Aus der Klinik für Radiologie
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DISSERTATION

Computed tomography for the diagnosis of coronary artery disease and magnetic resonance imaging for quantifying salvaged myocardium after myocardial infarction

Computertomographie zur Diagnose der koronaren Herzkrankheit und Magnetresonanztomographie zur Quantifizierung geretteten Myokards nach Herzinfarkt

zur Erlangung des akademischen Grades
Medical Doctor - Doctor of Philosophy (MD/PhD)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

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Datum der Promotion: 03. Dezember 2021

1 Manteltext

1.1 Abstract

In patients with low to intermediate probability of coronary heart disease, there is no generally applied diagnostic algorithm. We compared cardiac computed tomography (CT) angiography with direct referral to invasive coronary angiography in a randomized trial including 340 patients with low to intermediate pre-test probability. Cardiac CT angiography could be used as a safe gatekeeper for invasive coronary angiography without worsening long-term clinical outcomes or increasing radiation dosage but decreasing minor procedural complications. In a second prospective clinical study with 92 patients, we compared the diagnostic performance of myocardial CT perfusion in detecting coronary artery disease with that of myocardial magnetic resonance imaging (MRI) perfusion since the identification of flow-limiting lesions among anatomic stenoses can be helpful in therapeutic decision making. We found a comparable diagnostic accuracy of myocardial CT perfusion and the established myocardial MRI perfusion suggesting that CT perfusion reliably identifies flow-limiting coronary artery stenoses. Whether the combination of anatomical assessment with cardiac CT angiography and functional assessment with myocardial CT perfusion is similarly effective in guiding therapy decisions as invasive coronary angiography with fractional flow reserve should be answered in future research.

Salvage of ischemic myocardium is one of the principal therapeutic aims in patients with myocardial infarction. Consequently, the amount of myocardial salvage provides information on therapeutic efficiency. There is a controversial discussion whether MRI allows quantification of myocardial salvage by delineating post-infarctional myocardial edema and fibrosis. In a systematic review and meta-analysis with 38 studies, we evaluated whether the time from symptom onset until reopening of the culprit artery is related to the proportion of nonnecrotic myocardium inside edematous myocardium measured by MRI, the so-called myocardial salvage index. The meta-analysis revealed an inverse relation between the myocardial salvage index and the time from symptom onset until revascularization suggesting that MRI can be of use for assessing therapeutic efficiency. In a second systematic review and meta-analysis with ten studies, we assessed whether the myocardial salvage index on MRI predicts the incidence of major cardiovascular events. We found that a high myocardial salvage index is associated with a low risk of major cardiovascular events during follow-

up indicating prognostic value of quantifying myocardial salvage with MRI after myocardial infarction. Both meta-analyses revealed high between-study heterogeneity, which questions the informative value of single measurements. In both meta-analyses, a considerable part of the heterogeneity could be explained by differences in MRI methodologies. Standardization of post-infarctional MRI methodologies may thus address this concern in the future.

1.2 Zusammenfassung

Für Patienten mit geringer bis mittlerer Wahrscheinlichkeit des Bestehens einer koronaren Herzkrankheit gibt es keinen allgemein angewendeten diagnostischen Algorithmus. In einer randomisierten klinischen Studie erhielten 340 dieser Patienten entweder direkt eine Herzkatheteruntersuchung oder zunächst eine Computertomographie (CT)-Angiographie der Koronargefäße, um zu entscheiden, ob eine Herzkatheteruntersuchung nötig ist. Eine vorgeschaltete CT-Koronarangiographie konnte geringgradige prozedurale Komplikationen reduzieren, ohne dabei die Prognose zu verschlechtern oder die Strahlendosis zu erhöhen. In einer zweiten prospektiven klinischen Studie mit 92 Patienten verglichen wir die diagnostische Genauigkeit in der Erkennung der koronaren Herzkrankheit der myokardialen CT- mit der etablierten Magnetresonanztomographie (MRT)-Perfusion, da die Identifizierung von flusslimitierenden unter anatomischen Stenosen bei Therapieentscheidungen hilfreich ist. Die diagnostische Genauigkeit beider Verfahren zeigte sich ähnlich, sodass die myokardiale CT-Perfusion, flussbegrenzende Koronararterienstenosen effektiv zu identifizieren scheint. Ob die Kombination aus anatomischer Beurteilung mit CT-Koronarangiographie und funktioneller Einschätzung mit myokardialer CT-Perfusion Therapieentscheidungen so effektiv herbeiführen kann wie der Einsatz des Herzkatheters inklusive fraktionierter Flussreserve, sollte in Zukunft untersucht werden.

Die Rettung ischämischen Myokards ist ein Hauptziel der Herzinfarkttherapie und das Ausmaß des geretteten Myokards kann Aufschluss über die Therapieeffektivität geben. Ob die Darstellung des infarktbedingten myokardialen Ödems sowie der Nekrose mit MRT eine Quantifizierung des geretteten Myokards erlaubt, wird kontrovers diskutiert. In einer Metaanalyse mit Einschluss von 38 Studien fanden wir einen inversen Zusammenhang zwischen der Zeit von Symptombeginn bis zur Wiedereröffnung der verschlossenen Koronararterie und dem Anteil des nichtnekrotischen Myokards innerhalb des infarktbedingten myokardialen Ödems, dem so genannten *Myocardial Salvage Index*. Dies deutet darauf hin, dass die MRT-Bestimmung des *Myocardial Salvage Index* bei der Beurteilung der Therapieeffektivität von Nutzen sein kann. In einer zweiten Metaanalyse mit Einschluss von zehn Studien analysierten wir, ob die Bestimmung des *Myocardial Salvage Index* mit MRT schwere kardiovaskuläre Ereignisse während der Nachsorge vorhersagen kann. Es zeigte sich, dass ein hoher *Myocardial Salvage Index* mit einer niedrigen Inzidenz schwerer kardiovaskulärer Ereignisse assoziiert ist und somit prognostischen Wert hat. In beiden Metaanalysen

zeigte sich eine hohe Heterogenität in den Daten, was die Aussagekraft der Einzelmessungen in Frage stellt. Ein beträchtlicher Teil der Heterogenität konnte durch Unterschiede in der technischen MRT-Durchführung erklärt werden. Somit könnte eine Standardisierung der MRT-Durchführung dieses Problem in Zukunft reduzieren.

1.3 Introduction

Cardiovascular diseases are the most common cause of mortality worldwide today, and coronary artery disease is the most prevalent cardiovascular disease (1). Coronary artery disease is caused by arteriosclerotic deposits in the vessel walls, which may reduce the cross-sectional area of blood vessels and thereby the blood flow to the heart muscle. If coronary artery disease progresses, a coronary vessel can become completely blocked with the result of a myocardial infarction. Severe myocardial ischemia leads to hypoxia in the myocardial tissue, which in turn can lead to heart failure, cardiac arrhythmia, and other life-threatening complications (2). An early and reliable diagnosis of coronary artery disease, consequent treatment, and an effective management of myocardial infarction helps to reduce mortality from coronary artery disease. The progress has been remarkable in this regard in the last decade (3, 4), however, the reduction in the mortality rate is counteracted by a global rise in the prevalence of coronary artery disease (5). While education and prevention has thus become even more important, scientists across the globe are working on further improvements in diagnosis and treatment. Hereby, noninvasive imaging may play a key role since its relatively few procedural complications, a constant rise in image quality, and a wider availability in recent years.

The overall aim of this dissertation was to investigate the usage of computed tomography and magnetic resonance imaging in the diagnosis of coronary artery disease and management of myocardial infarction. Working at this aim resulted in four publications:

- Publication 1: Dewey M, Rief M, Martus P, Kendziora B, Feger S, Dreger H, Priem S, Knebel F, Bohm M, Schlattmann P, Hamm B, Schonenberger E, Laule M, Zimmermann E. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. BMJ (Clinical research ed). 2016;355:i5441.

- Publication 2: Rief M, Chen MY, Vavere AL, Kendziora B, Miller JM, Bandettini WP, Cox C, George RT, Lima J, Di Carli M, Plotkin M, Zimmermann E, Laule M, Schlattmann P, Arai AE, Dewey M. Coronary Artery Disease: Analysis of Diagnostic Performance of CT Perfusion and MR Perfusion Imaging in Comparison with Quantitative Coronary Angiography and SPECT-Multicenter Prospective Trial. Radiology. 2018;286(2):461-70.

- Publication 3: Kendziora B, Stier H, Schlattmann P, Dewey M. MRI for measuring therapy efficiency after revascularisation in ST-segment elevation myocardial infarction: a systematic review and meta-regression analysis. BMJ Open. 2020;10(9):e034359.

- Publication 4: Kendziora B, Dewey M. Prognostic value of the myocardial salvage index measured by T2-weighted and T1-weighted late gadolinium enhancement magnetic resonance imaging after ST-segment elevation myocardial infarction: A systematic review and meta-regression analysis. PLOS ONE. 2020;15(2):e0228736.

This text shall summarize these publications and show the linkage between them.

1.4 Computed tomography for the diagnosis of coronary artery disease

1.4.1 Background

If coronary artery disease is suspected, the probability of the existence of coronary artery disease, the so-called pre-test probability, can be estimated by using information on age, sex, and the nature of symptoms (6). In case of a very low pre-test probability, the likelihood for a false positive diagnostic test for coronary artery disease is high. A search for other causes of the symptoms should thus be performed instead. If the pre-test probability is high, invasive coronary angiography should be used as diagnostic test since therapeutic interventions can be performed during the same procedure (7). In case of a low to intermediate pre-test probability, the choice of a diagnostic test depends on local preferences and there is no generally applied diagnostic algorithm. In patients with low to intermediate pre-test probability, the diagnostic yield, defined as the probability that a selected diagnostic test will provide the information needed to establish a definitive diagnosis, of invasive coronary angiography is low (8). Additionally, the invasiveness of the procedure comes along with the risk of minor complications, such as a hematoma at the site of catheterization, and major complications, like dissection or embolism, which can lead to myocardial infarction and stroke (9). Cardiac computed tomography (CT) angiography is the most accurate noninvasive diagnostic test for coronary heart disease and can reliably rule out coronary artery disease (10). However, no randomized trial comparing the effectiveness of cardiac CT angiography to invasive coronary angiography in patients with symptoms of coronary heart disease had been undertaken.

Publication 1 of this dissertation compares the incidence of procedural complications, radiation dose, length of stay, patient acceptance, and long-term clinical outcomes between cardiac CT angiography and invasive coronary angiography in patients with a low to intermediate pre-test probability of coronary heart disease in a randomized trial (11).

If coronary artery disease has been detected, the identification of flow-limiting lesions among arteriosclerotic deposits can be helpful in therapeutic decision making (12). Flow-limiting lesions can be identified by invasive coronary angiography via measuring pressure differences across a coronary artery stenosis, the so-called fractional flow reserve (12). Noninvasively, flow-limiting arteriosclerotic lesions can be detected by single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) via measuring myocardial perfusion (13, 14). Unfortunately, both SPECT

and MRI cannot detect non-flow-limiting arteriosclerotic lesions reliably, which is possible with coronary CT angiography since it provides a relatively high spatial resolution (15). Until recent years, CT had not been able to measure myocardial perfusion, however, improvements in the CT hard- and software overrode this limitation.

To evaluate whether the assessment of myocardial perfusion using CT identifies flow-limiting coronary artery stenoses reliably, Publication 2 of this dissertation compares the diagnostic performance of myocardial CT perfusion in detecting coronary artery disease with that of the established myocardial MRI perfusion in a prospective two-center study (16).

1.4.2 Methods

Publication 1

The whole study (11) was designed, performed, and reported in accordance with the CONSORT Statement for randomized trials. The CONSORT Statement is part of a broader effort to improve the quality and transparency in medical research (17), which is supported by the Noninvasive Imaging Heisenberg Research Group of Marc Dewey at Charité – Universitätsmedizin Berlin, where this thesis originates.

We included patients with a clinical indication for a coronary angiogram based on an atypical presentation of angina pectoris. Typical angina pectoris is defined as retrosternal chest discomfort that is precipitated by physical activity and can be relieved by rest or sublingual nitroglycerin. Patients without the diagnosis of coronary artery disease who present with typical angina pectoris have a high likelihood of actually being affected by coronary artery disease (18). For reasons described in the Background section, our study aimed at patients with low to intermediate pre-test probability. We thus included patients with atypical angina pectoris, defined by the existence of not more than two out of the three typical signs of angina pectoris (chest pain or pressure, bodily exercise as trigger, relief by rest or sublingual nitroglycerin). We excluded patients with suspected myocardial infarction, two positive functional tests for myocardial ischemia, an age of less than 30 years, severe renal insufficiency since contrast agent had to be injected during cardiac CT angiography, and patients with the inability to stop breathing for five seconds because patients had to hold their breath during cardiac CT angiography briefly for technical reasons.

Patients were randomly allocated to direct invasive coronary angiography or cardiac CT angiography. Cardiac CT angiography was performed on 320-row CT scanners (Aquilion ONE or Aquilion ONE Vision Edition, Toshiba Medical Systems). Contrast agent was administered at a flow rate that was calculated according to the body weight (4 ml/s – 5 ml/s). Single, two, or three beat acquisition was performed depending on the heart rate. The acquisition length was adjusted by coronary calcium scoring. Invasive coronary angiography was performed according to the clinical practice at Charité – Universitätsmedizin Berlin. Imaging data was interpreted by two independent readers. In case of disagreement, a consensus was reached by discussion. Coronary artery disease was diagnosed in case of a stenosis of at least 50% in the left main coronary artery or 70% in one of the other coronary arteries. Patients with suspected coronary heart disease in the CT group received an MRI examination afterwards to assess the extent of myocardial necrosis. In absence of a myocardial necrosis of more than 50% transmural extent, the patients underwent invasive coronary angiography. Patients with myocardial necrosis of more than 50% transmural extent were suspected not to benefit from invasive revascularization. Noncalcified coronary artery plaques may be reversible and can be identified with cardiac CT angiography. Patients with noncalcified coronary artery plaques in the CT group thus received a recommendation for a marked reduction of cardiovascular risk factor and statin treatment (19). Patients in the invasive coronary angiography group underwent guideline-based management after the performance of invasive coronary angiography.

Major procedural complications occurring within two days after intervention, including death, cardiac infarction, stroke, or other complications prolonging the hospitalization for at least 24 hours, were the primary outcome. Secondary outcomes were minor procedural complications occurring within two days but not fulfilling the criteria for a major procedural complication, the length of stay in hospital, overall radiation dose, reduction in the need for invasive coronary angiography, the diagnostic yield of invasive coronary angiography, defined as the proportion of patients diagnosed with obstructive coronary heart disease by invasive coronary angiography among all patients who underwent cardiac catheterization, patients' acceptance and preference, the need for invasive coronary angiography during follow-up, and the incidence of a major cardiovascular event during follow-up, defined as myocardial infarction, cardiac death, stroke, unstable angina pectoris, or revascularization.

A power analysis revealed that the inclusion of 320 patients would be needed to detect a difference in the primary outcome between the two groups with a power of 80% when using a chi-square test with continuity correction at a two-sided alpha significance level of 0.05 and estimating a

rate of major procedural complications of 5% in the CT group and 15% in the invasive coronary angiography group. A drop-out rate of 5% was suspected, and we thus randomized 340 patients between February 18, 2009, and August 27, 2015. Follow-up was performed until August 16, 2016. Depending on the data structure of the respective primary or secondary outcome, a chi-square test, t test, Wilcoxon rank-sum test, Cox proportional-hazards model, or Poisson regression test was used for the statistical between-group comparison. A two-tailed significance level of 0.05 was used for all tests.

Publication 2

Publication 2 was conducted as a substudy of the CORE320 multicenter trial (20). The CORE320 study was conducted to evaluate the diagnostic accuracy of the combination of cardiac CT angiography and myocardial CT perfusion for detecting obstructive coronary artery disease, which was defined as stenosis identified by invasive coronary angiography with an appropriate perfusion deficit on SPECT. While the substudy of the CORE320 study/Publication 2 of this dissertation builds on Publication 1 in terms of content and was performed after Publication 1, the CORE320 study can be regarded as predecessor of Publication 1 of this dissertation. In contrast to Publication 1, in which patients were randomized to either cardiac CT angiography or direct invasive coronary angiography, patients in the CORE320 study received both cardiac CT angiography and invasive coronary angiography along with SPECT. Of the 381 patients included in the CORE320 study, 92 patients additionally underwent myocardial MRI perfusion. These 92 patients were included in the substudy of the CORE320 study/Publication 2 of this dissertation comparing the diagnostic performance between the newly developed myocardial CT perfusion and the established myocardial MRI perfusion.

The prospective two-center substudy was conducted according the criteria of the STARD statement (21). The centers involved were the National Institutes of Health located in Bethesda, Maryland, United States of America, and Charité – Universitätsmedizin Berlin (16).

The primary outcome measure was the diagnostic performance of myocardial CT perfusion and myocardial MRI perfusion with combined cardiac CT angiography and SPECT as reference standard reflecting anatomic and functional disease. Secondary outcomes were the diagnostic performance of myocardial CT perfusion and myocardial MRI perfusion with cardiac CT angiography alone as anatomic reference standard and SPECT alone as functional reference standard.

Myocardial CT perfusion was performed at least 20 minutes after sublingually administered nitrates for cardiac CT angiography on a 320-row CT scanner (Aquilion ONE, Toshiba Medical Systems). For both rest and stress myocardial CT perfusion, contrast agent was administered at a flow rate of 4-5 ml/s. For stress myocardial CT perfusion, continuous adenosine infusion (140 mcg/kg/min) was used for increasing the heart rate. Myocardial CT perfusion image date were reconstructed every 0.5 s with a 0.5 mm section thickness. Myocardial MRI perfusion was conducted on a 1.5 T MRI scanner (MAGNETON Espree or Avanto, Siemens Healthcare). Three short-axis sections were acquired for both rest and stress myocardial MRI perfusion. At Charité – Universitätsmedizin Berlin, a fast low-angle shot was applied as MRI sequence, and stress was induced by increasing the heart rate with continuous intravenous adenosine. At the National Institutes of Health, a steady-state free-precession sequence and a regadenoson bolus were applied. SPECT was performed using ^{99m}Tc-labelled contrast agents, with around 25 mCi for stress and 8 mCi for rest imaging. Stress testing was performed using symptom limited exercise, adenosine, or dipyridamole infusion. Clinically indicated invasive coronary angiography was performed within 60 days after performance of myocardial perfusion imaging. Standard techniques made uniform between the two involved centers were used.

All imaging data was analyzed by two independent investigators. In case of disagreement, a final consensus was reached by discussion with a third investigator. For myocardial CT perfusion, myocardial MRI perfusion, and SPECT, image analysis was performed by using a 12-segment model (22). Every segment was subjectively categorized into normal perfusion, mildly deficient perfusion, moderately deficient perfusion, severely deficient perfusion, or myocardial infarction with myocardial thinning. Analysis of myocardial CT perfusion also involved semiquantitative measures: transmural perfusion ratio, myocardial attenuation, as well as myocardial attenuation normalized to the arterial input function. In invasive coronary angiography, all coronary segments of 1.5 mm or larger in diameter were analyzed using the 29-segment standard model. A coronary stenosis of 50% or more was considered to represent coronary artery disease. Alignment between myocardial perfusion territories and coronary stenoses identified by invasive coronary angiography was reached by using vascular territory maps (22).

The diagnostic performance of myocardial CT perfusion and myocardial MR perfusion was assessed by calculating the diagnostic accuracy, sensitivity, specificity, negative predictive value, positive predictive value, negative predictive likelihood ratio, and positive predictive likelihood ratio with the combination of cardiac CT angiography and SPECT, cardiac CT angiography alone, and

SPECT alone as reference standards. The Mantel-Haenszel test stratified by disease status was applied as inferential statistical test to compare the diagnostic performance values of myocardial CT perfusion and myocardial MR perfusion.

1.4.3 Results

Publication 1

According to the power analysis of the randomized trial conducted to compare the incidence of procedural complications, radiation dose, length of stay, patient acceptance, and long-term clinical outcomes between cardiac CT angiography and invasive coronary angiography in patients with a low to intermediate pre-test probability of coronary heart disease (11), 340 patients with supposed coronary heart disease and clinically indicated cardiac catherization were randomized to either noninvasive cardiac CT angiography, followed by invasive coronary angiography in case of positivity for obstructive coronary artery lesions, or direct invasive coronary angiography. The pretest probability measured by the Duke clinical score (23) among all randomized patients was 34.6% (standard deviation: 23.5%). Of the 340 patients, 168 patients were assigned to the cardiac CT angiography group, while 172 patients were allocated to the invasive coronary angiography group. One patient in the cardiac CT angiography group withdrew informed consent, while ten patients in the invasive coronary angiography group withdrew informed consent. After excluding those who withdrew consent, 167 patients in the cardiac CT angiography group and 162 patients in the invasive coronary angiography group remained in the intention-to-treat groups and were included in the primary outcome analysis.

Two patients in the cardiac CT angiography group were sent directly to invasive coronary angiography per clinician request but stayed in the cardiac CT angiography group for the primary outcome analysis following the intention-to-treat principle. One of these two patients was diagnosed with obstructive coronary heart disease by conductance of invasive coronary angiography. Of the 165 patients who underwent cardiac CT angiography, 20 patients were diagnosed with obstructive coronary artery disease on cardiac CT angiography. Seventeen of these patients underwent cardiac MRI; two patients underwent invasive coronary angiography directly because of metal implants, another patient because of claustrophobia. None of the 17 patients undergoing cardiac MRI had a myocardial necrosis of more than 50% transmural extent, and thus, all 17 patients were sent to invasive

coronary angiography. In 17 of the 20 patients undergoing invasive coronary angiography after cardiac CT angiography, the diagnosis of obstructive coronary artery disease was confirmed. In 25 of the 162 patients in the invasive coronary angiography group, the diagnosis of obstructive coronary angiography was made. Overall, obstructive coronary angiography was excluded in 149 of 167 patients (88.6%) in the cardiac CT angiography intention-to-treat group and 137 of 162 patients (84%) in the invasive coronary angiography intention-to-treat group ($p = 0.28$).

The primary outcome of the trial (major procedural complications within two days after intervention) occurred only once. In particular, one myocardial infarction occurred in the cardiac CT angiography group, no major procedural complication occurred in the invasive coronary angiography group, and there was no statistically significant difference between the groups ($p = 1.00$).

Minor procedural complications were more common in the invasive coronary angiography group (3.6% vs. 10.5%, $p = 0.014$). This was primarily the result of a lower incidence of hematoma at the puncture site in the cardiac CT angiography group than in the invasive coronary angiography group (0.6% vs. 8.6%, $p < 0.001$). The incidence of other minor procedural complications was uncommon in both groups (secondary bleeding at the puncture site: 0.6% vs. 0.6%, $p = 1.00$; bradycardia: 1.2% vs. 0%, $p = 0.50$; angina without infarction: 0.6% vs. 0%, $p = 1.00$; allergoid reaction to contrast agent: 0.6% vs. 0%, $p = 1.00$; stent migration: 0% vs. 0.6%, $p = 1.00$; and hypotension requiring treatment: 0% vs. 0.6%, $p = 1.00$). In the cardiac CT group, there was a reduction of 86% in the need for invasive coronary angiography (95% confidence interval: 9-20, $p < 0.001$), a higher diagnostic yield of invasive coronary angiography, defined as the proportion of invasive coronary angiograms showing obstructive coronary heart disease (75% vs. 15%, $p < 0.001$), and a shorter median length of stay (30.0 hours [95% confidence interval: 3.5-77.3) vs. 52.9 hours [49.5-76.4], $p < 0.001$). There was no statistically significant difference in the median radiation dose between the groups (5.0 mSv [95% confidence interval: 4.2-8.7] vs. 6.4 mSv [3.4-10.7], $p = 0.45$). During a median follow up of 3.3 years, the necessity for cardiac catherization was lower in the cardiac CT angiography group (relative risk adjusted for observation time: 3.1, 95% confidence interval: 2.3-4.0, $p < 0.001$), while there was no statistically significant difference in the incidence of major cardiovascular events (4.2% vs. 3.7%, adjusted hazard ratio 0.90, 95% confidence interval: 0.30-2.69, $p = 0.86$). The question whether cardiac CT angiography or invasive CT angiography would be preferred for subsequent testing was answered by 278 of 329 patients (84.5%) included in the primary

outcome analysis. Of these 278 patients, 219 patients (78.8%) replied that they would prefer cardiac CT angiography.

Publication 2

As mentioned in the Methods section, 92 patients of the CORE320 multicenter trial (20) successfully underwent invasive coronary angiography, SPECT, myocardial CT perfusion, and myocardial MRI perfusion and were thus included in the substudy comparing the diagnostic performance of myocardial CT perfusion and myocardial MRI perfusion in detecting coronary artery disease (16). With invasive coronary angiography alone, obstructive coronary artery disease with at least one stenosis of 50% or more was diagnosed in 59 of 92 patients (64%). With SPECT alone, the prevalence of coronary heart disease was 53% (49 of 92 patients). With invasive coronary angiography and SPECT combined (stenosis of 50% or more on invasive coronary angiography and a fitting myocardial perfusion defect on SPECT), the diagnosis of obstructive coronary artery disease was made in 36 of 92 patients (39%).

Comparing the diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value between myocardial CT perfusion and myocardial MR perfusion on per-patient level, we found the following differences. When using combined invasive coronary angiography and SPECT as reference standard, the specificity of myocardial CT perfusion was lower than the specificity of myocardial MRI perfusion (45%, 95% confidence interval: 31-59 vs. 70%, 95% confidence interval: 56-81, p = 0.01). The sensitivity of myocardial CT perfusion was higher than the sensitivity of myocardial MRI perfusion when using invasive coronary angiography as reference standard (90%, 95% confidence interval: 79-96 vs. 69%, 95% confidence interval: 56-81, p = 0.01). When using SPECT alone as reference standard, the diagnostic accuracy and specificity of myocardial CT perfusion were lower than the diagnostic accuracy and specificity of myocardial MRI perfusion (58%, 95% confidence interval: 47-68 vs. 65%, 95% confidence interval: 55-75, p = 0.001; 37%, 95% confidence interval: 23-53 vs. 65%, 95% confidence interval: 49-79; p = 0.004).

On per-territory level, the specificity of myocardial CT perfusion was lower than the specificity of myocardial MRI perfusion when using combined invasive coronary angiography and SPECT as reference standard (68%, 95% confidence interval: 61-74 vs. 78%, 95% confidence interval: 71-83, p = 0.01). When using invasive coronary angiography alone as reference standard, the sensitivity of myocardial CT perfusion was higher than the sensitivity of myocardial MRI perfusion (63%, 95% confidence interval: 54-71 vs. 47%, 95% confidence interval: 38-56, p = 0.01). When

using SPECT alone as reference standard, the diagnostic accuracy and specificity of myocardial CT perfusion were lower than the diagnostic accuracy and specificity of myocardial MR perfusion (62%, 95% confidence interval: 56-68 vs. 67%, 95% confidence interval: 61-73, p = 0.03; 66%, 95% confidence interval: 59-73 vs. 78%, 95% confidence interval: 71-84, p = 0.02).

There were no other significant differences in the diagnostic accuracy, sensitivity, specificity, positive predictive value, or negative predictive value between myocardial CT perfusion and myocardial MR perfusion on per-patient or per-territory level using the combination of invasive coronary angiography and SPECT, invasive coronary angiography alone, or SPECT alone as reference standard. Especially, there was no significant difference (p = 0.11) in the diagnostic accuracy of myocardial CT perfusion (63%, 95% confidence interval: 52-73) and myocardial MR perfusion (75%, 95% confidence interval: 65-84) when using the combination of invasive coronary angiography and SPECT as reference standard (primary reference standard).

1.4.4 Discussion

In Publication 1, in which patients with low to intermediate pre-test probability of coronary heart disease were randomized to either cardiac CT angiography or direct invasive coronary angiography (11), cardiac CT angiography was found not to worsen long-term clinical outcomes, decrease minor but not major procedural complications, increase the diagnostic yield of conducted invasive coronary angiographies, defined as the proportion of invasive coronary angiograms showing obstructive coronary heart disease, shorten the length of in-hospital stay, not to increase radiation exposure, and improve patient acceptance. Publication 2 (16) showed a comparable diagnostic accuracy in the detection of coronary artery disease for the newly developed myocardial CT perfusion and the established myocardial MRI perfusion with the combination of invasive coronary angiography and SPECT as primary reference standard. The most notable differences were a higher sensitivity of myocardial CT perfusion compared to myocardial MRI perfusion with invasive coronary angiography as reference standard and a higher specificity of myocardial MRI perfusion in comparison to myocardial CT perfusion with the combination of invasive coronary angiography and SPECT or SPECT alone as reference standard.

The results of Publication 1 indicate that cardiac CT angiography can be used as a safe gatekeeper for invasive coronary angiography in patients with low to intermediate pre-test probability

of coronary heart disease without worsening long-term clinical outcomes or increasing major procedural complications or radiation dosage. In contrary, the decrease in the length of in-hospital stay and the reduction in minor procedural complications by using cardiac CT angiography as gatekeeper for invasive coronary angiography seem to improve patient acceptance and may likely reduce overall costs to the health care system compared with direct referral to invasive coronary angiography.

Besides cardiac CT angiography, functional non-invasive tests, i.e. exercise electrocardiogram (ECG), wall motion abnormalities by stress MRI or stress echocardiography, and perfusion changes by SPECT, MRI, positron emission tomography (PET), or contrast echocardiography, have been applied as gatekeeper for invasive coronary angiography. Randomized controlled trials showed similar clinical outcomes when comparing functional imaging tests and cardiac CT angiography as gatekeeper (24-26). Functional imaging tests thus are a valuable alternative to cardiac CT angiography as initial diagnostic test in patients with low to intermediate pre-test probability. Exercise ECG, being a functional non-imaging test, has shown inferior diagnostic performance compared to functional imaging tests and can therefore be considered less appropriate as gatekeeper for invasive coronary angiography (27).

Having to decide between cardiac CT angiography and the mentioned functional non-invasive imaging tests as gatekeeping test in patients with low to intermediate pre-test probability is difficult. Coronary artery stenoses of 50-90% do not necessarily result in myocardial ischemia (27, 28). Cardiac CT angiography is an anatomic test, and thus, an additional functional imaging test should be conducted before revascularization when a coronary artery stenosis of less than 90% is detected by cardiac CT angiography, either non-invasively or invasively by measuring the fractional flow reserve with invasive coronary angiography. Functional imaging tests cannot detect subclinical, non-obstructive coronary artery disease, which is possible with cardiac CT angiography (29). In patients with low pre-test probability of coronary heart disease, cardiac CT angiography may therefore be more appropriate as initial screening test. In contrast, one of the mentioned functional imaging tests may be more appropriate in patients with intermediate pre-test probability.

The problem of having to decide among different imaging modalities as gatekeeping test in patients with low to intermediate pre-test probability may be overcome by the newly developed myocardial CT perfusion, which can be performed during the same CT examination as cardiac CT angiography combing both anatomic and functional imaging. Having in mind that myocardial MRI

perfusion has shown its accuracy in detecting myocardial perfusion deficits with the currently most used ischemia imaging test SPECT as reference standard in a large multicenter study (30), the comparable diagnostic accuracy of myocardial MRI perfusion and myocardial CT perfusion shown in Publication 3 suggests that myocardial CT perfusion can be used as reliable technique for the detection of flow-limiting coronary artery stenoses. The greater sensitivity of myocardial CT perfusion may be a result of its higher spatial resolution compared to myocardial MRI perfusion. The higher specificity of myocardial MRI perfusion may be explained by the susceptibility of myocardial CT perfusion to beam-hardening artefacts imitating a lack of perfusion.

No previous study directly compared myocardial MRI perfusion and myocardial CT perfusion with combined invasive coronary angiography and SPECT as reference standard. However, Bettencourt et al. compared the diagnostic accuracy between myocardial CT perfusion and myocardial MRI perfusion with fractional flow reserve measured by invasive coronary angiography as reference standard in a study with 101 patients (31). While Bettencourt et al. measured a sensitivity of 68% and specificity of 93% for myocardial CT perfusion with fractional flow reserve measured by invasive coronary angiography as reference standard, our data revealed a higher sensitivity of 92% and a lower specificity of 45% for myocardial CT perfusion with combined invasive coronary angiography and SPECT as primary reference standard. For myocardial MRI perfusion, there were also considerable differences in the sensitivity (89% vs. 83%) and specificity (88% vs. 70%) between the study of Bettencourt et al. with fractional flow reserve and our study with combined invasive coronary angiography and SPECT as reference standard. These differences could at least partly be the result of the different primary reference standard.

De Bruyne et al. showed in 2014 that percutaneous intervention guided by the measurement of flow-limitation with fractional flow reserve plus the best available medical therapy improves the outcome in patients with stable coronary artery disease and hemodynamically significant stenosis compared to the best available medical therapy alone (32). Whether the combination of anatomical assessment with CT angiography and functional assessment with myocardial CT perfusion is similarly effective in guiding therapy decisions as invasive coronary angiography with fractional flow reserve should be tested in a randomized trial in the future. Moreover, the recently developed CT-derived fractional flow reserve for assessing the physiological consequences of an anatomical coronary stenosis should be given attention in the future (33).

Publication 1 and 2 both have limitations. In the preparation of Publication 1, the actual prevalence and revascularization rates were underestimated. The power analysis thus resulted in a study population that was too small to compare the primary outcome (major procedural complications) between cardiac CT angiography and invasive coronary angiography. Furthermore, cardiac CT angiography can be conducted in an outpatient setting with a short length of stay in hospital. However, we could not include patients undergoing invasive coronary angiography on an outpatient basis in the university hospital setting. Publication 2 is limited by the differences in the prevalence of coronary artery disease depending on the used reference standard. A widely accepted reference standard for comparing myocardial ischemia imaging tests is currently not available, and we decided to use combined invasive coronary angiography and SPECT as primary reference standard and invasive coronary angiography alone as well as SPECT alone as secondary reference standards. While the study may include one of the highest amounts of patients undergoing various myocardial ischemia imaging tests (myocardial CT perfusion, myocardial MRI perfusion, and SPECT) along with invasive coronary angiography, the patient number was not based on a power analysis since Publication 2 was conducted as substudy of the CORE320 multicenter trial (20).

1.5 Magnetic resonance imaging for quantifying salvaged myocardium after myocardial infarction

1.5.1 Background

Salvage of ischemic myocardium is one of the main aims of revascularization by percutaneous coronary intervention or fibrinolysis in myocardial infarction. Consequently, the amount of myocardial salvage provides information on therapeutic efficiency (34). Myocardial salvage after myocardial infarction is defined as the spatial difference between the previously ischemic myocardial tissue distal to the obstructed coronary artery/arteries, the so-called area at risk, and the finally resulting necrotic infarct size. The gold standard for quantifying myocardial salvage after myocardial infarction is myocardial perfusion SPECT (35). However, the procedure of measuring myocardial salvage with SPECT involves radiation exposure and is lengthy requiring two examinations one month apart. MRI has been used as a newer method for quantifying myocardial salvage that may overcome these limitations since it can be performed without radiation exposure in one examination during the first days after revascularization (36). For this purpose, myocardial edema is quantified using T2-weighted MRI, and fibrotic myocardium is delineated by T1-weighted late gadolinium enhancement MRI. For calculating the myocardial salvage index, it is assumed that the measured myocardial edema represents the previously ischemic myocardium, which is subject of a controversial discussion in the field (37, 38).

To analyze whether there is a relation between the time from symptom onset until reopening of the culprit artery and the proportion of nonnecrotic myocardial tissue inside edematous myocardial tissue measured by T1-weighted late gadolinium enhancement and T2-weighted MRI after myocardial infarction, the so-called myocardial salvage index, we performed a systematic review and meta-analysis with existing data (39), which constitutes Publication 3 of this dissertation.

From an academic point of view, quantifying myocardial salvage with MRI after myocardial infarction could be helpful for comparing cardioprotective therapies. From a clinical perspective, it is interesting whether the measurement of myocardial salvage on MRI has prognostic value. The risk of future major cardiovascular events should be assessed in all patients with myocardial infarction before discharge (40, 41). Depending on the estimated risk, interventions reducing the risk should be

considered. The backbone of the risk assessment are clinical markers, including age, heart rate, blood pressure, Killip classification, location of the myocardial infarction, serum creatinine level, heart failure, history of myocardial infarction, and peripheral artery disease. In addition, the left ventricular ejection fraction has strong predictive value and is routinely assessed in all patients with myocardial infarction, mostly by echocardiography. Noninvasive tests for myocardial ischemia, such as stress echocardiography, pharmacological stress myocardial perfusion using SPECT or MRI, or electrocardiographic treadmill testing, should be performed in patients who have not been treated with primary percutaneous coronary intervention and at least be considered in patients with arteriosclerotic lesions in a coronary artery not responsible for the past myocardial infarction (40, 41). Noninvasive quantification of salvaged myocardium has been suggested as another prognostic marker. As mentioned above, SPECT is the current gold standard for measuring myocardial salvage but requires two examinations: A radioactive tracer must be injected prior to the reopening of the culprit artery for measuring the ischemic area at risk and one month later for quantifying the final fibrotic infarct size (36). Quantification of myocardial salvage with SPECT can thus not be included in the risk assessment during hospitalization after myocardial infarction. MRI can be performed without radiation exposure at one point in time during hospitalization, and quantification of myocardial salvage with MRI could therefore be included in the risk assessment (35). However, the opinions on the prognostic value of measuring myocardial salvage with MRI after myocardial infarction differ.

We therefore summarized and analyzed published data on the prognostic value of the myocardial salvage index measured by MRI after myocardial infarction in a second systematic review and meta-analysis (42) representing Publication 4 of this dissertation.

1.5.2 Methods

Publication 3

The meta-analysis conducted to analyze whether there is a relation between the time from symptom onset until reopening of the culprit artery and the myocardial salvage index measured by MRI in published data (39) was performed and reported according to the PRISMA guidelines (43).

The following eligibility criteria for the inclusion of studies in the review were applied: All studies had to include patients diagnosed with ST-segment elevation myocardial infarction, use percutaneous coronary intervention as part of the acute management, and report the time from

symptom onset until revascularization. In addition, studies had to perform MRI in the first week after cardiac infarction and report the myocardial salvage index assessed by T1-weighted late gadolinium enhancement and T2-weighted MRI. Alternatively, the studies could report the extent of necrotic left ventricular cardiac tissue assessed by T1-weighted late gadolinium enhancement MRI along with the extent of edematous left ventricular cardiac tissue assessed by T2-weighted MRI, which allowed the post hoc calculation of the myocardial salvage index. All studies had to use a volumetric unit convertible to the percentage of left ventricular cardiac tissue for their measurements of necrotic and edematous cardiac tissue on T1-weighted late gadolinium enhancement and T2-weighted MRI and state the confidence interval, standard deviation, or interquartile range for the myocardial salvage index or the spatial extents of necrotic and edematous tissue. Publication in English, French, or German was necessary. Animal studies were excluded.

MEDLINE (via PubMed), ISI Web of Science, and EMBASE (via Ovid) were searched for eligible studies from their inception until May 15, 2019. Search terms for ST-segment elevation myocardial infarction, T1-weighted late gadolinium enhancement, and T2-weighted MRI were combined. The titles and abstracts of retrieved references were scanned, and a full text review of potentially eligible articles was performed afterwards. The bibliographies of eligible studies and reviews found by searching the databases were screened for studies missed by the database search.

General information on the included studies, the time from symptom onset until revascularization, and the myocardial salvage index assessed by T1-weighted late gadolinium enhancement and T2-weighted MRI or the extent of necrotic left ventricular cardiac tissue measured by T1-weighted late gadolinium enhancement MRI and the extent of left ventricular edematous myocardium measured by T2-weighted MRI were extracted into a prespecified database.

Random effects models were applied for descriptive statistics of continuous variables. Study was embedded in these models as random effect for considering non-independent observations within studies. A logit transformation was performed for the percentage of male patients to stabilize the variance and prevent a variance-on-mean relationship (44). Frequency distributions were used for descriptive statistics of categorical variables. A mixed effects model was used to analyze whether the time from symptom onset until revascularization was a significant predictor of the myocardial salvage index measured by T1-weighted late gadolinium enhancement and T2-weighted MRI. Again, study was included as random effect for considering non-independent observations within studies. Between-study heterogeneity in the mixed effects model was explored by including patient characteristics (age

and gender distribution) and MRI parameters (timing of MRI, type of MRI sequences, and MRI interpretation methods for delineating edema and necrosis) in the mixed effects model. First, each of these parameters was included in the mixed effects model separately. Afterwards, all parameters that explained a significant part of the heterogeneity in the likelihood ratio test were included in the final mixed effects model together.

Risk of bias in individual studies was assessed using the component approach (45). We thus developed a set of items to evaluate the domains of bias we regarded as most important to the meta-analysis: attrition, selection, and detection bias. Funnel plots, Begg and Mazumdar's correlation test, and Egger's regression test were applied to search for publication bias across studies.

Publication 4

Similarly to Publication 3, Publication 4 performed to summarize and analyze existing data on the prognostic value of measuring myocardial salvage with MRI after myocardial infarction (42) was conducted and reported according to the PRISMA guidelines (43).

The eligibility criteria, electronic search strategy, and data extraction were equal to Publication 3 with the exception that studies included in Publication 4 had to report the incidence of major cardiovascular events during follow-up, defined as hospital admission for heart failure, nonfatal cardiac infarction, or cardiac death, instead of the time from symptom onset until revascularization.

Random effects models with study as random effect for considering non-independent observations within studies and frequency distributions were used for the description of extracted numerical and categorical data. A mixed effects model was applied to identify a correlation between the myocardial salvage index measured by MRI and the incidence of major cardiovascular events during follow-up. Similarly to the random effects models, study was incorporated as random effect in the mixed effects model for considering non-independent observations within studies. The length of follow-up was incorporated as fixed effect to account for differences in the follow-up length between studies. To identify reasons for between-study heterogeneity, a heterogeneity analysis with the incorporation of two major cardiovascular risk factors (diabetes and age) and two crucial MRI technique parameters (interpretation and timing of MRI) in the mixed effects model was conducted.

Depending on the study design of the respective included study, different quality assessment tools were used to assess the risk of bias in included studies, which stands in contrast to Publication 3. Randomized controlled trials were evaluated by the Cochrane Risk of Bias tool (46),

nonrandomized cohort studies and case control studies by the Newcastle Ottawa Quality Assessment Scale (47), and case series studies by the 18-item tool by Moga et al. (48). Similarly to Publication 3, a funnel plot, Egger's regression test, and Begg and Mazumdar's rank correlation test with continuity correction were used to assess publication bias across studies.

1.5.3 Results

Publication 3

The search strategy for the meta-analysis on the relation between the time from symptom onset until revascularization and the myocardial salvage index measured by MRI (39) revealed 1785 references. Of these 1785 references, 436 references were duplicates and 1163 excluded after title and abstract review. Full-text review of the remaining articles resulted in the exclusion of 148 articles, so that 38 studies with 5106 patients remained for inclusion in the meta-analysis.

The pooled myocardial salvage index measured by T1-weighted late gadolinium enhancement and T2-weighted MRI in these studies was 42.6% (95% confidence interval: 38.9-47.0). The pooled time from symptom onset until revascularization was 3.8 hours (95% CI: 3.5 to 4.0).

The mixed effects model revealed an inverse relation between the time from symptom onset until revascularization and the myocardial salvage index: Every hour of delay in revascularization resulted in an absolute decrease of 13.1% (95% confidence interval: 11.5-14.6; $p < 0.001$) in the myocardial salvage index on MRI. The unexplained variance between the studies' reported myocardial salvage indices was considerable ($\tau^2 = 167.8$).

The heterogeneity analysis revealed that differences in the timing of MRI ($\chi^2(1) = 11.5$, $p < 0.001$), T1-weighted late gadolinium enhancement MRI interpretation method ($\chi^2(5) = 15.3$, $p = 0.009$), T2-weighted MRI interpretation method ($\chi^2(2) = 7.8$, $p = 0.020$), and gender distribution ($\chi^2(1) = 11.3$, $p < 0.001$) among studies explained a significant part of this unexplained variance, respectively. Inclusion of these parameters as confounding variables in the mixed effects model reduced the unexplained heterogeneity between studies by 45.2% to $\tau^2 = 91.9$.

The component approach used to evaluate the risk of bias in included studies showed one study with high and 13 studies with unclear selection bias, one study with high and three studies with unclear attrition bias, and ten studies with unclear detection bias. Publication bias was not found in a funnel

plot with data on the myocardial salvage index, nor by applying Egger's regression test ($t = 0.7$; $p = 0.507$) and Begg and Mazumdar's rank correlation test ($z = -1.4$, $p = 0.173$).

Publication 4

The meta-analysis performed to summarize and analyze published data on the prognostic value of measuring myocardial salvage with MRI after myocardial infarction (42) included a total of ten studies with 2,697 patients. The systematic search in MEDLINE (via Pubmed), ISI Web of Science, and EMBASE (via Ovid) revealed 1625 references. Of these 1625 references, 434 references were duplicates and excluded. After reviewing the respective title and abstract, 1019 references were excluded. Full-text review resulted in the exclusion of 163 additional references. One eligible study was revealed by screening the bibliographies of eligible studies and reviews found by the systematic search in electronic databases. We thus included ten studies comprising two randomized controlled trials, six nonrandomized cohort studies, one case control study, and one case series.

Pooling the data of included studies revealed an overall MRI-measured myocardial salvage index of 43.0% (95% confidence interval: 37.4-48.6), an overall incidence of major cardiovascular events during follow-up of 10.6% (95% confidence interval: 5.7-15.5), and an overall length of follow-up of 12.3 months (95% confidence interval: 7.0-17.6).

There was a negative correlation between the mean myocardial salvage index in included study populations and the incidence of major cardiac events during follow-up in these patient groups. In particular, the incidence of major cardiac events during follow-up increased by 1.7% (95% confidence interval: 1.6-1.9) with every 1% of decrease in the MRI-measured myocardial salvage index. The between-study heterogeneity was substantial with an unaccounted standard deviation between studies τ of 21.3.

The conducted heterogeneity analysis showed that 65.3% of the unexplained between-study standard deviation could be accounted for by incorporation of two major cardiovascular risk factors (diabetes and age) and two crucial technical MRI parameters (interpretation and timing of MRI).

The risk of bias analysis in included studies revealed that the risk of bias was increased in one study by retrospective conductance and the uncertainness whether the dropouts were equally distributed within included study groups. In four studies, the risk of bias was increased by a short follow-up. Publication bias was not found by conducting Egger's regression test ($t = -1.17$, $p = 0.26$)

and Begg and Mazumdar's rank correlation test (z = -1.67, p = 0.097), nor by visually assessing a funnel plot created with data on the myocardial salvage index.

1.5.4 Discussion

The meta-analysis on the relation between the time from symptom onset until revascularization and the myocardial salvage index measured by MRI (39) showed an inverse relation between the time from symptom onset until revascularization and the myocardial salvage index on MRI. The meta-analysis on the prognostic value of measuring myocardial salvage with MRI after myocardial infarction (42) shows and inverse relation between the myocardial salvage index measured by MRI and the follow-up incidence of major cardiac events.

We did not find any other meta-analysis on the relation between reperfusion delay and the myocardial salvage index measured by MRI or the relation between the myocardial salvage index on MRI and the incidence of major cardiovascular events after myocardial infarction in electronic databases. Francone et al. compared the myocardial salvage index on MRI between four patient groups categorized by the time between symptom onset and revascularization (49). In accordance with the results of Publication 3, Francone et al. found an inverse relation between revascularization delay and the myocardial salvage index on MRI. Two other clinical studies by Eitel et al. (50) and de Waha et al. (51) compared the myocardial salvage index on MRI between patients suffering from at least one major cardiovascular event during follow-up and patients without the occurrence of a major cardiovascular event (50, 51). In both studies, the myocardial salvage index showed a significant difference between patients with and without at least one major cardiovascular event during follow-up, which is in line with the results of our meta-analysis.

The decrease of the myocardial salvage index with increasing reperfusion delay suggests a gradual extension of fibrotic myocardium within edematous myocardium during ischemia, which makes a connection between the extent of myocardial edema and the area at risk seem likely. This insight contributes to but cannot end the controversial discussion on whether myocardial edema on MRI delineates the area at risk mentioned in the Introduction section since underestimation or overestimation is possible, even if the myocardial edema and the area at risk are connected. However, it may not be of utmost practical importance if the myocardial edema on MRI exactly delineates the area at risk. More importantly, the gradual extension of infarction-induced fibrotic myocardium within

edematous myocardium with increasing reperfusion delay suggests that the myocardial salvage index calculated as proportion of non-necrotic cardiac tissue inside edematous cardiac tissue can be used as measure of therapy efficiency and may thus be applied for comparing cardioprotective strategies. The inverse relation between the myocardial salvage index on MRI and the incidence of major cardiovascular events during follow-up shown in Publication 4 suggests that quantification of myocardial salvage with MRI has prognostic value after myocardial infarction. According to the current European guideline, a risk assessment should be performed in all patients hospitalized for ST-segment elevation myocardial infarction before discharge (52). Cardiac ejection fraction and valve function, which are standard parameters of the risk assessment and mostly measured by echocardiography in current clinical routine, can be assessed using cardiac cine MRI. Including T1-weighted late gadolinium enhancement and T2-weighted sequences in the same MRI examination used to obtain cine MRI sequences could add value to the risk assessment by providing the myocardial salvage index as another prognostic parameter. Patients needing intensified care may be identified more reliably, which in turn could improve long-term outcome. A randomized trial allocating patients to either standard risk assessment or risk assessment including MRI with measurement of the myocardial salvage index could be used to test this hypothesis.

The considerable heterogeneity in the mixed effects model on the relation between the time from symptom onset until revascularization calculated in Publication 3 indicates that other parameters than the time from symptom onset until revascularization have an impact on the myocardial salvage index measured by MRI. The heterogeneity analysis suggests that these parameters include MRI technique parameters. A standardization of post-myocardial infarction MRI methodologies thus is desirable (53). Differences induced by the MRI technique may be reduced in the future by the application of T1- and T2-weighted mapping, which provides a less subjective and more reliable depiction of fibrotic and edematous myocardium (54). The fact that the gender distribution in included study populations explained a significant part of the between-study heterogeneity emphasizes that gender differences should be accounted for when interpreting the myocardial salvage index, which is in line with previous findings (55, 56). Of course, cardioprotective strategies other than shortening of the time interval between symptom onset and revascularization may explain a part of the heterogeneity that remains after inclusion of the described confounding variables (57, 58). The finding of considerable statistical heterogeneity in the mixed effects model on the relation between the myocardial salvage index and the incidence of major cardiovascular events in Publication 4 implies

that the results of the meta-analysis cannot be used to set a single reliable threshold for the myocardial salvage index that defines a high risk of major cardiovascular events after discharge. The myocardial salvage index measured by MRI should in contrast be interpreted by taking into account other cardiovascular risk factors and the applied MRI technique since nearly two thirds of the heterogeneity between studies were explainable by disagreements in cardiovascular risk factors among the study populations and the applied MRI technique.

Both meta-analyses are limited by an absent online registration of a review protocol, which can lead to bias in post-hoc decisions (43). Additionally, both publications do not include data on the relatively new MRI technique of mapping, which may replace conventional T1-weighted late gadolinium enhancement and T2-weighted MRI in the assessment of myocardial edema and necrosis in the future. In Publication 4, the electronic search, data extraction, risk of bias assessment, and statistical analysis, was performed by a single reviewer, me, leading to a higher likelihood of errors in these procedures when compared with a two-fold approach (59).

1.6 Conclusion

The results of a randomized trial allocating patients with low to intermediate pre-test probability of coronary heart disease to either cardiac CT angiography or direct invasive coronary angiography indicate that cardiac CT angiography can be used as a safe gatekeeper for invasive coronary angiography without worsening long-term clinical outcomes or increasing radiation dosage but decreasing minor procedural complications. The comparable diagnostic accuracy of myocardial MRI perfusion and myocardial CT perfusion shown in a prospective multicenter study with the combination of invasive coronary angiography and SPECT as primary reference standard suggests that myocardial CT perfusion can be used as effective technique for identifying flow-limiting coronary artery stenoses. Whether the combination of anatomical assessment with cardiac CT angiography and functional assessment with myocardial CT perfusion is similarly effective in guiding therapy decisions as invasive coronary angiography with fractional flow reserve is a question for the future.

Summary and analysis of existing data on salvaged myocardium measured by MRI in two systematic reviews and meta-analyses indicates that quantification of myocardial salvage by MRI can be of use for assessing therapy efficiency and provides prognostic value after myocardial infarction. Both meta-analyses revealed high heterogeneity in the data, which questions the informative value of single measurements of myocardial salvage with MRI. A considerable component of the heterogeneity could be explained by disagreements in MRI methodologies. Standardization of post-infarctional MRI methodologies may thus address this concern in the future.

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1.8 Word counts

Abstract: 2,986 characters (max. 3,000 characters including spaces)

Zusammenfassung: 2.971 Zeichen (max. 3.000 Zeichen mit Leerzeichen)

Total: 9,201 words (max. 10,000 words excluding references)

2 Eidesstattliche Versicherung

„Ich, Benjamin Kendziora, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Computed tomography for the diagnosis of coronary artery disease and magnetic resonance imaging for quantifying salvaged myocardium
after myocardial infarction / Computertomographie zur Diagnose der koronaren Herzkrankheit und Magnetresonanztomographie zur Quantifizierung geretteten Myokards nach Myokardinfarkt“
selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Erstbetreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

06. März 2021, Benjamin Kendziora

3 Anteilserklärung an erfolgten Publikationen

Ich, Benjamin Kendziora, hatte folgenden Anteil an den Publikationen dieser Dissertation:

Publikation 1

Dewey M, Rief M, Martus P, Kendziora B, Feger S, Dreger H, Priem S, Knebel F, Bohm M, Schlattmann P, Hamm B, Schonenberger E, Laule M, Zimmermann E. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. BMJ (Clinical research ed). 2016;355:i5441.

Beitrag im Einzelnen: Für diese Publikation rekrutierte ich im Laufe eines halben Jahres als Teil eines dreiköpfigen Doktorandenteams unter Aufsicht der Studienärzte und des Studienleiters Prof. Dewey in etwa 30 Patienten, wofür wir bei ca. 70 Patienten eine Screeninguntersuchung durchführten. Außerdem führten wir als Doktorandenteam die in diesem Zeitraum anfallenden Studien- und Follow-Up-Untersuchungen durch, ebenfalls unter Anleitung des ärztlichen Studienpersonals. Die von uns erhobenen Daten pflegten wir in die Studiendatenbank ein. Nach Abschluss der Rektrutierung wurde die Studiendatenbank von einer wissenschaftlichen Mitarbeiterin und mir für die statistische Auswertung vorbereitet. Die Statistik selber wurde von einem professionellen Statistiker durchgeführt. In das hauptsächlich von Prof. Dewey geschriebenen Manuskript arbeitete ich Kommentare ein.

Publikation 2

Rief M, Chen MY, Vavere AL, Kendziora B, Miller JM, Bandettini WP, Cox C, George RT, Lima J, Di Carli M, Plotkin M, Zimmermann E, Laule M, Schlattmann P, Arai AE, Dewey M. Coronary Artery Disease: Analysis of Diagnostic Performance of CT Perfusion and MR Perfusion Imaging in Comparison with Quantitative Coronary Angiography and SPECT-Multicenter Prospective Trial. Radiology. 2018;286(2):461-70.

Beitrag im Einzelnen: Für diese Studie erstellte ich zunächst eine Datentabelle für die Auswertung der myokardialen Magnetresonanztomografie-Perfusionen. Anschließend wertete ich alle Magnetresonanztomografie-Perfusionen als einer der radiologischen Auswerter aus. In das hauptsächlich von Dr. Rief geschriebene Manuskript arbeitete ich Kommentare ein.

Publikation 3

Kendziora B, Stier H, Schlattmann P, Dewey M. MRI for measuring therapy efficiency after revascularisation in ST-segment elevation myocardial infarction: a systematic review and meta-regression analysis. BMJ Open. 2020;10(9):e034359.

Beitrag im Einzelnen: Diese Studie konzipierte ich zuammen mit meinem Doktorvater Prof. Marc Dewey. Die elektronische Suchstrategie erstellte ich eigenständig. Die elektronische Studiensuche sowie Datenextraktion aus eingeschlossenen Studien wurde von Heli Stier und mir doppelt durchgeführt. In Rücksprache mit meinem Kobetreuer Prof. Schlattmann führte ich die statistische Auswertung durch. Alle in der Publikation enthaltenen Werte und Grafiken wurden von mir errechnet bzw. erstellt. Das Manuskript wurde von mir verfasst und von Prof. Dewey korrigiert.

Publikation 4

Kendziora B, Dewey M. Prognostic value of the myocardial salvage index measured by T2-weighted and T1-weighted late gadolinium enhancement magnetic resonance imaging after ST-segment elevation myocardial infarction: A systematic review and meta-regression analysis. PLOS ONE. 2020;15(2):e0228736.

Beitrag im Einzelnen: Diese Studie konzipierte ich zusammen mit meinem Doktorvater Prof. Marc Dewey. Die Erstellung der elektronischen Suchstrategie, elektronische Studiensuche, Datenextraktion aus eingeschlossenen Studien und statistische Auswertung führte ich eigenständig durch. Alle in der Publikation enthaltenen Werte und Grafiken wurden von mir errechnet bzw. erstellt. Das von mir verfasste Manuskript wurde von Prof. Dewey korrigiert.

06. März 2021, Benjamin Kendziora

4 Druckexemplare der Publikationen mit Auszügen aus den jeweiligen Journal Summary Lists

4.1 Publikation 1: Dewey M, Rief M, Martus P, Kendziora B, Feger S, Dreger H, Priem S, Knebel F, Bohm M, Schlattmann P, Hamm B, Schonenberger E, Laule M, Zimmermann E. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. BMJ (Clinical research ed). 2016;355:i5441.

Veröffentlicht im *British Medical Journal (BMJ)*: Rang 5 bei 154 Journalen in der Kategorie: *Medicine, General, and Internal*.

Journal Data Filtered By: Selected JCR Year: 2014 Selected Editions: SCIE,SSCI Selected Categories: 'MEDICINE, GENERAL & INTERNAL' Selected Category Scheme: WoS Gesamtzahl: 154 Journale				
Rank	**Full Journal Title**	**Total Cites**	**Journal Impact Factor**	**Eigenfactor Score**
1	NEW ENGLAND JOURNAL OF MEDICINE	268,652	55.873	0.676340
2	LANCET	185,361	45.217	0.395550
3	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	126,479	35.289	0.260990
4	ANNALS OF INTERNAL MEDICINE	48,356	17.810	0.106290
5	BMJ-British Medical Journal	89,031	17.445	0.169220
6	ARCHIVES OF INTERNAL MEDICINE	38,021	17.333	0.066730
7	PLOS MEDICINE	18,649	14.429	0.068770
8	JAMA Internal Medicine	2,934	13.116	0.017550
9	BMC Medicine	5,708	7.356	0.024100
10	Journal of Cachexia Sarcopenia and Muscle	713	7.315	0.002080
11	MAYO CLINIC PROCEEDINGS	9,990	6.262	0.019720
12	JOURNAL OF INTERNAL MEDICINE	8,802	6.063	0.015070
13	Cochrane Database of Systematic Reviews	43,592	6.035	0.149280
14	CANADIAN MEDICAL ASSOCIATION JOURNAL	12,121	5.959	0.023260
15	MEDICINE	4,912	5.723	0.005850
16	ANNALS OF FAMILY MEDICINE	3,556	5.434	0.011160
17	Translational Research	2,112	5.030	0.007570
18	AMERICAN JOURNAL OF MEDICINE	22,662	5.003	0.027500
19	AMERICAN JOURNAL OF PREVENTIVE MEDICINE	15,857	4.527	0.041770
20	MEDICAL JOURNAL OF AUSTRALIA	10,268	4.089	0.017800
21	ANNALS OF MEDICINE	3,881	3.886	0.008020
22	BRITISH MEDICAL BULLETIN	3,502	3.658	0.004930
23	Deutsches Arzteblatt International	2,016	3.518	0.006420
24	JOURNAL OF GENERAL INTERNAL MEDICINE	13,886	3.449	0.030490
25	PREVENTIVE MEDICINE	11,686	3.086	0.021810
26	European Journal of Internal Medicine	2,549	2.891	0.007870

Publikation 1 wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht. Die Publikation ist zu finden unter:

https://doi.org/10.1136/bmj.i5441

Dewey M, Rief M, Martus P, Kendziora B, Feger S, Dreger H, Priem S, Knebel F, Bohm M, Schlattmann P, Hamm B, Schonenberger E, Laule M, Zimmermann E. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. BMJ (Clinical research ed). 2016;355:i5441.

4.2 Publikation 2: Rief M, Chen MY, Vavere AL, Kendziora B, Miller JM, Bandettini WP, Cox C, George RT, Lima J, Di Carli M, Plotkin M, Zimmermann E, Laule M, Schlattmann P, Arai AE, Dewey M. Coronary Artery Disease: Analysis of Diagnostic Performance of CT Perfusion and MR Perfusion Imaging in Comparison with Quantitative Coronary Angiography and SPECT-Multicenter Prospective Trial. Radiology. 2018;286(2):461-70.

Veröffentlicht in *Radiology*: Rang 2 bei 124 Journalen in der Kategorie: *Radiology, Nucleaer Medicine, and Medical Imaging*.

Journal Data Filtered By: **Selected JCR Year: 2015** Selected Editions: SCIE,SSCI Selected Categories: **'RADIOLOGY, NUCLEAR MEDICINE & MEDICAL IMAGING'** Selected Category Scheme: WoS

Gesamtzahl: 124 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JACC-Cardiovascular Imaging	5,248	7.815	0.023520
2	RADIOLOGY	48,521	6.798	0.072370
3	JOURNAL OF NUCLEAR MEDICINE	22,728	5.849	0.038680
4	Circulation-Cardiovascular Imaging	3,562	5.771	0.018570
5	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	3,592	5.752	0.011980
6	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	11,996	5.537	0.026190
7	NEUROIMAGE	79,475	5.463	0.179770
8	HUMAN BRAIN MAPPING	17,184	4.962	0.040350
9	INVESTIGATIVE RADIOLOGY	6,024	4.887	0.011910
10	RADIOTHERAPY AND ONCOLOGY	14,095	4.817	0.032880
11	MEDICAL IMAGE ANALYSIS	4,764	4.565	0.010690
12	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	39,558	4.495	0.069300
13	ULTRASCHALL IN DER MEDIZIN	1,866	4.434	0.004290
14	CLINICAL NUCLEAR MEDICINE	3,463	4.278	0.006270
15	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	9,842	4.254	0.017490
16	MAGNETIC RESONANCE IN MEDICINE	28,628	3.782	0.038740
17	IEEE TRANSACTIONS ON MEDICAL IMAGING	13,784	3.756	0.024430
18	EUROPEAN RADIOLOGY	14,583	3.640	0.034790
19	SEMINARS IN RADIATION ONCOLOGY	2,013	3.556	0.003900
20	INTERNATIONAL JOURNAL OF HYPERTHERMIA	2,517	3.361	0.003770
21	Biomedical Optics Express	4,669	3.344	0.019490
22	Contrast Media & Molecular Imaging	1,199	3.286	0.002930
23	JOURNAL OF MAGNETIC RESONANCE IMAGING	14,860	3.250	0.031900
24	AMERICAN JOURNAL OF NEURORADIOLOGY	20,164	3.124	0.032430
25	RADIATION RESEARCH	8,727	3.022	0.011430
26	NMR IN BIOMEDICINE	5,917	2.983	0.014830
27	JOURNAL OF NUCLEAR CARDIOLOGY	2,495	2.929	0.005100
27	Journal of the American College of Radiology	2,201	2.929	0.007230

Publikation 2 wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht. Die Publikation ist zu finden unter:

https://doi.org/10.1148/radiol.2017162447

Rief M, Chen MY, Vavere AL, Kendziora B, Miller JM, Bandettini WP, Cox C, George RT, Lima J, Di Carli M, Plotkin M, Zimmermann E, Laule M, Schlattmann P, Arai AE, Dewey M. Coronary Artery Disease: Analysis of Diagnostic Performance of CT Perfusion and MR Perfusion Imaging in Comparison with Quantitative Coronary Angiography and SPECT-Multicenter Prospective Trial. Radiology. 2018;286(2):461-70.

4.3 Publikation 3: Kendziora B, Stier H, Schlattmann P, Dewey M. MRI for measuring therapy efficiency after revascularisation in ST-segment elevation myocardial infarction: a systematic review and meta-regression analysis. BMJ Open. 2020;10(9):e034359.

Veröffentlicht im *British Medical Journal Open (BMJ Open)*: Rang 50 bei 160 Journalen in der Kategorie: *Medicine, General, and Internal*.

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"MEDICINE, GENERAL and INTERNAL"**
Selected Category Scheme: WoS
Gesamtanzahl: 160 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NEW ENGLAND JOURNAL OF MEDICINE	344,581	70.670	0.686700
2	LANCET	247,292	59.102	0.427870
3	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	156,350	51.273	0.300810
4	Nature Reviews Disease Primers	4,339	32.274	0.019740
5	BMJ-British Medical Journal	112,901	27.604	0.152760
6	JAMA Internal Medicine	15,215	20.768	0.095580
7	ANNALS OF INTERNAL MEDICINE	57,057	19.315	0.096020
8	PLOS MEDICINE	30,689	11.048	0.071200
9	Journal of Cachexia Sarcopenia and Muscle	2,799	10.754	0.005870
10	BMC Medicine	13,630	8.285	0.045220
11	Cochrane Database of Systematic Reviews	67,607	7.755	0.158690
12	MAYO CLINIC PROCEEDINGS	14,695	7.091	0.025750
13	CANADIAN MEDICAL ASSOCIATION JOURNAL	15,351	6.938	0.016500
14	JOURNAL OF INTERNAL MEDICINE	10,547	6.051	0.015700
15	Journal of Clinical Medicine	2,315	5.688	0.007210
16	MEDICAL JOURNAL OF AUSTRALIA	11,134	5.332	0.012600
17	PALLIATIVE MEDICINE	5,682	4.956	0.009860
18	AMYLOID-JOURNAL OF PROTEIN FOLDING DISORDERS	1,335	4.919	0.003270

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
19	Translational Research	3,669	4.915	0.008530
20	AMERICAN JOURNAL OF MEDICINE	25,051	4.760	0.026650
21	JOURNAL OF GENERAL INTERNAL MEDICINE	19,431	4.606	0.028130
22	Deutsches Arzteblatt International	4,331	4.469	0.007630
23	AMERICAN JOURNAL OF PREVENTIVE MEDICINE	22,339	4.435	0.041750
24	BRITISH JOURNAL OF GENERAL PRACTICE	6,489	4.434	0.009370
25	ANNALS OF FAMILY MEDICINE	5,314	4.185	0.010880
26	JOURNAL OF TRAVEL MEDICINE	2,229	4.155	0.003410
27	European Journal of Internal Medicine	4,559	3.660	0.009420
28	JOURNAL OF THE ROYAL SOCIETY OF MEDICINE	4,051	3.538	0.003080
29	AMERICAN JOURNAL OF CHINESE MEDICINE	3,152	3.510	0.002950
30	PREVENTIVE MEDICINE	16,004	3.449	0.029820
31	JOURNAL OF PAIN AND SYMPTOM MANAGEMENT	11,229	3.378	0.015750
32	Frontiers in Medicine	1,598	3.113	0.005060
33	ANNALS OF MEDICINE	4,437	3.049	0.005440
34	Polish Archives of Internal Medicine-Polskie Archiwum Medycyny Wewnetrznej	1,287	2.882	0.002000
35	JOURNAL OF THE FORMOSAN MEDICAL ASSOCIATION	3,274	2.844	0.004420
36	BRITISH MEDICAL BULLETIN	4,435	2.804	0.003670
37	EUROPEAN JOURNAL OF CLINICAL INVESTIGATION	5,946	2.784	0.006180

Selected JCR Year: 2018; Selected Categories: "MEDICINE, GENERAL und INTERNAL"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
38	PAIN MEDICINE	6,988	2.758	0.013020
39	UPSALA JOURNAL OF MEDICAL SCIENCES	1,109	2.747	0.001980
40	MEDICAL CLINICS OF NORTH AMERICA	2,990	2.716	0.004280
41	KOREAN JOURNAL OF INTERNAL MEDICINE	1,887	2.714	0.003600
42	QJM-AN INTERNATIONAL JOURNAL OF MEDICINE	5,711	2.649	0.004350
43	INTERNATIONAL JOURNAL OF CLINICAL PRACTICE	5,439	2.613	0.005980
44	AMERICAN FAMILY PHYSICIAN	6,860	2.580	0.005110
45	Journal of the American Board of Family Medicine	3,654	2.511	0.006540
46	Diagnostics	533	2.489	0.001350
47	MINERVA MEDICA	817	2.475	0.000950
48	BMC Family Practice	4,209	2.431	0.009370
49	Archives of Medical Science	2,581	2.380	0.005110
50	BMJ Open	26,298	2.376	0.108600
51	CURRENT MEDICAL RESEARCH AND OPINION	7,181	2.345	0.010810
52	Internal and Emergency Medicine	1,978	2.335	0.004390
53	International Journal of Medical Sciences	3,358	2.333	0.006330
54	Journal of Hospital Medicine	3,068	2.276	0.009200
55	POSTGRADUATE MEDICINE	2,311	2.237	0.003640
56	CANADIAN FAMILY PHYSICIAN	3,761	2.186	0.005200
56	PANMINERVA MEDICA	653	2.186	0.000620

Selected JCR Year: 2018; Selected Categories: "MEDICINE, GENERAL und INTERNAL"

Publikation 3 wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht. Die Publikation ist zu finden unter:

https://doi.org/10.1136/bmjopen-2019-034359

Kendziora B, Stier H, Schlattmann P, Dewey M. MRI for measuring therapy efficiency after revascularisation in ST-segment elevation myocardial infarction: a systematic review and meta-regression analysis. BMJ Open. 2020;10(9):e034359.

4.4 Publikation 4: Kendziora B, Dewey M. Prognostic value of the myocardial salvage index measured by T2-weighted and T1-weighted late gadolinium enhancement magnetic resonance imaging after ST-segment elevation myocardial infarction: A systematic review and meta-regression analysis. PLOS ONE. 2020;15(2):e0228736.

Veröffentlicht in *PLOS ONE*: Rang 24 bei 69 Journalen in der Kategorie: *Multidisciplinary Sciences*.

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI Selected Categories: **"MULTIDISCIPLINARY SCIENCES"** Selected Category Scheme: WoS

Gesamtanzahl: 69 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE	745,692	43.070	1.285010
2	SCIENCE	680,994	41.037	1.070190
3	National Science Review	1,842	13.222	0.006500
4	Science Advances	21,901	12.804	0.110010
5	Nature Communications	243,793	11.878	1.103290
6	Nature Human Behaviour	1,230	10.575	0.006550
7	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	661,118	9.580	1.022190
8	Science Bulletin	3,569	6.277	0.009840
9	Scientific Data	3,240	5.929	0.015610
10	Frontiers in Bioengineering and Biotechnology	1,994	5.122	0.006540
11	Journal of Advanced Research	2,691	5.045	0.004780
12	Research Synthesis Methods	1,932	5.043	0.005420
13	GigaScience	2,674	4.688	0.012510
14	Annals of the New York Academy of Sciences	46,385	4.295	0.025840
15	Scientific Reports	302,086	4.011	1.061540
16	Journal of the Royal Society Interface	12,933	3.224	0.029190
17	NPJ Microgravity	203	3.111	0.000670
18	PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	19,227	3.093	0.028200

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
19	FRACTALS-COMPLEX GEOMETRY PATTERNS AND SCALING IN NATURE AND SOCIETY	1,429	2.971	0.001120
20	Journal of Radiation Research and Applied Sciences	860	2.963	0.001860
21	MIT Technology Review	929	2.893	0.001910
22	JOURNAL OF KING SAUD UNIVERSITY SCIENCE	1,120	2.835	0.001670
23	PROCEEDINGS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	18,683	2.818	0.018940
24	PLoS One	650,727	2.776	1.706770
25	COMPLEXITY	2,753	2.591	0.003890
26	Royal Society Open Science	4,118	2.515	0.017150
27	PeerJ	11,911	2.353	0.045900
28	SCIENCE AND ENGINEERING ETHICS	1,719	2.275	0.003450
29	INTERNATIONAL JOURNAL OF BIFURCATION AND CHAOS	7,008	2.145	0.007390
30	Symmetry-Basel	2,097	2.143	0.002590
31	SCIENTIFIC AMERICAN	6,609	1.946	0.003540
32	Science of Nature	508	1.839	0.002000
33	PROCEEDINGS OF THE JAPAN ACADEMY SERIES B-PHYSICAL AND BIOLOGICAL SCIENCES	1,532	1.833	0.001960
34	Journal of Taibah University for Science	779	1.640	0.001240
35	Frontiers in Life Science	241	1.622	0.000500
36	ARABIAN JOURNAL FOR SCIENCE AND ENGINEERING	3,838	1.518	0.005840
37	SCIENCE PROGRESS	521	1.500	0.000400

Selected JCR Year: 2018; Selected Categories: "MULTIDISCIPLINARY SCIENCES"

Publikation 4 wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht. Die Publikation ist zu finden unter:

https://doi.org/10.1371/journal.pone.0228736

Kendziora B, Dewey M. Prognostic value of the myocardial salvage index measured by T2-weighted and T1-weighted late gadolinium enhancement magnetic resonance imaging after ST-segment elevation myocardial infarction: A systematic review and meta-regression analysis. PLOS ONE. 2020;15(2):e0228736.

5 Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

6 Publikationsliste

Originalarbeiten

1. Schlager J G, Kendziora B, Patzak L, Kupf S, Rothenberger C, Fiocco Z, French L E, Reinholz M, Hartmann D. Impact of COVID-19 on wound care in Germany. International Wound Journal. 2021. Journal Impact Factor (2019): 2.8.
2. Kendziora B, Guertler A, Ständer L, Frey S. French L E, Wollenberg A, Reinholz M. Evaluation of the frequency of hand hygiene and onset of hand eczema after the outbreak of SARS-CoV-2 in Munich. European Journal of Dermatology. 2020. Journal Impact Factor (2019): 2.8.
3. Drick N, Milger K, Seeliger B, Juge J, Korn S, Buhl R, Schuhmann M, Herth F, Kendziora B, Kneidinger N, Bergmann K, Taube C, Welte T, Suhling H. Switch from IL-5 to IL-5-receptor antibody treatment in severe eosinophilic asthma. Journal of Asthma and Allergy. 2020. Journal Impact Factor (2019): 3.7.
4. Kendziora B, Stier H, Schlattmann P, Dewey M. MRI for measuring therapy efficiency after revascularisation in ST-segment elevation myocardial infarction: a systematic review and meta-regression analysis. BMJ Open. 2020;10(9):e034359. Journal Impact Factor (2019): 2.5.
5. Senner S, Seegräber M, Frey S, Kendziora B, Eicher L, Wollenberg A. Dupilumab for the treatment of adolescents with atopic dermatitis. Expert Review of Clinical Immunology. 2020. Doi: 10.1080/1744666X.2020.1801420. Journal Impact Factor (2019): 3.8.
6. Guertler A, Moellhoff N, Schenck T, Hagen C, Kendziora B, Giunta R, French L, Reinholz M. Onset of Occupational Hand Eczema Among Healthcare Workers During the SARS-CoV-2 Pandemic – Comparing a Single Surgical Site With a COVID-19 Intensive Care Unit. Contact Dermatitis. 2020. Doi: 10.1111/cod.13618. Journal Impact Factor (2019): 2.5.
7. Kendziora B, Dewey M. Prognostic value of the myocardial salvage index measured by T2-weighted and T1- weighted late gadolinium enhancement magnetic resonance imaging after ST-segment elevation myocardial infarction: A systematic review and meta-regression analysis. PLOS ONE. 2020**.** doi: 10.1371/journal.pone.0228736. Journal Impact Factor (2019): 2.8.

8. Rief M, Chen MY, Vavere AL, Kendziora B, Miller JM, Bandettini WP, Cox C, George RT, Lima J, Di-Carli M, Plotkin M, Zimmermann , Laule M, Schlattmann P, Arai AE, Dewey M. Coronary Artery Disease: Analysis of Diagnostic Performance of CT Perfusion and MR Perfusion Imaging in Comparison with Quantitative Coronary Angiography and SPECT-Multicenter Prospective Trial. Radiology. 2018. doi: 10.1148/radiol.2017162447. Journal Impact Factor (2018): 7.6.
9. Dewey M, Rief M, Martus P, Kendziora B, Feger S, Dreger H, Priem S, Knebel F, Böhm M, Schlattmann P, Hamm B, Schöneberger E, Laule M, Zimmermann E. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. BMJ. 2016. doi: 10.1136/bmj.i5441. Journal Impact Factor (2016): 20.8.

Abstracts und Poster

1. Kendziora B, Dewey M. Prognostic value of the myocardial salvage index measured by T2-weighted and T1-weighted late gadolinium enhancement magnetic resonance imaging after ST-segment elevation myocardial infarction: A systematic review and meta-regression analysis. European Society of Radiology Annual Congress. 2020.
2. Drick N, Milger K, Korn S, Buhl R, Schumann M, Felix H, Kendziora B, Bergmann K, Taube C, Welte T Suhling H. Umstellung der Antikörpertherapie bei schwerem eosinophilen Asthma bronchiale von anti-IL5- auf anti-IL5-Rezeptor Antikörper. 61. Kongress der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin e.V. 2020.
3. Kendziora B, Topal F, Joshi P, Fluhr J, Bergmann K, Zuberbier T. Validierung der mobilen GA^{2}LEN Pollenkammer für Expositionstests mit Ozon. 14. Deutscher Allergiekongress. 2019.
4. Topal F, Kendziora B, Zuberbier T, Kimpe T, Hofmann M. Ein neues elektronisches Dermatoskopiegerät zur Erkennung von entzündlichen Hauterkrankungen neben malignen Hautläsionen. 14. Deutscher Allergiekongress. 2019.
5. Kendziora B, Schlattmann P, Dewey M. Myocardial Edema and Necrosis after ST- Segment Elevation Myocardial Infarction by T2-Weighted and Late Gadolinium Enhancement MR

Imaging: A Meta-Analysis. The Radiological Society of North America's 104th Scientific Assembly. 2018.

Fallberichte

1. Frey S, Kendziora B, Holch J W, Lindner L, French L E, Wollenberg A. Immune Thrombocytopaenic Purpura in a Patient with Atopic Dermatitis Treated with Dupilumab. Acta Dermato-Venereologica. 2020.

Populärwissenschaftliches

1. Kendziora B, Ruëff F. Acne inversa: gar nicht so selten – häufig übersehen. Medizin professionell. 2020.

06. März 2021, Benjamin Kendziora

7 Danksagung

Für die jahrelange fachliche und organisatorische Unterstützung bei der Umsetzung der gesamten Arbeit gilt mein besonderer Dank meinem Doktorvater Prof. Marc Dewey.

Dr. Matthias Rief möchte ich für Beratung in klinischen Fragen danken und dafür, immer ein offenes Ohr für mich gehabt zu haben.

Prof. Peter Schlattmann möchte ich für die statistische Beratung danken und diese selbst dann nicht eingestellt zu haben, nachdem er dafür mehrmals in seiner privaten Wohnung aufgesucht wurde.

Mirjam Groh möchte ich für kreative Diskussionen danken.

Jakob Kottmann, Andreas Dorn und Maximilian Jork möchte ich für ihr Verständnis während ihrer Zeit in Berlin danken.

Jan Simmler, Yuan Lyu, Véronique Peters und meiner Schwester Elena Kendziora gilt mein Dank für die Ermutigung.

Meinen Eltern Marlis und Wolfgang Kendziora möchte ich dafür danken, mich auf meinem bisherigen Lebensweg immer weitgehend bedingungslos unterstützt zu haben, sowohl finanziell als auch geistig.

06. März 2021, Benjamin Kendziora