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Habilitation thesis

Evaluation of novel diagnostic and therapeutic tools to improve outcomes in patients with coronary artery disease

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by

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Content

Abbreviations and Acronyms

ACS ….. acute coronary syndrome

BMS ….. bare metal stent

CAD ….. coronary artery disease

CCT ….. coronary computed tomography

CRT ….. cardiac resynchronization therapy

DEB ….. drug eluting balloon

DES ….. drug eluting stents

FFR ….. fractional flow reserve

ICA ….. invasive coronary angiography

IVUS ….. intravascular ultrasound

LLL ….. late lumen loss

MACE ….. major adverse cardiac events

NSTEMI ….. non-ST elevation myocardial infarction

PCI ….. percutaneous coronary intervention

PPCI ….. primary percutaneous coronary intervention

PTA ….. percutaneous transluminal angioplasty

RCT ….. randomized controlled trial

RI ….. reperfusion injury

RIC ….. remote ischaemic pre-conditioning

SCAD ….. stable coronary artery disease

ST ….. stent thrombosis

STEMI ….. ST elevation myocardial infarction

TC ….. Takotsubo cardiomyopathy

TLR ….. target lesion revascularization

TVR ….. target vessel revascularization

Introduction

Cardiovascular diseases are the dominant cause of death in Western countries.[1] In particular, coronary artery disease does not only go along with a significant mortality rate (about 7.4 million deaths in 2012 worldwide), but also morbidity.[1] A significant proportion of patients with acute coronary syndromes may suffer from long term sequelae of myocardial damage. About 5% of patients treated for ST-elevation myocardial infarct will develop heart failure after 1 year and 7.5% are afflicted by arrhythmia like ventricular tachykardia or ventricular fibrillation.[2, 3] Another 3-5% of these patients will face a severe impairment of their left ventricular function and low cardiac output, which will indeed impact on their quality of life.[4]

It was demonstrated, that the quality of life is closely related to heart failure symptoms.[5] Contemporary heart failure treatment has indeed achieved a significant improvement in terms of long-term survival.[6] However, heart failure managment does not only include medical management, but also device therapy, for example with cardiac resynchronization therapy (CRT). [7] As each CRT implant is 37.000 $ this is a quite costly therapy, even on top of the long term medical therapy, which means a significant burden for national health insurance expenses.[8]

For the reasons highlighted above, the prevention of myocardial damage and its deleterious effects on heart function appears to be the most appealing and particularly cost effective therapy approach.

Coronary angiography and stenting in patients with stable angina

The Goldstandard diagnostic approach for evaluation of coronary artery stenoses in patients presenting with stable angina is heart catheterization and coronary angiography either via a right femoral artery or via a right radial artery access route.[9]

Coronary angiography also offers the possibility of a percutaneous treatment of significant stenoses, which are amenable for stenting in the same session. However, there was some criticism about the low diagnostic yield of invasive coronary angiograms and its widespread overuse - or vice versa - the underuse of alternative non-invasive diagnostic modalities.[10] One study revealed that only 38% of diagnostic angiograms demonstrated obstructive coronary artery disease.[10] According to current guidelines, non-invasive diagnostic facilities like cardiac magnetic resonance imaging (MRI), computed tomography or stress echo should indeed be used as a gate keeper for the invasive coronary angiograms (ICA), which carry a low but existent risk for severe complications.[11] As a matter of fact, <0.08% of patients die during diagnostic angiograms, 2-5% of patients may develop severe bleeding complications and the use of the contrast agent may affect kidney function (3.3-16.5%), or cause allergic reactions (3.6%).[12] Non-invasive imaging also offers a functional assessment of the myocardium and provides evidence of ischaemic myocardium, rather than a purely morphologic assessment with ICA.[13] Sometimes eyeballing may indeed proof difficult to judge a coronary stenosis of intermediate significance and further testing is required, to target stent implantation only to those patients who really need it.[14]

In those cases, where ICA alone leaves some uncertainty and does not allow to conclude, if stenting of the lesion is beneficial for the patient or even might be harmful, new devices were developed to alleviate this decision for or against the stent.[15] Potential side effects of a stent might be procedural and long-term risks, like severe bleeding complications under dual antiplatelet therapy (1% per year), coronary dissection or perforation (<1%), in-stent restenosis (3-15%), stent thrombosis (1% per year) which is associated with a high mortality rate, and which may occur as late as two years or later after the index procedure.[16] Therefore, the benefits of a stent implantation need to be weighed carefully against its potential risks in every patient. A

relatively novel tool for intra-procedural assessment of the haemodynamic significance of a coronary lesion is the pressure wire.[17] It is designed to measure the mean blood pressure distal to a coronary lesion during adenosine vasodilation and correlate this blood pressure to the aortic reference blood pressure.[17] The proportion of the measurements distal to the coronary stenosis compared to the aortic pressure is called fractional flow reserve (FFR). [17] It was the concept of FFR to tailor stent implantation to only those patients who will benefit finally.[18]

In contrast, intravascular ultrasound (IVUS) was designed for a purely morphologic assessment of coronary lesions.[19] While data from several large randomized trials exist, that haemodynamic assessment of a coronary lesion gives reliable information on the prognostic impact of the stenosis and if stent implantation will be beneficial, the role of IVUS for this purpose has been less well described so far.[20, 21]

Drug eluting balloons

As highlighted above, stents are not only beneficial, but they also carry potential risks and side-effects. Therefore, drug eluting balloons appeared to be an appealing option in those cases, where no permanent vascular implant is possible or needed.[22] The drug eluting balloon concept essentially is a balloon which is designed to release a drug into the vessel wall during balloon inflation.[23, 24] In common, drug eluting balloons are coated with the lipophilic drug paclitaxel and a hydrophilic excipient to facilitate drug penetration into the vessel wall.[24] Paclitaxel shall prevent the development of neointima and restenosis by inhibition of inflammation and smooth muscle cell proliferation at the site of the balloon inflation.[25] It is indeed a challenge to achieve

sufficient drug release from the balloon into the vessel wall within only 30-50 seconds of contact time of the inflated balloon with the vessel wall.[26] However, several smaller studies did support the idea of the drug eluting balloon, in particular in patients with in-stent restenosis, where a stent-in-stent treatment would create two metal layers of stent in the vessel, which should be avoided.[27, 28] A meta-analysis found, that drug coated balloons yield similar outcomes to drug eluting stents for therapy of in-stent restenosis.[29, 30] In addition, drug coated balloons were superior to pure balloon angioplasty with a conventional balloon. [29]

DEB were also investigated in native lesions in peripheral artery disease, where PTA is usually preferred over stenting.[31] Indeed, DEB were successfully tested in patients with femoro-popliteal interventions, where DEB proofed to be superior to conventional balloon angioplasty.[32]

Data on other indications of drug coated balloons in the coronary system are sparse. In particular, their use in native coronary lesions and/or in complex bifurcation lesions might be beneficial.[33] Some authors do for example suggest hybrid approaches in bifurcation lesions, where the main branch is stented and the side branch should be treated with a drug eluting balloon.[34, 35]

So far, only some smaller studies were published in this field and more data are needed, before a final recommendation may guide clinical practice.

Stress induced cardiomyopathy

In contrast to patients with stable angina, where invasive coronary angiography may be planned electively, acute coronary syndromes mandate immediate treatment. However, several cardiac conditions, that do not go along with significant coronary

stenoses may mimick an acute coronary syndrome and patients are unnecessarily forwarded to an ICA. One of these conditions is called stress induced or Takotsubo cardiomyopathy and affects up to 2% of all patients but up to 7% of women referred as acute coronary syndrome to the emergency departement.[36] It is typically triggered by an extraordinary emotional stress situation (e.g. death of a relative) and goes along with chest pain, ECG changes similar to those found in STEMI and severe left ventricular dysfunction, where an apical ballooning of the left ventricle is considered to be typical for this entity.[36] However, when these patients undergo ICA, no relevant coronary stenoses may be found.[37] Takotsubo is mainly defined by the Mayo clinic criteria, which were first proposed in 2004[37]:" (1) transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger; (2) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) the absence of pheochromocytoma and myocarditis."[37]

In as many as 10% of patients with Takotsubo coronary stenosis up to 75% are found, which leave some final uncertainty to whether ischaemia provoked the symptoms or if Takotsubo might be the underlying condition; there is indeed flowing transitions to whether the event was an ACS or a Takotsubo cardiomyopathy?[38] In general, the prognosis of Takotsubo is benign in general with a full recovery of the left ventricular function in 96% of patients within several weeks to months.[39] But, in about 11% Takotsubo may re-occur and in a minority of 2% of cases, even severe complications and death may occur.[39] These facts highlight the importance to define criteria to support or reject the diagnosis of stress induced cardiomyopathy at an early stage.[36]

Therefore strategies for a safe and non-invasive diagnosis of this condition are needed, to avoid the risk of an invasive procedure, which is clearly not helpful in this patient cohort.

ST elevation myocardial infarct (STEMI) and the reperfusion injury (RI)

In patients, who are admitted to the emergency department with a STEMI, it is the main goal to reopen the occluded coronary artery by Primary PCI (PPCI) to save myocardium.[11] However, the abrupt restoration of blood flow by heart catheterization does not only have beneficial effects. Indeed, reactive oxygen species, inflammatory cells and conglomerates of granulocytes and platelets cause the so called „reperfusion injury“ (RI).[40, 41] Interestingly enough, this RI may account for up to 50% of the final infarct size, but currently, there is no treatment for this phaenomenon.[42] Several calcium channel blockers, antioxidants and anti-inflammatory drugs were investigated to mitigate the RI.[42] Moreover, systemic cooling of STEMI patients to 34°C yielded mainly frustrating results.[43] The only intervention which appeared to improve the reperfusion injury was the intracoronary application of adenosine, but only in patients presenting to the cath lab within 3 hours after onset of symptoms.[42, 44] One smaller study demonstrated promising effects with cyclosporine A.[45] Cyclosporine is indeed an inhibitor of the mitochondrial transition pore, which has been closely associated to the RI.[40, 45] Several trials are currently investigating this concept in a larger patient cohorts (NCT01650662, NCT02390674).[46, 47] Recently, the „myocardial pre- and post-conditioning“ strategies were suggested.[48] In post-conditioning, a balloon is inflated for several minutes again after re-opening of the occluded artery. In theory, this manoevre reduces the brisk exposure of the culprit vessel to the pathways of reperfusion injury (inflammation, oxidative stress…).[48] However, data are still sparse – and conflicting.[48]

In myocardial pre-conditioning, an iatrogenic ischaemia is provoked in an area or organ remote from the heart to trigger the release of cardioprotective peptides.[49] In an animal myocardial infarct model where the left anterior descending coronary artery was temporarily clamped, an additional intestinal ischaemia was produced before the coronary blood flow was restored.[49] Interestingly, in these animals the final infarct size was found to be smaller if compared to no pre-conditioning.[49] In humans, remote ischaemia is induced in the upper or lower limbs by inflation of a blood pressure cuff for usually 5 minutes.[50] Then the cuff is released and after some minutes of recovery, the procedure is repeated, in total about five cycles.[50]

Meanwhile this concept has been investigated in different settings, like cardioprotection in bypass surgery and also is currently under investigation in transcatheter aortic valve implantation.[51, 52] Moreover, this strategy has fuelled some enthousiasm in transplant medicine, where this concept is currently tested in liver and kidney transplant recipients.[53]

Pre-conditioning would indeed be a low cost and low-risk intervention to reduce the myocardial infarct size. It is well known, that a large infarct size is associated to impaired left ventricular function which goes along with poor long term prognosis. Therefore, novel approaches are needed to specifically target the reperfusion injury to further reduce infarct size and long-term heart failure sequelae after STEMI.

Aims

1. To find novel diagnostic and therapeutic tools to reduce the burden of coronary artery disease.
2. To target invasive therapies to only those patients with proven benefit and avoid overdiagnosis and overtreatment.
3. To find less invasive therapies for stable coronary artery disease and acute coronary syndromes with sufficient efficacy and to identify to those patients who will benefit.

Results

Original studies

1. ***Long-term survival in patients undergoing percutaneous interventions with or without intracoronary pressure wire guidance or intracoronary ultrasonographic imaging: a large cohort study.***
   Fröhlich GM, Redwood S, Rakhit R, MacCarthy PA, Lim P, Crake T, White SK, Knight CJ, Kustosz C, Knapp G, Dalby MC, Mali IS, Archbold A, Wragg A, Timmis AD, Meier P. *JAMA Intern Med*. 2014 Aug;174(8):1360-6. http://dx.doi.org/10.1001/jamainternmed.2014.1595

Fractional flow reserve (FFR) and intravascular ultrasound (IVUS) provide functional and morphologic data that can be used to guide coronary intervention. However, only limited data exist about their impact on hard end points. Therefore it was the aim of this study to evaluate the effect of FFR and IVUS guided percutaneous coronary intervention on long-term survival in a large study population (n = 41,688) from the pan-London (United Kingdom) PCI registry. All patients who underwent elective or urgent PCI (for NSTEMI or unstable angina) in the eight Primary PCI hospitals in London between January 1, 2004, and July 31st 2011, were included. Patients underwent PCI solely guided by angiography, PCI guided by FFR, or IVUS-guided PCI. The primary outcome measure was overall survival. No difference in mortality was observed between patients who underwent angiography-guided PCI compared with patients who underwent FFR-guided PCI. In a propensity score-based analysis, patients who underwent IVUS had a similiar mortality compared with patients who underwent angiography-guided PCI. The number of implanted stents was lowest in the FFR group (1.1±1.2 stents) compared with the IVUS group (1.6±1.3) and the angiography-guided group (1.7±1.1; P < .001). In summary, this large observational study could demonstrate, that neither FFR- nor IVUS-guided PCI are associated with superior survival, if compared with standard angiography. However, the use of FFR reduced the number of implantated stents.

Beside the invasive haemodynamic and morphologic assessment of coronary lesions with FFR and IVUS, several non-invasive methods like myocardial perfusion scans or coronary computed tomography exist to detect myocardial ischaemia and relevant coronary stenoses. Non-invasive tests are indeed an appealing approach as they do not carry any risks of any invasive procedures, like bleeding complications or coronary perforation. However, it remained to be determined if the availability of these non-invasive imaging modalities finally increases the diagnostic yield of ICA and helps to target this invasive measure to mainly those patients who will also undergo a percutaneous therapy (stent) in the same session.

2. ***The impact of modern noninvasive cardiac imaging on coronary intervention rates.***
   Fröhlich GM, Schoch B, Wolfrum M, Osranek M, Enseleit F, Herzog BA, Hasun M, Lüscher TF, Meier P, Gaemperli O, Kaufmann PA, Corti R. *J Interv Cardiol*. 2014 Feb;27(1):50-7. http://dx.doi.org/10.1111/joic.12079

The low diagnostic yield of coronary angiography challenged the concept of angiography as a first line diagnostic approach to detect significant coronary artery disease. Non-invasive imaging modalities were developed to avoid redundant invasive coronary angiography (ICA). Current guidelines give clear recommendations on where to use ICA and when non-invasive tests should be preferred. However, it remains to be determined if the availability of non-invasive diagnostic tests for evaluation of relevant CAD (e.g. coronary computed tomography (CCT) or nuclear myocardial perfusion imaging (MPI)) changed the accuracy of invasive ICA. This study analysed the total number of ICA in the years 2000-2009 in a tertiary health care facility in relation to the number of percutaneous interventions (PCIs). It was investigated if there was a significant trend for a change in the diagnostic yield of ICA over time using time series analyses. Moreover, these data were compared with the number of patients undergoing CCT and nuclear MPI in the same time period. During the 10-year observational period, 23.397 ICA were performed. The proportion of purely diagnostic ICA (without PCI) remained stable over the whole study period (tau = -0.111, P = 0.721). A CCT program was launched in 2005 and 1,407 examinations were performed until 2009. Similarly, the number of nuclear MPI increased from 2,284 in the years 2000-2004 to 5,260 in the years 2005-2009 (P = 0.009)**.** In summary, although several more non-invasive tests became available, they did not significantly alter the rate of redundant ICA. CCT and nuclear MPI are currently not used according to guideline recommendations and do serve as gatekeeper to ICA.

As highlighted initially, a less aggressive and invasive approach appears to be the preferred treatment option in many patients. While invasive and non-invasive tests to detect relevant coronary stenoses aim to avoid unnecessary stent implantation, there exist different interventional strategies to treat relevant coronary stenoses. Potential complications and side effects of stents were already discussed above. One appealing treatment option, which may be seen as a compromise between stenting and purely medical management, is the use of DEB. Promissing niche indications for the use of DEB are investigated in the following article.

3. ***Drug eluting balloons for de novo coronary lesions - a systematic review and meta-analysis.***
   Fröhlich GM, Lansky AJ, Ko DT, Archangelidi O, De Palma R, Timmis A, Meier P. *BMC Med*. 2013 May 8;11:123.
   http://dx.doi.org/10.1186/1741-7015-11-123

DES implantation mandates dual antiplatelet therapy (DAPT) for 6-12 months, which may be contraindicated in patients who are at an increased bleeding risk. In these patients the use of DEB might be a valuable alternative. Several studies have indeed shown a benefit for the treatment of in-stent restenosis with DEB. However, its effect on de novo coronary lesions is more controversial. Several smaller randomized trials found conflicting results. This is a systematic review and meta-analysis of randomized controlled trials (RCT) evaluating the effect of local Paclitaxel delivery/drug eluting balloons (DEB) (+/- bare metal stent) compared to current standard therapy (stenting) for de novo coronary lesions. The main outcome measures were target lesion revascularization (TLR), binary in-segment restenosis, stent thrombosis (ST), myocardial infarction (MI), late lumen loss (LLL) and overall survival. In total, eight studies including 1.706 patients were analysed. Overall, DEB therapy yielded similar results to the control groups. The relative risk (RR) for mortality it was 0.79 (0.30 to 2.11), P = 0.644, for stent thrombosis it was 1.45 (0.42 to 5.01), P = 0.560, for MI it was 1.26 (0.49 to 3.21), P = 0.629, for TLR it was 1.09 (0.71 to 1.68); P = 0.700 and for binary in-stent restenosis it was 0.96 (0.48 to 1.93), P = 0.918. Compared to bare metal stents (BMS), DEB showed a lower LLL (- 0.26 mm (-0.51 to 0.01)). Overall, drug-eluting balloons (+/- bare metal stent) are not superior to current standard therapies (BMS or drug eluting stent (DES)) in treating de novo coronary lesions. However, the performance of DEB seems to lie in between DES and BMS with a trend towards superiority over BMS alone. Therefore, DEB may be considered in patients with contraindications for DES.

As discussed previously, the least invasive approach for diagnosis and treatment in patients with suspected coronary artery disease should be preferred, in order to avoid complications from invasive procedures. While patients presenting with STEMI are usually forwarded to emergent coronary angiography, in those with NSTEMI, ICA may be delayed for up to 48 hours. In those cases, where immediate ICA is not mandated, additional non-invasive tests and algorythms may be helpfull to identify patients, who present with conditions that mimick ACS, but which do not necessarily have to trigger ICA. Takotsubo cardiomyopathy is one of these entities, where ICA might be avoided in future, and only non-invasive testing allows to establish the diagnosis.

4. ***Takotsubo cardiomyopathy has a unique cardiac biomarker profile: NT-proBNP/myoglobin and NT-proBNP/troponin T ratios for the differential diagnosis of acute coronary syndromes and stress induced cardiomyopathy.***
   Fröhlich GM, Schoch B, Schmid F, Keller P, Sudano I, Lüscher TF, Noll G, Ruschitzka F, Enseleit F. *Int J Cardiol*. 2012 Feb 9;154(3):328-32. http://dx.doi.org/10.1016/j.ijcard.2011.09.077

Takotsubo cardiomyopathy (TC) is defined by a transient impairment of the left ventricular function, which is characterized by an apical ballooning pattern. Clinical presentation and ECG changes may mimick an acute coronary syndrome. However, heart catheterization reveals only non-obstructive coronary artery disease in these patients. To avoid unnecessary heart catheterization in patients with suspected TC, it was our aim to identify this condition by its unique cardiac biomarker profile at an early stage and. Ratios of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and myoglobin, NT-proBNP and troponin T (TnT), NT-proBNP and creatinekinase-MB (CK-MB) were compared in patients with TC (n=39), patients with ST-elevation myocardial infarction (STEMI, n=48) and patients with non-ST-elevation myocardial infarction (NSTEMI, n=34). Biomarkers were recorded serially at admission and at the three consecutive days. Optimal cut-off values to distinguish TC from STEMI and NSTEMI were calculated with receiver operator characteristic (ROC) curves. Best differentiation of TC and ACS was possible with the ratio of peak levels of NT-proBNP (ng/l)/TnT (µg/l). A cut-off value of NT-proBNP (ng/l)/TnT (µg/l) ratio of 2889, distinguished TC from STEMI (sensitivity: 91%, specificity: 95%), while a NT-proBNP (ng/l)/TnT (µg/l) ratio of 5000 separated well between TC and NSTEMI (sensitivity: 83%, specificity: 95%). In summary, TC is associated with a unique cardiac biomarker profile, which might be useful to identify patients with TC among patients presenting with acute coronary syndromes (ACS).

Typically sounding chest pain and ST elevation on ECG in patients presenting with TC may be misinterpreted as „STEMI“ initially. While TC is a relatively rare condition without significant myocardial damage and good prognosis in the vast majority of patients, STEMI is inevitably associated with myocardial cell death which may lead to deterioration of left ventricular function and heart failure. The main treatment goal is to restore blood flow and oxygen supply to the myocadium quickly. However, the reperfusion injury, which happens within minutes after reopening of the occluded artery and which may impact significantly on the final infarct size is not targeted by any contemporary therapeutic strategies. Therefore new concepts are needed to further reduce the damage to the myocardium in patients presenting with STEMI.

5. ***Remote Ischemic Conditioning Reduces Myocardial Infarct Size and Edema in Patients With ST-Segment Elevation Myocardial Infarction.*** White SK, Fröhlich GM, Sado DM, Maestrini V, Fontana M, Treibel TA, Tehrani S, Flett AS, Meier P, Ariti C, Davies JR, Moon JC, Yellon DM, Hausenloy DJ. *JACC Cardiovasc Interv*. 2015 Jan;8(1 Pt B):178-88. http://dx.doi.org/10.1016/j.jcin.2014.05.015

Myocardial infarct size is closely related to long-term prognosis. Therefore novel methods to reduce the damage to myocardium need to be developed. Interestingly, 50% of the final infarct size are not determined by ischaemia, but by the reperfusion injury (RI). Following promising data from animal studies, this trial investigated, if remote ischemic conditioning (RIC), which is commenced prior to PPCI could mitigate myocardial infarct (MI) size by reducing the RI. 197 patients with ST-segment elevation myocardial infarction with TIMI (Thrombolysis In Myocardial Infarction) flow grade 0 were randomly assigned to receive RIC (four 5-min cycles of upper arm cuff inflation/deflation) or control (uninflated cuff placed on upper arm for 40 min) prior to PPCI. The primary study endpoint was MI size, measured by cardiac magnetic resonance imaging on days 3 to 6 after admission. RIC reduced MI size by 27%, when compared with the MI size of control subjects (18.0 ± 10% [n = 40] vs. 24.5 ± 12.0% [n = 43]; p = 0.009). At 24 h, high-sensitivity troponin T was lower with RIC (2,296 ± 263 ng/l [n = 89] vs. 2,736 ± 325 ng/l [n = 84]; p = 0.037). RIC also reduced the extent of myocardial edema measured by T2-mapping CMR (28.5 ± 9.0% vs. 35.1 ± 10.0%; p = 0.003). In summary, this trial found that RIC, which is started prior to PPCI, reduced MI size, increased myocardial salvage, and reduced myocardial edema. These data will need to be confirmed in appropriately powered prospective trials with clinical endpoints now.

Discussion

Coronary artery disease is a chronic condition, which may even start in young adults. First coronary plaques were detected in one of six teenagers in a population of heart transplant donors.[54] The presence of hypertension, diabetes, smoking or genetic predisposition may lead to a progress of these first plaques and may then cause haemodynamic flow impairment and cause angina symptoms after years.[55] While a slow progression of coronary plaques typically leads to stable angina symptoms, so called „vulnerable plaques“ are associated with a high risk of sudden rupture of the endothelial cap, which may then cause immediate thrombotic coronary occlusion and acute coronary syndromes.[56, 57] Of note, vulnerable plaques are difficult to detect as they do not necessarily compromise coronary blood flow before rupture.[57] While there is no virtual significant myocardial damage in patients with stable coronary artery disease, in those patients presenting with acute coronary syndromes, myocardial cell death is inevitable.[58] As highlighted above, coronary artery disease is an entity with no clear boundaries between stable coronary artery disease, which may suddenly turn to an acute coronary syndrome.[59] Interestingly enough, more than half of patients present with an ACS as first manifestation of their CAD.[60] Therefore, it was the goal of the present habilitation thesis, to a) identify patients with significant CAD with a sufficient accuracy before myocardial damage happens and b) to avoid overdiagnosis and overtreatment with potentially harmful invasive therapies, as slowly progressing plaques might not need interventional but medical treatment and c) to investigate and develop strategies for gentle treatment of coronary lesions and reduce myocardial damage in patients with acute coronary syndromes.

Tools to improve the diagnostic yield of ICA and avoid unnecessary therapies

In 1974 Andreas Grüntzig invented the „percutaneous transluminal coronary angioplasty“ (PTCA).[61] But the very early hope and expectations were relativized, as the procedural success rate was as low as 75% initially with a high restenosis rate >20% and a significant proportion of patients who needed emergent bypass surgery (8%) due to coronary dissections.[62] With the advent of bare metal coronary stents in 1986, immediate recoil and coronary dissections were better controlled, but the long-term restenosis rate was still unacceptably high (up to 30%).[63] In the late 1990ies, drug eluting stents became available and dramatically reduced the rate of restenosis (<10%).[63] With the latest generation stents the need for target vessel revascularization within 12 months dropped to 1-3%.[64, 65] This first enthusiasm led to a steep increase of stent implantations and even complex PCI in distal left main stem lesions appeared to yield reasonable long-term results, with 12 months need for TVR of 3-6%.[66] But the use of drug eluting stents mean a longer requirement for dual antiplatelet therapy, which is usually 6-12 months, if compared to bare metal stents, where it is only 1 month, at least in patients with SCAD.[11] As a consequennce, the risk for moderate to severe bleeding under aspirin and clopidogrel therapy is increased by the use of DES and equals 1-2% within the first 12 months.[67] Secondly, DES carry a higher risk for late in-stent thrombosis (1-3% within 12 months).[68] And if used in mid to distal vessel segments, metal stents may preclude bypass surgery. For these reasons, several land mark trials did not only challenge the concept of using coronary angiography as first line diagnostic tool for diagnosis of CAD, but it became obvious, that optimal medical treatment in patients with stable CAD is non-inferior to stenting in a large proportion of patients.[69] Therefore, new diagnostic tools to tailor stent implantation only to those patients who will benefit most were developed: The FAME and FAME II trials investigated the usefullness of pressure wire assessment in patients with stable

coronary artery disease or NSTEMI.[20, 21, 70] The pressure wire was designed to calculate the proportion of the mean arterial pressure distal to a coronary stenosis, if compared to the aortic reference pressure during adenosine stress conditions (Fractional Flow Reserve).[17] Interestingly enough, only if the FFR was ≤0.80, a stent implantation was recommended, while FFR values above predicted an excellent long-term prognosis with freedom from major cardiovascular events, even without stent deployment.[20] But, the number of patients in the FAME trials was relatively low and FAME II was terminated prematurely, which further reduced its statistical power.[20, 21] In contrast to the FFR measurement, where the haemodynamic impact of a coronary lesion is assessed, intravascular ultrasound (IVUS) provides only morphologic lesion assessment.[71] While clinical trials have proven the beneficial effect of FFR, the benefits for use of IVUS are less clear.[11] In our study we could demonstrate in a large population of more than 40.000 patients that there was no clear trend for improved survival in those patients with FFR guided PCI, if compared to angiography alone.[72] But, there was a reduced need for stent implantation in the FFR group.[72] Although stent implantation was less common in the FFR group, survival was comparable to the angiography guided PCI group.[72]

In contrast, the use of intravascular imaging (IVUS), was associated with an increased number of implanted stents and a longer stented segment.[72] There was also a trend towards unfavorable long-term survival in a Cox proportional hazard model, but this was no longer evident after a propensity match analysis.[72]

These results show, that „less might sometimes be more“, when it comes to percutaneous stenting.[72]

In a different analysis we investigated the diagnostic yield of of invasive coronary angiography.[10, 73] Interventional cardiologists are sometimes critizised for the low

threshold to use ICA.[74] European guidelines give clear recommendations and algorithms on which patients should proceed to ICA straight away and who should preferentially undergo non-invasive testing first (e.g. exercise test, stress perfusion MRI, coronary computed tomography…).[11] Surprisingly, we found in a large cohort of patients referred for coronary angiography to a tertiary care facility, that a significant proportion of patients with only moderate cardiovascular risk, in who coronary artery disease was finally excluded on ICA, did not receive any non-invasive tests before ICA.[73]

Over the years, CCT was introduced as new non-invasive imaging modality.[73] The main strength of CCT is to exclude significant CAD in patients at a low to moderate cardiovascular risk.[75] While CCT numbers were rapidly increasing over the years, in parallel, the numbers of low cost examinations like exercise test and ECG were falling, but the diagnostic yield of ICA remained unchanged.[73] In summary, a) non-invasive imaging modalities are not used according to current guidelines recommendations and b) more money is spent on more expensive non-invasive tools, but the results from these investigations are finally ignored by the treating cardiologists, who still forward their patients to ICA.[73]

In contrast to stable coronary artery disease, where time consuming non-invasive testing may be appropriate, in acute coronary syndromes quick decisions need to be made on whether timely ICA needs to be arranged or not.[76] „Time is muscle“ summarizes the main goal of emergency or urgent angiography following a NSTEMI or STEMI.[76, 77] Notably, there exist certain cardiac conditions, like the „broken heart syndrome“ or „Takotsubo“ syndrome, that may mimick an ACS.[36] This stress induced cardiomyopathy is typically triggered by an extraordinary emotional stress situation (e.g. death of a relative) and the patients do present with symptoms and ECG changes which are commonly found in ACS patients.[36] But on angiography, clear coronaries

are documented, where the left ventricular function may be severely impaired by an apical or mid-ventricular ballooning.[36] Left ventricular function usually normalizes within several weeks to months.[36] As highlighted above, these Takotsubo patients receive somhow futile ICA, and this potentially harmful invasive test might be avoided. Alternative non-invasive testing might be more desirable for these patients though. Some authors tried to define ECG criteria to distinguish Takotsubo from STEMI and ACS, but this method turned out to be not precise enough.[78] Also, cardiac MRI was proposed for clarifying the diagnosis of Takotsubo in patients with elevated myocardial enzymes but normal coronaries on ICA.[79] This would be a quite costly approach and may not be feasible in patients with contraindications for MRI. Other authors tried to find echocardiographic parameters to facilitate the diagnosis of Takotsubo cardiomyopathy. For example, speckle tracking was suggested in a small case series.[80] Although, a genetic pattern was postulated in patients with Takotsubo, genetic testing does not play any role in the diagnosis of this cardiomyopthy so far.[81] As highlighted above, so far no robust non-invasive tests are available that are precise enough to discriminate Takotsubo from ACS. Therefore we suggested a two step approach in patients with suspected stress induced cardiomyopathy.[82] 1) As Takotsubo cardiomypathy is not associated with permanent myocardial damage, a troponin rise is commonly only mild. In contrast, the left ventricular ejection fraction may indeed be severely impaired in the acute phase of apical ballooning.[82] This quite typical biomarker pattern leads to a significant increase in NT-proBNP, which may even be more pronounced if compared to STEMI.[82] While a modest troponin rise or an increased proBNP value per se do not exclude an ACS, we tried to increase the diagnostic yield from these biomarkers by calculating the proportion of NT-proBNP and troponin.[82] Next, we established cut-off values, where either Takotsubo or ACS crystallize to be the more likely diagnosis.[82] If Takotsubo is the diagnosis according to

the biomarker ratio, non-invasive imaging, for example with CCT might be the preferred diagnostic tool over ICA to confirm the diagnosis and to avoid the underdiagnosis of ACS.[82] However, a prospective study will be needed to confirm the feasibility and safety of this diagnostic approach before it may be adopted into daily clinical practice.

Less invasive therapies for SCAD and STEMI

The „less is more“ principle may also apply to patients with significant de novo coronary lesions, who are at an increased bleeding risk. These patients should receive only very limited dual antiplatelet therapy after stenting. The concept of drug eluting balloons (DEB) - where no stent, but only a drug coated balloon is inflated - was previously tested successfully for in-stent restenosis, where the use of DEB was indeed the best treatment option if compared to Taxus stent-in-stent therapy.[83] Even current practice guidelines recommend DEB as valid choice for in-stent restenosis.[11] Drug eluting balloons deliver paclitaxel to the vessel wall to reduce restenosis rate.[84] Although the immediate vessel recoil after balloon deflation may flaw long-term results if used in de novo lesions, the potential advantages like the lack of a foreign body in the coronary vessel and in particular the lack of a potentially prothrombotic stent polymer might be beneficial.[28] Therefore, we performed a meta-analysis including smaller studies that compared DEB in de novo lesions with either bare metal stents or drug eluting stents.[85] We found, that in general that there is a trend for a superior long-term outcome after DEB treatment of de novo coronary lesions if compared to bare metal stents but an inferior outcome compared to drug eluting stents.[85] As such, DEB might indeed be a reasonable treatment for patients at increased bleeding risk, where long-standing dual antiplatelet therapy needs to be avoided.[85] Also, in diabetic patients, where the in-stent restenosis rate is even doubled with the use of bare metal stents the additional use of

DEB was demonstrated to be beneficial, with results comparable to DES.[86] Of note, while DES struts cover only about 20% of the vessel wall, the DEB may release drug to the entire target vessel area, where the balloon is inflated.[85] These data do support not only the DEB stand alone approach for de novo lesions, but also a hybrid strategy, where the DEB is used on top of bare metal stent implantation. Indeed, a randomized study found that bare metal stents, which were post-dilated with a DEB yielded similar 6 month in-stent restenosis rates if compared to Xience DES.[87] The main advantage of this hybrid concept is, that dual antiplatelet therapy needs to be applied for no more than 1-3 months, in patients with SCAD.[11] Our results are in line with a study which was published recently. Naganuma and collegues randomized 182 patients with de novo coronary lesions to receive either paclitaxel eluting stents or DEB. Interestingly enough, up to the 2-years follow-up there was no difference in terms of MACE or target lumen revascularization.[88]

As discussed initially, in patients presenting with STEMI, the final myocardial infarct size is not only determined by the ischaemia itself, but to a large proportion by the reperfusion injury (RI).[40] To date, no efficient treatment exists to target the reperfusion injury.[42] Therefore, novel treatment strategies are needed. Several previous attempts by using intracoronary adenosine, NO donors or verapamil did not proof to be beneficial.[42] In animal studies, the concept of remote ischaemic preconditioning yielded promising results.[40] Thereby, induction of ischaemia in the intestine or a limb in a STEMI animal model, reduced the final infarct size by up to 50%.[42] The theory behind this strategy was, that remote limb ischaemia induces the release of peptides from limb tissues, that protect the myocardium after restoration of blood flow. Indeed, bradykinin, the opioid receptor, the calcitonin gene-related peptide (CGRP), noradrenalin, inducible nitric oxide synthase (iNOS), proteinkinase C and corticosteroids were found to affect the pathways of RI.[89] We conducted a clinical multicentre trial to investigate

the efficacy of remote ischaemic conditioning which was intiated before primary PCI.[90] The infarct size as assessed on cardiac MRI was significantly reduced by 27% if compared to the control group.[90] Similarily, the myocardial edema as assessed by T2 mapping was reduced significantly by RIC.[90] In line with these imaging results, also the troponin at 24h was reduced by the RIC.[90]

Crimi and collegues presented a randomized study, where 100 patients undergoing PPCI received remote ischaemic post-conditioning or not.[91] A blood pressure cuff was inflated to induce ischaemia of the lower limb.[91] The authors found, that the enzymatic infarct size was significantly reduced by post-conditioning, and also myocardial edema, as assessed by magnetic resonance imaging was improved.[91]

A recent meta-analysis including 731 patients undergoing percutaneous intervention found, that RIC significantly lowered the incidence of periprocedural myocardial infarction, in particular, if lower limb ischaemia was induced and in those patients with complex PCI.[92]

RIC appears to be beneficial also in liver and kidney transplantation, where animal trials as well as early human studies demonstrate, that RIC has a protective effect on the donated organ.[93-95]

However, although RIC is a very appealing approach to reduce the myocardial infarct size, its mechanisms are not yet fully understood and will need further investigations.

Now larger clincial trials with hard endpoints are needed to confirm the results from these early pilot studies.

Summary

It was the aim of the present thesis to evaluate novel diagnostic and therapeutic tools and to investigate their impact on outcomes in patients with stable coronary artery disease and ACS.

Heart catheterization and ICA has revolutionized the minimally invasive therapy of coronary stenosis with stents rather than coronary bypass surgery. However, stents are associated with potential side effects and compliations and some trials challenged the pracitce of low threshold stenting. A haemodynamic assessment of the coronary lesion with FFR is an easy to use tool to tailor stents only to those patients who will finally benefit. The number of stents may indeed be reduced by FFR guided PCI – with an excellent long-term prognosis. Apart from invasive FFR measurement, also non-invasive tests like coronary computed tomography may be used to assess for relevant coronary stenoses. Interestingly enough, these non-invasive tests are not used according to current guideline recommendations in many cases or test results are ignored and patients are forwarded to ICA despite negative test results. As highlighted above, stents do carry potential risks and side effects. One of them is the need for dual antiplatelet therapy up to 12 months after DES implantation. In a meta-analysis it was demonstrated, that DEB do indeed offer a valuable alternative in de-novo coronary lesions. Outcomes were indeed slightly superior to bare metal stents, but inferior to DES.

Coronary artery disease is still one of the major causes of death. Although mortality rates after STEMI could be reduced to 3% with contemporary primary percutaneous intervention if compared to 8% with thrombolysis therapy in the 1990ies , morbidity due to heart failure following STEMI is still unaccepably high. Treating the reperfusion injury after restoration of blood flow to the culprit vessel would be an appealing new strategy on top of PPCI. A pilot randomized clinical trial could demonstrate that remote

ischaemic preconditioning by inducing transient upper limb ischaemia with a blood pressure cuff may indeed reduce the final infarct size, as assessed by cardiac MRI. Now larger trials with clinical endpoints are needed to confirm these preliminary results.

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Erklärung

§4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- Weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt wurde oder angemeldet wurde,
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Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Berlin, 02.04.2015 Georg Fröhlich