SUMMARY

This thesis includes twelve manuscripts from seven original prospective cohort studies and two clinical trials addressing two important issues associated with vascular injury after PCI in patients with stable coronary artery disease and acute coronary syndrome.

**Clinical insights in the consequences of transradial access.** Radial artery injury is probably the most common complication after transradial (TR) coronary procedures, mostly caused by vascular access, placement of the introducer sheath, manipulation of the catheter and might be aggravated by radial artery spasm. Optical coherence tomography shows radial artery intimal tears, media dissections and thrombi in a large proportion of patients after TR procedures. In Chapter 1, the R-RADAR study addressed the rate of radial artery injury with very-high resolution ultrasound at the puncture site. Acute radial artery injuries are ubiquitous with signs of dissection in 90%, hematoma in 74% and pseudo aneurysm in 15% of patients. After one month radial artery dissection and hematoma persisted in the majority of patients (dissection 83%, hematoma 65%) with an increase of pseudo aneurysm (56%) and total arterial wall thickness. In this relatively small cohort of patients, radial artery injury was not associated with radial artery occlusion or functional complaints of the upper extremity. In Chapter 2, The ACrA study addressed the short-term effect of TR coronary procedures on self-reported upper extremity function with the validated QuickDASH questionnaire and cold intolerance with the validated CISS questionnaire. Despite ubiquitous injury and functional changes of the radial artery, upper extremity function and cold intolerance were not decreased one month after TR intervention. Access site related extremity complaints (pain in particular) were similarly reported after TR and transfemoral (TF) access at 1 month. The long-term outcome data of the ACrA study are described in Chapter 3. Self-reported upper extremity function and cold intolerance were not affected by TR coronary procedures at 1 year. Access site related extremity complaints diminished considerably over time and were equally reported at 1 year by TR patients (3%) and TF patients (4%).

In the aforementioned studies radial artery spasm was present in 10-12% of patients and may cause severe discomfort, arterial wall injury and procedural failure. The ACrA spasm study was designed to evaluate if endothelial dysfunction might serve as a predictor for radial artery spasm to optimize patient selection for TR procedures, as described in Chapter 4. Unlike radial artery-sheath mismatch and the RAS risk score (including body mass index, height, smoking, peripheral artery disease and hypertension) endothelial dysfunction by pulse amplitude tonometry was not found to be an additional predictor of radial artery spasm in patients undergoing elective TR procedures. Vascular injury might lead to radial artery occlusion (RAO) with ischemic complications of the hand. The application of non-invasive tests to assess palmar arch patency and prevent ischemic complications of the hand are controversial. We therefore designed the ACRA
Anatomy study, described in Chapter 5. While angiographic incompleteness of the superficial palmar arch (SPA) was present in 46% of patients, digital perfusion of the hand was preserved through a complete deep palmar arch (DPA) in all patients. Digital blood supply of the hand was additionally preserved by interosseous collateral arteries in 54%, a persistent median artery in 6% and anastomoses between palmar arches in 49% of patients. The pre-procedural application of non-invasive patency tests did not prevent acute ischemic complications of the hand. Furthermore, the modified Allen Test and Barbeau test had low diagnostics accuracy for palmar arch completeness (57-62%). Future loss of hand function was not associated with incompleteness of the SPA. However, a tendency for delayed thumb perfusion was present in patients with incompleteness of the SPA, which was the basis for the design of the ACRA Perfusion Study (Chapter 6). The consequences of TRI on digital hand perfusion were assessed with sequential Laser Doppler Perfusion Imaging. Tissue perfusion of the hand was reduced during radial access and TR band application, though not associated with incompleteness of the SPA or future loss of hand function. The restoration of tissue perfusion at discharge and homogenous reduction in the contralateral thumb, suggested a systemic effect of TR intervention. In Chapter 7, the Nexfin monitoring system was compared with the LDPI as gold standard for quantification of the collateral hand perfusion. Non-invasive patency tests are liable to misinterpretation and are unable to predict clinical events. Nexfin is a non-invasive, inexpensive bedside test that may calculate the palmar collateral flow index (PCFI) by dividing the average uncorrected systolic blood pressure of the thumb prior to and during radial artery occlusion. Nexfin-derived PCFI showed reasonable correlation with LDPI-derived PCFI for measuring collateral perfusion (R=0.48, p<0.001) and was correlated with self-reported upper extremity function one-month post TR procedure (QuickDASH, R=0.54, p<0.01).

In Chapter 8, the HIRADO study evaluated if chronic radial artery occlusion might lead to exercise induced ischemia of the hand. Manual stress was induced by pinch grip, using an electronic pinch grip gauge. For the primary outcome of exercise induced hand ischemia, no difference in mean transcutaneous oxygen pressures was measured between the RAO hand and the contralateral hand after 5 minutes of manual stress (51 mmHg ± 17 vs. 44 ± 16 mmHg, p=0.18). A similar proportion of significant increased thumb capillary lactate (> 15%) was observed in the RAO hand and the contralateral hand after manual stress (33% vs. 28% respectively, p=1.00). Chronic RAO resulted into increased compensatory flow in the ipsilateral ulnar artery and would not cause impaired digital tissue perfusion of the hand.

Insights in microvascular injury and endothelial function after ACS. Microvascular injury (MVI) is present in 40-50% of patients with STEMI, despite successful treatment with primary PCI. MVI is associated with increased infarct size and has significant prognostic implications\(^2\), which makes this condition an important treatment target in mechanically reperfused STEMI. MVI is angiographically characterized by the “no reflow”
phenomenon. The mechanism of MVI is probably multifactorial and currently no clinical effective therapy is available. Ticagrelor has been reported to increase plasma adenosine levels by inhibition of the adenosine transporter ENT1 and by induction of adenosine triphosphate (ATP) release from erythrocytes\(^3\), which provides protection for adenosine from intracellular metabolism and might have a protective effect on the coronary microcirculation\(^4\). Other P2Y12 antagonists and the active metabolites of clopidogrel and prasugrel do not display any significant activity versus any of the ENT transporters. Elevations of endogenous adenosine may reduce the inflammatory response after AMI and the production of oxygen species, reducing ischemia-reperfusion injury\(^5\)\(^6\). Adenosine also has the capacity to induce endothelial progenitor cell migration\(^7\), which is suggested to be important in regulating angiogenesis in myocardial infarction. Ticagrelor improved peripheral endothelial function in ACS patients, which could not be observed with clopidogrel or prasugrel\(^8\). It was also demonstrated that adenosine-induced coronary blood flow and adenosine-induced coronary vasodilatory response were increased by ticagrelor\(^9\)\(^10\). Moreover, coronary blood flow velocity could only be enhanced by ticagrelor and not by prasugrel in ACS patients\(^11\), and was correlated with the plasma concentration of ticagrelor\(^12\). These observational data suggest a superior effect of ticagrelor over other clinically prescribed P2Y12 inhibitors on the micro- and macro-circulation, which was the rationale to initiate the REDUCE-MVI trial and HITECH trial, as described in **Chapter 9 and Chapter 11**. The REDUCE-MVI trial was a multicenter superiority trial with a Prospective Randomized Open Blinded Endpoint designed to determine if ticagrelor therapy after revascularized STEMI was associated with less MVI compared to prasugrel therapy at 1 month, as determined by the index of microcirculatory resistance (IMR). The primary outcome of IMR in the infarct-related artery was not superior in ticagrelor or prasugrel treated patients (ticagrelor 21 [15-39] U, prasugrel 18 [11-29] U, p=0.08), as described in **Chapter 10**. At one month no difference in infarct size was observed between ticagrelor and prasugrel treated patients (ticagrelor 21 [15-39] g, prasugrel 9.9 [IQR 5.7-16.6] g, p=0.17). Also, CMR-derived microvascular obstruction was not different in patients on ticagrelor (28%) or prasugrel (41%, p=0.35), though intramyocardial hemorrhage was observed less frequently in patients with ticagrelor (23% vs. 43%, p=0.04). No difference in adenosine plasma concentrations at baseline and during ticagrelor or prasugrel maintenance therapy could be detected. The HITECH trial was a randomized open-label multi-center study in patients more than one month following PCI for ACS, randomized to ticagrelor, prasugrel or clopidogrel following a 3-period balanced Latin square crossover design with 4 weeks per treatment period, as described in **Chapter 11**. The primary endpoint of endothelial function by pulse amplitude tonometry, expressed by the reactive hyperemia index (RHI), was not different in stabilized ACS patients after 4 weeks of maintenance with ticagrelor (RHI
1.970 ± 0.535) as compared with prasugrel (RHI 2.007 ± 0.64, p= 0.557) or clopidogrel (RHI 2.072 ± 0.646, p= 0.685), as described in Chapter 12.

**Clinical perspectives**

Part II – Although transradial coronary intervention induces radial artery injury in a large proportion of patients, it will generally not affect self-reported upper extremity function. However, the induced anatomic and functional changes may have negative implications for the subsequent use of the radial artery in CABG or reconstructive surgery. Importantly, radial artery occlusion precludes future ipsilateral TR intervention, though will not lead to exercise induced ischemia of the hand. This thesis demonstrates that digital hand perfusion is preserved by the palmar arch circulation and collateral arterial anastomoses during TR intervention and radial artery occlusion and suggest the redundancy of the modified Allen Test and Barbeau test in clinical practice. Despite modern equipment and techniques, radial artery spasm is still present in a large proportion of patient and might lead to discomfort and access site conversion without affecting procedural success. The association with radial artery dimensions and discordance with angiographic signs of radial artery spasm, suggest that this clinical syndrome is not merely caused by smooth muscle cell contraction. The results of this thesis are important to inform patients and physicians adequately about the safety of TR access, especially when optimal upper extremity function is essential.

Part III - This thesis shows that coronary microvascular injury is present in a substantial amount patients. The attributed pleiotropic effects of ticagrelor through the adenosine metabolism could not be confirmed in patients with acute coronary syndrome, resulting in a similar extent of microvascular injury, infarct size and endothelial function as compared to prasugrel maintenance therapy after PCI. Future randomized trials with sufficient power will establish the difference in long-term clinical outcome between ticagrelor and prasugrel treated patients 13.

**Future perspectives**

Prognosis of patients with CAD has improved significantly over the last decades 14, though remains the most frequent cause of death according to the World Health Organization. Percutaneous coronary intervention is an important minimally invasive technique to limit major adverse cardiac events and morbidity and improve quality of life. As discussed in this thesis, further improvement of this technique is mandatory to overcome remaining issues related to vascular injury.

Slender technologies have been developed to reduce access site related vascular injury and radial artery occlusion 15. Miniaturization of TR equipment to reduce the sheath-to-artery mismatch might also reduce pain and the occurrence of radial artery spasm during TR procedures, as supported by chapter 4 of this thesis. The impact of sheathless
radial artery access and Glidesheath Slender technology on vascular complications and upper extremity dysfunction will be subject of future research. Patients with complex coronary lesions requiring treatment with large-bore guiding catheters may also benefit from TR intervention with slender technology\textsuperscript{16}. Still, the femoral artery is often used for complex PCI with large-bore guiding catheters due to the radial artery-sheath mismatch \textsuperscript{17, 18} and fear of insufficient back-up, which is in return associated with vascular bleeding complications \textsuperscript{19} and adverse clinical outcome. The COLOR trial is a multicenter randomized trial that has been initiated to compare radial with femoral access for complex PCI with large-bore 7Fr. guiding catheters with regard to safety and efficacy (ClinicalTrials.gov Identifier:NCT03846752). Extremity dysfunction will also be compared between patients treated with radial and femoral access. Although limb dysfunction after cardiac procedures is rare, data around this important endpoint is limited\textsuperscript{20}. Future consensus documents should critically address the different methods for upper extremity function and radial artery spasm evaluation.

An alternative access site that gained much attention is the distal radial artery located in the anatomical snuffbox on the dorsal side of the hand\textsuperscript{21}. Next to a potentially more comfortable position for both patient and operator, TR procedures through the anatomical snuffbox might prevent tissue ischemia when occlusion occurs distal to the superficial branch of the radial artery, maintaining antegrade flow to the SPA. Distal RAO still enables future TR procedures through the ipsilateral radial artery. However, damage to the superficial branch of the radial nerve, located near the distal radial artery in the anatomical snuffbox, might lead to severe extremity complaints and hand dysfunction. Future studies with sufficient power should address this specific topic.

Ultrasound guided puncture of the (distal) radial artery, ulnar artery and femoral artery might be a solution to prevent injury to the vasculature and adjacent structures\textsuperscript{22}. Evidence to apply ultrasound guided puncture for jugular and femoral venous access is compelling and is supported by guidelines\textsuperscript{23}. Ultrasound guided access will reduce injury to adjacent structures, the number of punctures, procedural time and improves success rate of vascular access. For femoral artery access, vascular access site complications were reduced by 59% and first pass success rate by 83 % in comparison to angiography guided puncture\textsuperscript{24}. Ultrasound guidance for radial artery access leads to improvement of first pass success rate, access time and number of punctures\textsuperscript{25}. Future randomized trial should address the potential benefit of ultrasound guidance over traditional palpation (landmark) with regard to radial artery occlusion and procedural pain by reducing the number of puncture, as suggested in chapter one of this thesis. Furthermore, the importance of reducing hemostasis and occlusive compression time in patients at increased risk of RAO, especially when using larger sheath sizes, was recently demonstrated in a substudy of the Rap and Beat trial\textsuperscript{26}, and should probably be emphasized in future consensus documents.
Injury to the microcirculation remains an important issue in STEMI patients despite restoration of epicardial vessel patency with primary PCI. In this thesis, we have outlined the high incidence and prognostic implications of MVI, which may not be attenuated by ticagrelor. Distal embolization of thrombotic material and/or atherosclerotic plaque components with mechanical obstruction of the microcirculation and the release of cytokines and other vasoactive substances has been suggested as important mechanism of MVI. Routine thrombus aspiration during primary PCI has been tested for the prevention and treatment of myocardial no-reflow, though failed to show a clinical benefit in large randomized trials. However, trends toward reduced cardiovascular death and increased stroke provide a rationale for future trials of improved thrombus aspiration technologies in patients with high-thrombotic burden. Moreover, outcome data need confirmation in every day clinical practice because trial participants have a different clinical profile and outcome (selection bias). Novel technologies, such as pressure-controlled intermittent coronary sinus occlusion (PICS0), may be attractive to improve microcirculatory perfusion in STEMI but also require further testing in randomized trials. The mechanism of MVI is probably multifactorial, though an important role of innate inflammatory cells is suggested. Next to neutrophilic granulocytes, monocytes may have a significant effect on the occurrence of MVI. Non-selective beta-blockers have the potential to reduce recruitment of innate inflammatory cells through regulation of hematopoietic progenitor cells by antagonizing the beta3-adrenergic receptors and may therefore be a potential therapy in the acute phase of STEMI to reduce MVI. Selective beta-1 adrenoceptor blockers do not have the properties to block the production of monocytes and early IV administration of metoprolol in STEMI patients was not associated with a reduction in infarct size.

Currently, timely reperfusion remains the cornerstone for MVI and infarct size reduction. This may be accomplished by a well-organized primary PCI network to secure short door to balloon times. Also, early administration of drugs that interfere with reperfusion (injury) should be the focus of future research. It was recently demonstrated that infarct size in transient STEMI is small and is not influenced by an early invasive strategy, though might be affected by early administration of more potent antiplatelet or anticoagulant therapy. However, CMR-derived MVI is closely correlated with pathological disruption of the microcirculation and intra-myocardial hemorrhage (IMH). This implies that future therapies should aim to preserve vascular integrity and early treatment with potent anticoagulants or P2Y12 inhibitors may paradoxically aggravate MVI. Further research is needed to understand the pathophysiological mechanisms of MVI to develop personalized management for each STEMI patient in the spirit of contemporary “precision medicine”. New intracoronary physiology indices, e.g. absolute microvascular resistance, might also be useful for better understanding and identification of patients...
at risk for MVI after primary PCI that might be treated with targeted therapies in the early phase of acute myocardial infarction\textsuperscript{40}. 
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