studies is difficult. Studies with the focus on cognitive function in patients undergoing percutaneous cardiac procedures are rare. Selnes and co-workers did not find cognitive impairment in patients three months after CABG or PCI treatment, concluding that cognitive impairment is transient and reversible (134). By using the MoCA test we did not detect cognitive decline within 3 or 30 days of CA or PCI. The MoCA test is reported to detect mild cognitive impairment MCI with a sensitivity of 80% to100% and a specificity of 50% to76% (117). Although the MoCA test has in comparison with mini-mental state examination (MMSE) a higher sensitivity and specifity, it is still a screening tool for MCI and subtle post-procedural changes may not be detected (135). Lund and co-workers have previously shown affected attention demanding tests following CA and PCI using a test battery of neuropsychological tests (27). In the subgroup monitored with TCD we also detected cerebral microemboli, but in disparity with the aforementioned study, in a lower number, possibly due to the exclusion of patients with previous CABG, the avoidance of ventriculography and a low number of PCI procedures, all factors associated with a higher load of microembolisation (27).

No correlation between cognitive impairment and cerebral microemboli or vascular access site was present in our study. Lund and co-workers linked cerebral microemboli to new

cerebral lesions, detected on MRI, but interestingly post-procedural cognitive impairment was rather related to pre-catheterisation MRI injury and not the number of cerebral microemboli detected (27). This implies that microembolisation may have various impacts in different individuals influenced by pre-existing cerebral lesions.

Of note is that the occurrence of MCI before the catheterisation procedure was greater than expected (105, 136). Patients with MCI may have difficulties in decision making, following instructions and may have a higher risk for further cognitive decline based on an impaired cognitive reserve (137). The risk for conversion to dementia varies between 2-20% (105).

This study has several limitations. The inclusion rate was low, mainly depending on the patients´ preference for vascular access site, precluding randomisation. Furthermore, the limited number of patients with both completed MoCA tests and TCD recordings makes it difficult to draw any firm conclusions regarding the relationship between cognitive impairment and cerebral microemboli. Moreover, selection bias due to in-hospital follow-up MoCA tests and statistical type II error could have influenced our results. Using a test lacking sensitivity for detection of subtle changes in the brain function could also have contributed to the lack of detecting an association between cardiac catheterisation and cognitive impairment. Also, by including possibly healthier patients in our study, subtle changes may not be detectable due to a normal “brain reserve”. This highlights the importance of representative patient inclusion, which is not only influenced by exclusion criteria; it is also strongly influenced by the chosen study design.

In summary, no cognitive decline in patients undergoing CA or PCI was detected. Thus, we found no significant correlation to cerebral microemboli or vascular access site. Mild cognitive impairment was highly prevalent in patients undergoing routine CA or PCI, underlining the importance of carefully performed procedures as those patients have a higher risk of further cognitive decline.

General Discussion

For more than three decades CA and PCI have been performed for diagnosis and treatment of patients with CAD. Procedure-related complications are described to occur in 0.8-5% of all procedures in large registries (60-62, 106) including 0.1-0.4% neurological complications (89, 91, 92). Despite pharmacological and technical advancements the rate of procedure-related stroke seems to be unchanged over time, possibly due to there now being interventions in higher risk groups previously excluded (138). By regression analysis, most recognised risk factors, including a few procedural factors, have been identified (89, 91, 93, 94, 133). However, evidence of how to perform the procedure technically in order to reduce neurological complications is limited. The present thesis focuses therefore on the impact of different techniques for CA and PCI on procedure-related ischemic cerebral complications.

Procedure-related stroke or TIA

Outcome

Procedure-related stroke is associated with a 5 to 10-fold increase in mortality compared with survival after PCI without stroke (127, 133, 139). Surviving a procedure-related stroke implies not only increased length of in-hospital stay (91, 133) but more than every other patient is left with residual neurological deficits, requiring skilled home-care in 26% (91). Despite the different impact of stroke and TIA for the affected patient, we have chosen to combine the entities in our analysis for several reasons. First, medical charts did not always include statements of a thorough neurological examination at 24h from the occurrence of symptoms, which made it impossible to conclude if symptoms were present or had been resolved at this time-point and thus if they were to be coded as ischemic stroke or TIA. Second, by combining stroke and TIA, the event rate increased enhancing statistical power. The impact of procedure-related TIA on mortality varies according to different studies. In PCI register studies Dukkipatti and co-workers and Genereux and co-workers did not find an association of procedure-related TIA with in-hospital (91) or 1-year mortality (140). In contrast, a recent study by Kwok and co-workers revealed that procedure-related TIA was independently associated with similar odds for death within 30 days compared to stroke (127). Likewise, a recently published study including over 2,800 patients hospitalised for "common" TIA or stroke reported that the 1-year all-cause mortality was similar among those with TIA compared to stroke (141).

Definition of procedure-related stroke and contributing factors

From different register studies it is recognised that patients with ACS undergoing cardiac catheterisation have an increased risk of cerebrovascular events (91, 94, 127, 133, 142). The GRACE registry, evaluating outcome in ACS patients, showed an overall high in-hospital stroke rate (0.88%) and also a correlation to the severity of the ACS (with stroke incidence of 1.3%, 0.9%, 0.5% for patients with STEMI, NSTEMI, UAP, respectively) (143). Only 35% of all strokes occurred during the first 6 days, with an increasing cumulative stroke incidence during in-hospital stay. Similarly, Guptill and co-workers found in patients with STEMI treated with primary PCI that only 27% of all strokes occurred within 24h whereas 43% of

all strokes occurred within 48h, with in median, 6 days to stroke manifestation (144). This implies that factors others than the procedure itself may be causal. Indeed, atrial fibrillation (AF) was, after congestive heart failure, the second most common in-hospital event in the GRACE study (143). AF occurs in 2-21% of all patients with NSTE-ACS (51) and in 28% of all STE-ACS patients (56) and is one of the most important predictors for stroke in the community setting (145). In most register studies procedure-related stroke is defined as occurring anytime after the catheterisation until discharge. Another limitation is that prevalent and incident AF is not considered (91, 92, 94, 127, 133). Underlining the importance of the time interval in which stroke occurs, Kawamura and co-workers showed in patients with non-STEMI and STEMI that risk factors for stroke differed with time, stroke within 24h from PCI was associated with PCI of a vein graft and less frequent use of glycoprotein IIb/IIIa inhibitors whereas stroke after 24h was associated with diabetes mellitus, anterior wall STEMI and affected haemodynamics (142). Anterior wall STEMI is associated with lower ejection fraction and higher risk for ventricular thrombus formation (146). Thus, for the distinction between patient- and procedure-related risk factors for stroke or TIA, a narrow time frame in relation to the procedure and the exclusion of present AF as potential embolic source is crucial, which is one of the main strengths in our study.

We found a 30% higher risk for procedure-related stroke or TIA within 24h with the radial compared with the femoral access, when adjusting for known patient- and procedure-related risk factors. Also, most patient-related risk factors shown in other studies were confirmed in our study (91, 94, 128, 130). Contrary to the TOTAL trial, thrombectomy was not independently associated with procedure-related stroke in our study, a fact that may be explained by the low number of thrombectomies performed in patients with stroke or TIA in our study cohort (131). We included in our study CA and PCI procedures comprehensively, enhancing generalisability. Compared with PCI register studies, more patients with previous CABG, known to be at high-risk of procedure-related stroke, were included in our study (42, 127, 133).

While subgroup analysis in RCTs showed a beneficial outcome of patients treated in high volume radial centres, in our study centre experience was not independently associated with procedure-related stroke or TIA (37, 40), possibly explained by various definitions of centre expertise and the absence of consensus regarding radial expertise. The radial access was increasingly used over time with 70% of radial procedures performed in 2011. In parallel, between 2009 and 2011, the risk for procedure-related stroke or TIA with the radial access was 40% higher compared with 2006-2008, although there was no statistically significant interaction between the time intervals. The reason for this is not clear. Factors associated with longer procedure time like access site crossover, and the number of procedures due to ACS, were stable compared with the earlier time periods. Noteworthy, patients with ACS had significantly higher radial access related stroke or TIA risk compared with procedures in stable patients. More severe vascular calcification, longer procedural times and enforced catheter advancement due to the urgent situation could be possible explanations.

Previous studies have shown that debris from aortic plaques are dislodged from the vascular wall through catheter advancement and is suggested causal for procedure-related stroke (124, 125). When using the radial access, plaque in the ascending aorta may be at higher risk of displacement, since the catheter bends sharply from the brachiocephalic trunk into the ascending aorta. Other embolic sources may be clots formed in and around the catheters, as

catheters and guidewires are highly prothrombotic, known to cause endothelial damage and reduced thromboresistance (126). Thus, procedural time, and number and size of the catheters used are factors shown to be independently associated with procedure-related stroke (91, 93). Accordingly, using the radial access with longer procedural times and higher crossover rates, compared with the femoral access, may constitute an additional embolic risk (19).

In **Study III,** by analysing more than 300,000 CA and PCI procedures, the incidence of verified procedure-related stroke or TIA within 24h was 0.16% and the radial access was associated with a 30% higher risk. Although statistically not significant, with increased use of the radial access over time, the risk for procedure-related stroke or TIA increased.

The radial access in different patient groups

Due to reduced access site bleedings, the radial access is nowadays preferred for patients with STE-ACS leading to mortality benefits (25). The MATRIX trial gave indications for similar benefits also for NSTE-ACS patients (40). Thus, the radial access is recommended over the femoral access, given the operator´s radialis expertise, in patients with ACS according to the ESC guidelines (51). However, the risk/benefit ratio in favour of the radial access may not be applicable to all patients. The adoption of the radial access in some subgroups is discussed below.

Women, underrepresented in clinical trials (37, 40), undergoing PCI are recognised to have a high risk of bleeding (147-149). In the SAFE-PCI trial women were randomised to either access site. This trial was stopped early due to the low event-rate, but did not show significant differences in bleeding or vascular access site complications following PCI between the access sites. On the contrary, a recently published register study addressing gender specific outcomes according to access site found a significant reduction in bleeding complications for both genders with greater benefit for women undergoing PCI (150). Approximately 40% of the PCIs included in this comprehensive analysis were elective PCIs. Here the radial, access was not associated with a decrease in 30 day mortality, whereas the opposite was shown for NSTE-ACS and STE-ACS in men and STE-ACS in women (150). Thus, male patients with stable angina may not benefit from the radial access. At the same time, as discussed above, ACS patients have been shown to have a higher risk of procedure-related stroke or TIA, possibly enhanced with the use of the radial access.

Another high-risk group for procedure-related stroke or TIA comprises patients with previous CABG. Michael and co-workers reported longer procedural times, greater contrast use and radiation exposure in patients with previous CABG undergoing CA and PCI with the radial compared with the femoral access (151). Also, as discussed above, longer procedural time is per se a risk factor for procedure-related stroke, further augmented with the radial access.

Patients with cardiogenic shock (CS) have the worst prognosis and also more bleeding complications (71) among patients with ACS (152). A meta-analysis by Pancholy and co-workers assessing outcome in patients with CS undergoing PCI showed reduced 30-day mortality and major adverse cardiac and cerebral event rate (see Table 1) with the radial access (36). Interestingly, bleeding rates, partly underreported, did not differ between the access sites, assuming that the sickest patients may not have been included in the analysis. In the absence of a palpable radial pulse due to haemodynamic instability, the femoral access is likely to be preferred, for the placement of haemodynamic support devices as well.

In summary, there is good evidence for a favourable risk/benefit ratio when using the radial access in patients with ACS. However, in special patient groups, such as procedures in stable CAD and for patients with previous CABG as well as for critically ill patients, it has not been shown that outcome benefits with the radial access outweigh the potential risk for procedure-related stroke or TIA. Our findings should be the subject of future research given the further expanded use of the radial access.

Silent ischemic cerebral infarction and cognitive impairment

Contrary to the low incidence of procedure-related stroke and TIA following CA and PCI, the occurrence of clinically silent cerebral infarctions is considerably higher. According to a recently published meta-analysis, silent cerebral infarctions are found in 2-35% on MRI following cardiac catheterisation procedures (107). These parenchymal lesions have imaging characteristics of an infarct but the patient lacks clinical symptoms of stroke or TIA (153). Silent cerebral infarcts have been shown to more than double the risk of subsequent stroke (100) and are also associated with cognitive decline, dementia and depression (154-157).

In the context of CABG

As a substantial proportion of patients develop cognitive decline after CABG (158), cerebral microemboli have been extensively studied with TCD, MRI and in postmortem studies, as they are thought to be implicated in the pathogenesis of cognitive impairment (159, 160). Autopsy studies following cardiopulmonary by-pass have shown microvascular lesions suggested to be caused by microembolic occlusions (161) and atherosclerotic emboli associated with severe atherosclerosis of the ascending aorta (162). The clinical impact of cerebral microemboli causal of cognitive impairment is yet undecided. Whereas five TCD studies in patients undergoing cardiac surgery showed an association between the number of microembolic signals and low post-operative performance, nine studies could not establish an association between microemboli and cognitive outcome, summarised by Kruis and co-workers in a systematic review (163). This could be attributable to different TCD techniques used, as the earlier studies could not distinguish between gaseous and particulate microemboli, the latter suggested as being more harmful. In parallel, MRI studies in patients undergoing cardiac surgery have frequently shown new ischemic lesions reported in a meta-analysis (164). A recently published systematic review, aimed at exploring the association of post-operative cognitive decline after cardiac surgery and new MRI lesions, included 20 studies with pre- and post-operative neuropsychological testing, whereof 6 showed an association between new MRI lesions and cognitive impairment whereas in 12 other MRI studies no association between ischemic lesions and cognitive decline was evident, in two studies no MRI changes have been observed (165). It should be noted that the authors refrained from performing a meta-analysis because of the studies´ heterogeneity (165).

In the context of vascular procedures

Also, other invasive cardiovascular procedures are associated with new ischemic lesions on MRI. It has been reported that new MRI lesions after endarterectomy and carotid angioplasty correlate with the number of intraoperative microembolic signals on TCD (99, 108).

Cerebral microemboli and ischemic lesions on MRI are frequently observed after cardiac and cerebrovascular procedures and can potentially cause cognitive decline, yet a causal link needs to be confirmed.

In the context of cardiac catheterisation

We and others have used TCD to assess microembolisation in real-time during cardiac catheterisation to elucidate which procedural steps are associated with the occurrence of microemboli in the MCAs (27, 120-122). Thus, in **Study I** and **Study II** we showed that the vascular access site as a starting point for the catheterisation procedure and the technique used for catheter advancement when using the femoral access does have an impact on microembolisation. Our findings are limited by the absence of cerebral MRI. However, MRI studies have demonstrated a correlation between cerebral microemboli and silent cerebral infarctions (27, 99, 108). In contrast, Hamon and co-workers did not find an association between microemboli recorded with TCD and silent ischemic lesions on MRI following CA (96, 97, 119), possibly influenced by the limited number of TCD recordings in a subset of included patients (97, 119). Also, the TCD techniques used were different between the studies: while Lund and co-workers used a traditional TCD technique (27), Hamon worked with power M-mode (PMD) (96, 97, 119). PMD is a more recently used TCD method which simultaneously displays the power and direction of blood flow signals over a range of depths, facilitating the "track" of microemboli but can potentially over-detect emboli (166, 167). Thus, cerebral microemboli, detected with TCD during different cardiovascular procedures are

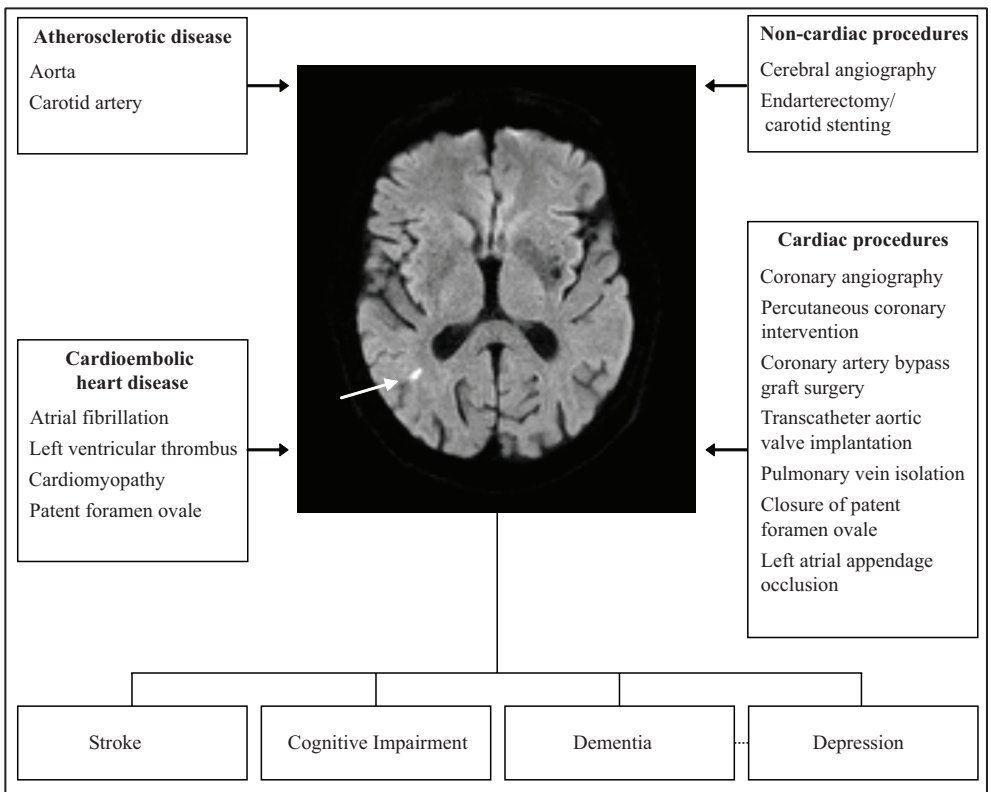

Figure 15. Overview of different sources by which silent cerebral infarcts can derive. Adapted from Hassel, ME. Silent cerebral infarcts associated with cardiac disease and procedures (107). The arrow shows a small, hyper-intense lesion indicating cerebral infarction using dw-MRI.

linked to silent cerebral infarcts on MRI. The association between microemboli and ischemic lesions is not yet explained in detail, as it is possibly influenced by multiple factors including the presence of aortic atheroma and the type of procedure performed.

Mechanism of brain damage

To explore the mechanism by which cerebral microemboli may damage the brain, Wu and co-workers showed in an animal model, that injection of microemboli in the carotid artery (cut whole blood clots) did not lead to cerebral infarcts but to neuronal apoptosis, via induction of inflammatory factors (168). This may indicate that the effect of cerebral microembolisation is more complex than anticipated with occlusion of cerebral microvessels. While gaseous microemboli are suggested as being more benign as they probably dissolve, they are linked to neurocognitive decline after CABG (169) and increased brain reactivity due to bioelectrical disturbances (170). The influence of pharmacological treatment on the occurrence of microemboli has been explored in patients with symptomatic carotid stenosis. Monotherapy with aspirin, showed in comparison with dual antiplatelet therapy, more microemboli detected with TCD (171). In parallel, Kim and co-workers showed in MRI studies that insufficient platelet inhibition and angiography of the internal mammary artery were associated with silent cerebral infarcts (172, 173). Using TCD, we found no correlation to anticoagulation treatment within **Study I, II** and **IV**. When comparing the count of microemboli, a similar number was detected regardless of monotherapy in **Study I** or dual antiplatelet therapy in **Study II** and **IV**, possibly explained by the overall low number of microemboli detected.

Silent cerebral lesions and cognitive impairment

While it has been shown in population-based studies that silent cerebral lesion are associated with an increased stroke risk (174, 175), the risk for subsequent stroke following procedure-related ischemic lesions has not been investigated. The theory of cumulative burden of multiple ischemic lesions contributing to cognitive decline is supported by TCD and MRI studies in patients with dementia (176, 177). However, an increased risk for stroke, cognitive decline, dementia and depression has yet not been observed following cardiac procedures in the absence of long-term follow up in these patients. We assessed cognitive function in **Study IV** in patients undergoing CA or PCI and did not find cognitive impairment when using the MoCA test. There was no correlation between cerebral microemboli detected with TCD and MoCA test results. Although the MoCA test discriminates cognitive impairment better than MMSE, the MoCA test is still a screening tool for dementia and might lack the sensitivity of the subtle cognitive assessment (135). Rodés-Cabau and co-workers studied patients with severe aortic stenosis undergoing TAVI and found no difference in cognitive function assessed with MMSE between patients with and without ischemic lesions with MRI (178). In the study by Lund and co-workers, previously mentioned, cognitive impairment following CA or PCI was not correlated with the number of microemboli detected, but with pre-catheterisation MRI injury, supporting the theory on cumulative burden of ischemic lesions discussed above (27). However, two tests with the highest demand on learning and attention out of a neuropsychological test battery were associated with new lesions on MRI (27). This highlights that subtle changes in cognitive function after CA and PCI are difficult to detect.

In retrospect, when considering the results in **Study IV**, neuropsychological testing may have been more appropriate for the assessment of cognitive function. However, neuropsychological testing, widely used following CABG, differs substantially regarding methodology, criteria

for cognitive impairment, and choice of time-points for assessment (179). In addition, studies of assessment of cognitive function in patients undergoing PCI are rare. Selnes and co-workers compared cognitive function in patients treated with CABG to those treated with PCI without finding a difference at three months and one year (134). Interestingly, one third of the patients in **Study IV** had MoCA test results indicating MCI (118) which is a symptomatic pre-dementia stage on the continuum of cognitive decline (102). In support of this finding Rosengart and co-workers reported an already high incidence of cognitive impairment in patients with CAD before treatment (137). The conversion of MCI to dementia varies between 2-20% per year (105). Thus, cardiac procedures aiming to increase quality-of-life need to be critically reviewed according to the potential risk they may imply for impairment of cognitive function. Even though the clinical impact of cerebral microemboli is yet undecided, their number should be kept as low as possible.

Future directions

The present thesis shows that different techniques used for CA and PCI have implications for the development of cerebral ischemic lesions, both overt and silent. To further elucidate the association between vascular access site and post-procedural cerebral injury, MRI studies could be an option. Given the low incidence, RCTs with the primary endpoint of procedure-related stroke or TIA are difficult to implement. Thus, assessment of new ischemic cerebral lesions after CA of patients randomised to either access site could be a sufficient alternative. Preferably, patients with aortic stenosis, reported to have a high incidence of new ischemic lesions on MRI following CA, should be included. According to comparable data in this patient group (119), approximately 1,200 patients (600 in each group) are needed to detect a difference in the number of patients observed with new lesions on MRI after CA between the radial and femoral access site, with 80% power and a two-tailed significance level of 0.05.
Beyond vascular access site, various catheter and guidewire techniques should be assessed with the aim of individualising catheterisation techniques according to the patient´s risk profile and situation in which the procedure is performed. As TCD detects microemboli in real-time this technique can be used to understand the impact of different procedural stages during the catheterisation. MRI studies may be included to assess the procedure-related ischemic injury. Above all, future studies should include cognitive assessment. Cognitive function is insufficiently investigated in patients with CAD. There is need for a standardised reliable cognitive test with the ability to identify subtle cognitive changes feasible in the clinical context. More research is required to further investigate the impact of cerebral microemboli caused by different cardiac procedures to enable long-term follow up relating to the risk of future stroke, dementia and depression.

Conclusions

Specific conclusions

1. The number of cerebral microemboli was significantly higher when CA was performed with the right radial access compared with the femoral access. Additionally, more cerebral microemboli were detected in the right middle cerebral artery with the right radial access whereas no difference occurred between the middle cerebral arteries when the femoral access was used. This might entail a causal linkage as catheters, advanced through the right radial artery, bend sharply from the brachiocephalic trunk into the ascending aorta on their way to the coronary orifices.

2. The number of cerebral microemboli detected in the middle cerebral arteries was significantly higher when coronary catheters were advanced over a leading guidewire and subsequently flushed in the ascending compared with the descending aorta during CA with the femoral access. Guidewire technique has an impact on the occurrence of cerebral microemboli and might therefore influence the risk for silent ischemic cerebral lesions.

3. The radial access used for CA or PCI, may be associated with procedure-related stroke or TIA. Despite the low incidence of procedure-related stroke or TIA, these findings need to be confirmed in further studies, as the radial access will continue to be increasingly used.

4. No cognitive impairment was detected after CA and PCI using the Montreal Cognitive Assessment. There was no significant correlation between results of the MoCA test and the number of cerebral microemboli or vascular access site. Mild cognitive impairment was found frequently, entailing a higher risk for post-procedural cognitive decline.

General conclusions

Even though procedure-related neurological complications are rare, the high volume of annually performed CAs and PCIs worldwide leads to a high number of affected patients underlining the importance of research in this field. We showed that the technique used for CA and PCI does have an influence on the occurrence of overt and silent ischemic cerebral complications. There are indications that the radial access is associated with procedure-related stroke or TIA. Throughout published studies have used varying definitions of procedure-related stroke, this makes comparison of study-results difficult and complicates the understanding of related risks. Previously, a wide range of definitions of bleeding complications in the context of ACS treatment were used. After the introduction of a consensus on standardised bleeding definition for cardiovascular trials (Bleeding Academic Research Consortium), the comparability between different studies significantly improved (180). In a similar manner, a standardised definition for procedure-related stroke or TIA would augment future research.

In parallel, the association between cerebral microemboli, silent ischemic cerebral lesions and their clinical impact is yet unclear, probably due to the heterogeneity of the conducted studies. Refined and standardised cognitive assessment, preferably in a multicentre setting may resolve this question.

Little research is published regarding different techniques for performing CA and PCI. If cerebral microemboli are harmful, it is important to find and use the best evidence-based technique. As investigation methods have developed, we have today better conditions for conducting clarifying studies.

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