Multimodality imaging in ischemic heart disease, from prevention to outcome

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Thesis outline


MULTIMO
MAGING
SCHEMIC
DISEASE
PREVENT
TOOLS

Chapter 1

General Introduction and Outline of the Thesis

General introduction

The function of the heart was first described in 1628 by the British physician William Harvey.[1] Since then, our knowledge of the heart has grown tremendously, with great advances having been made in the development of diagnostic tools and therapeutic options for cardiac diseases. However, despite these improvements, ischemic heart disease remains the number one cause of death, accounting for 1 in 3 deaths globally.[2] There are several reasons for this high prevalence.

Firstly, a substantial number of patients that presents with a fatal acute myocardial infarction does not experience any prior symptoms from the presence of (premature) coronary atherosclerosis (**Part I**). Secondly, in the current treatment of patients with an acute myocardial infarction and multivessel coronary artery disease (CAD) on the initial angiogram, there are still areas that are not yet fully elucidated (**Part II**). And finally, in ST-elevation myocardial infarction (STEMI) patients it is difficult to determine which patients are at increased risk of (fatal) ventricular arrhythmias after the acute phase since it are not only patients with a decreased left ventricular ejection fraction (LVEF) that experience arrhythmias (**Part III**).[3]

The aim of the studies presented in this thesis then was to determine the clinical value of different imaging techniques and invasive treatments to improve the prevention, management as well as the prognosis of ischemic heart disease.

PART I · DETECTION OF ATHEROSCLEROSIS AND VARIATION IN CORONARY ANATOMY

To reduce the incidence of fatal myocardial infarction it is important to identify which patients are at increased cardiovascular (CV) risk and might need preventive treatment with statins and/or aspirin. Coronary computed tomography angiography (CTA) is a validated and non-invasive imaging method to screen the coronary arteries for (premature) atherosclerosis as indicated by the presence of coronary plaques and stenosis.[4] The great value of this non-invasive imaging technique lies in ruling out the presence of CAD in patients with a low to intermediate priori CV risk. Hence, coronary CTA avoids the need of direct screening with invasive angiography of patients with atypical chest pain or asymptomatic patients with an elevated CV risk profile. One of the largest groups known to be at increased risk of the development of CAD is patients with diabetes mellitus (DM). Previous data even suggest that

this patient group has as high a risk of myocardial infarction as non-diabetic patients with a previous myocardial infarction.[5] Therefore, the European Society of Cardiology (ESC) guidelines recommends to consider aspirin use for the primary prevention of CAD in patients at high-risk and DM.[6] However, the definition of patients at high-risk of CAD is not entirely clear, while the efficacy and safety of aspirin as preventive therapy also needs more research.[7-9] To tailor aspirin treatment in patients with DM, the assessment of CAD using coronary CTA could be of superior value over established traditional CV risk factors to identify patients without CAD who do not need aspirin.[10, 11] Therefore, **Chapter 2** of this thesis investigates the prevalence of CAD on coronary CTA in high-risk patients with DM without chest-pain syndrome and evaluates associations between the presence and number of traditional CV risk factors and the presence of CAD on coronary CTA. Screening patients for the presence of CAD by means of coronary CTA not only provides information about the presence of coronary atherosclerosis, it also frequently discovers variations in coronary anatomy and extracardiac abnormalities. One of the most common variations in coronary anatomy is an intramural course of the epicardial artery, which is defined as a coronary artery covered by ≥ 1 mm of superficial muscle fibers throughout its course. The literature reports widely varying prevalence rates of 6% up to 58% as based on findings from coronary CTA.[12] The difference in reported prevalence of an intramural course of a coronary artery on coronary CTA can partly be explained by variations in the definition of intramural course (depth, length) and the minimal lumen area of the vessel taken into account. Not much is known about the influence of an intramural course of a coronary artery (on coronary CTA) on prognosis and outcome. Therefore, it is uncertain whether this finding on coronary CTA should have consequences for management and therapy. **Chapter 3** therefore evaluates whether an intramural course of a coronary artery as indicated by coronary CTA in patients with a low to intermediate CV risk profile without obstructive CAD is associated with poorer outcomes than are seen in patients without an intramural course.

PART II · MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

For patients with acute STEMI, immediate invasive coronary angiography with the intention to proceed to instant revascularization is recommended.[13] In more than half of these patients, interventional cardiologists detect multi-vessel

CAD on the initial coronary angiography.[14, 15] However, the best strategy in STEMI patients with multi-vessel CAD regarding completeness of revascularization of the non-culprit lesion(s) is still unclear. [16, 17] Advocates of complete revascularization state that in this way multiple plaque ruptures are stabilized with faster recovery of the left ventricular (LV) function, which may avoid the development of hibernation due to myocardial ischemia of the non-culprit lesion(s).[18] However, revascularization of the non-culprit lesions is not without risk. It increases the risk of procedural complications, while in the acute phase the degree of stenosis in the non-culprit lesions is often overestimated, potentially resulting in overtreatment. In addition, it has been suggested that in the acute phase patients are in a heightened pro-inflammatory and pro-thrombotic state, where a conservative approach (i.e. fewer interventions) is to be preferred.[19] To overcome current issues about the optimal revascularization strategy in patients with STEMI and multi-vessel CAD, not only short-term results should be taken into account. **Chapter 4** concerns an analysis whether complete revascularization is associated with superior long-term outcomes in these patients compared to peers having received incomplete revascularization. In addition, subgroups are analysed to determine which group has the most benefit from complete revascularization as compared to incomplete revascularization. Specifically, gender differences may exist regarding outcome after complete or incomplete revascularization. **Chapter 5** investigates whether in patients with a first STEMI and multi-vessel CAD, there are gender-related benefits on all-cause mortality between both revascularisation strategies.

PART III · PROGNOSIS OF ISCHEMIC HEART DISEASE

The location and extent of acute myocardial infarction and the presence of myocardial ischemia both play an important role in the prognosis of and need for additional treatment in patients having suffered a STEMI.[20-22] It is crucial that patients with a large myocardial infarction are monitored closely to prevent re-infarction and progression to heart failure. Additionally, patients with a reduced LVEF often require primary prevention with an implantable cardioverter defibrillator (ICD) to reduce the risk of sudden cardiac death.[23] A wide range of non-invasive imaging tools is available to assess the post-STEMI residual LV systolic function. In contrast to single-photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI), and magnetic resonance imaging (MRI), echocardiography is a safe, inexpensive, quick and non-invasive imaging technique suitable for bedside use. Although the most

widely used echocardiographic parameter for the assessment of residual LV systolic function is LVEF,[24] left ventricular global longitudinal strain (LV GLS) as visualized by means of speckle-tracking echocardiography might be a better index of the extent of the infarction and the residual LV systolic function. However, not all factors that influence the correlation between LV GLS and infarct size have been clarified. Perhaps, the presence of myocardial ischemia may further impair LV GLS due to repetitive stunning. **Chapter 6** thus explores the influence of myocardial ischemia on the correlation between LV GLS and myocardial infarction size in patients after STEMI.

To determine the prognosis of post-STEMI patients not only the residual LV systolic function but also cardiac denervation should be considered, particularly since cardiac sympathetic denervation is a powerful predictor of ventricular arrhythmias and sudden cardiac death.[25, 26] ^{123}Iodine-meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy is a non-invasive imaging technique providing (semi-)quantitative information about myocardial sympathetic activity.[27] Different parameters can be obtained from planar ^{123}I-MIBG images. First, from the early and late planar ^{123}I-MIBG images the heart-to-mediastinum (H/M) ratio can be derived, which parameter reflects the relative distribution of cardiac sympathetic nerve terminals and offers information about the neuronal function. In addition, the washout rate of the tracer between the early and late planar images provides information about the sympathetic drive. In patients with heart failure, the myocardial sympathetic neuronal uptake is decreased, which is reflected by a low H/M ratio and an increased washout rate.[26] Furthermore, focal innervation defects can be analysed with ^{123}I-MIBG SPECT. **Chapter 7** gives an overview of recent trends and the latest results obtained with ^{123}I-MIBG SPECT imaging.

Besides the clinical indication to assess prognosis in patients with heart failure with ^{123}I-MIBG imaging there is a growing number of other indications in the cardiology, for instance to evaluate the effects of cardiac medication.[28, 29] **Chapter 8** provides a summary of these potential indications.

With the growing use of ^{123}I-MIBG imaging there is a need for standardization of the data-acquisition procedure.[30] In addition, shortening of the waiting period between the early and late acquisition (which is now over 4 hours) is preferred. **Chapter 9** of this thesis evaluates whether performing the late cardiac ^{123}I-MIBG scan earlier than 4 hours post-injection (pi) has a relevant impact on the late H/M ratio in patients with heart failure. Moreover, a model to compare acquisitions derived from different late acquisition times would be of value to ease comparison of study results. Accordingly, **Chapter 10** evaluates

whether a developed direct comparison model enables comparison of data from different acquisition times.

Objectives and Outline of the Thesis

The aim of the studies presented in this dissertation is to evaluate the clinical relevance of different imaging techniques and invasive strategies to improve the early detection, management and prognosis of ischemic heart disease.

Part I of this thesis evaluates the diagnostic value of coronary CTA in the early detection of CAD. More specifically, **Chapter 2** provides an estimate how many patients with DM and one or more CV risk factors have CAD on coronary CTA. In addition, associations between the presence and number of traditional CV risk factors and the presence of CAD on coronary CTA is determined in high-risk DM patients without chest-pain syndrome. **Chapter 3** describes the influence of an intramural course of a coronary artery on the long-term outcome of patients screened for CAD using coronary CTA.

Part II of this thesis addresses the influence of different revascularization strategies on survival in patients with STEMI and multi-vessel CAD. In more detail, **Chapter 4** evaluates the short- and long-term prognosis of such patients following complete versus incomplete revascularization during first admission. In addition, **Chapter 5** investigates gender-related disparities in the outcomes of the two strategies in these patients.

Part III considers the respective values of 2-dimensional strain echocardiography and ^{123}I-MIBG scintigraphy in patients with ischemic heart disease. These techniques provide information on systolic LV function and cardiac innervation/denervation, which indices are both important for the prognosis of patients with ischemic heart disease. **Chapter 6** describes the influence of myocardial ischemia extent on LV GLS in patients with previous STEMI **Chapters 7 and 8** focus on the current role of ^{123}I-MIBG scintigraphy. **Chapter 7** provides a review on the respective relevance of planar and SPECT ^{123}I-MIBG imaging. An overview of the increasing number of potential clinical indications for ^{123}I-MIBG imaging in cardiology beyond heart failure is provided in **Chapter 8**.

Chapters 9 and 10 address the optimization of planar ^{123}I-MIBG imaging protocols, with a special focus on shortened scan-time intervals and easier comparison of data from different acquisition times.

Finally, in **Chapter 11** the results obtained in the various studies are summarized and conclusions drawn.

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PART I

DETECTION OF ATHEROSCLEROSIS AND VARIATION IN CORONARY ANATOMY


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Chapter 2

Value of Coronary Computed Tomography Angiography in Tailoring Aspirin Therapy for Primary Prevention of Atherosclerotic Events in Patients at High-risk with Diabetes Mellitus

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Dimitriu-Leen AC, Scholte AJHA, van Rosendael AR, van den Hoogen IJ, Kharagjitsingh AV, Wolterbeek R, Knuuti J, Kroft LJM, Delgado V, Jukema JW, de Graaf MA, Bax JJ.

Abstract

Aspirin use for primary prevention in patients at high-risk with diabetes mellitus (DM) is often recommended under the assumption that most patients with DM have coronary artery disease (CAD). However, not all patients may have CAD. The present study evaluated, in 425 patients at high-risk with DM (without chest pain syndrome or a history of cardiac disease), the prevalence of CAD on coronary computed tomography angiography (CTA). Moreover, the association between the presence and number of traditional cardiovascular (CV) risk factors and CAD (on coronary CTA) was evaluated. The median coronary artery calcium score was 29 (interquartile range 0 to 298). On coronary CTA, 116 patients (27%) had no CAD (defined as <30% stenosis). Of the 309 patients (73%) with any CAD (≥30% stenosis), 35% had obstructive CAD (≥50% stenosis). The number of traditional CV risk factors was not associated with the presence of any CAD (≥30% stenosis; P=0.18) or obstructive CAD (≥50% stenosis; P=0.13). Hypertension was the only traditional CV risk factor associated with a higher frequency of any CAD (≥30% stenosis; odds ratio = 2.21, 95% CI 1.43 to3.41, P<0.001) and obstructive CAD (≥50% stenosis; odds ratio = 2.03, 95% CI 1.33 to 3.11, P=0.001). In conclusion, in patients at high-risk with DM without chest pain syndrome, any CAD was ruled out by coronary CTA in 27%, whereas 65% of the patients did not have obstructive CAD. The number of CV risk factors was not associated with the presence of CAD. Hypertension was the only traditional CV risk factor that was associated with a higher frequency of CAD. These observations support potential use of coronary CTA to tailor aspirin therapy in patients at high-risk with DM.

Introduction

The European Society of Cardiology (ESC) guidelines recommend to consider aspirin use for primary prevention in patients at high-risk with diabetes mellitus (DM).[1] However, the definition of patients at high-risk with DM is not entirely clear. The 2012 ESC guidelines on cardiovascular (CV) disease prevention suggested that patients with DM, and at least one other CV risk factor or target organ damage, should be considered to be at very high-risk and all other patients with DM to be at high-risk.[2] Traditional risk scores such as the Framingham CV Risk Equation or Systematic Coronary Risk Evaluation were not specifically developed for patients with DM.[3,4] There have been attempts to design risk engines for patients with DM such as the United Kingdom Prospective Diabetes Study and the Swedish National Diabetes Register, but the applicability of these scores for clinical practice needs further validation.[5,6] Moreover, current risk engines do not incorporate (non-invasive) imaging tests, which have been shown to be of great value for risk stratification in patients with DM and without DM.[7,8] Treatment with aspirin has been proved to reduce CV events in secondary prevention (in patients with coronary artery disease [CAD]).[9] However, the efficacy and safety in primary prevention are still unclear and need more research.[10-12] Patients with DM often have (severe) CAD, but are frequently free of chest pain symptoms. However, not all patients with DM have CAD.[13] Therefore, it is important to identify which patients at high-risk with DM are free of CAD and may not need aspirin. Assessment of CAD on coronary computed tomography angiography (CTA) could be of value over established traditional CV risk factors to identify patients without CAD who do not need aspirin. Therefore, aims of this study were: 1) to investigate the prevalence of CAD on coronary CTA and 2) to evaluate the association between the presence and number of traditional CV risk factors and the presence of CAD on coronary CTA in patients at high-risk with DM without chest pain syndrome.

Methods

The population consisted of 448 patients with DM without chest pain syndrome who were clinically referred for coronary CTA for evaluation of CAD. The inclusion criteria were 1) a diagnosis of type 1 or 2 DM, 2) absence of chest pain syndrome defined as atypical or typical angina and 3) one or more traditional CV risk factors besides DM. The risk factors included hypercho-

lesterolemia (defined as a self-reported history of hypercholesterolemia and/or therapeutic treatment with lipid lowering drugs), hypertension (defined as the self-reported history of hypertension and/or the use of antihypertensive medication, or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg), family history of CV disease, current smoker and obesity (body mass index (BMI) ≥ 30 kg/m^2). Patients with a history of CAD (history of myocardial infarction (MI), percutaneous coronary intervention or coronary artery bypass graft surgery), heart failure, valvular heart disease, arrhythmia or congenital heart disease were excluded.

Demographic data were prospectively entered into the departmental Cardiology Information System (EPD-Vision©, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. For retrospective analysis of clinically acquired data, the institutional review board waived the need for patient written informed consent.

Coronary CTA was performed using a 64- or 320-detector row computed tomography scanner (64-slice: Aquillon 64, Toshiba Medical Systems, Otawara, Japan 320-slice: Aquillon ONE, Toshiba Medical System, Otawara, Japan). Data acquisition protocol has been previously described.[14] In summary, a nonenhanced and contrastenhanced CT scans were performed. Postprocessing of scans was performed with dedicated software (Vitrea FX 1.0, Vital Images, Minnetonka, Minnesota). Uninterpretable scans were excluded from the analysis.

The coronary artery calcium (CAC) score was performed according to the algorithm of Agatston, which was categorized in four risk categories: 0, 1 to 100, 101 to 400 and >400. All coronary CTAs were analyzed, according to the modified 17-segment American Heart Association classification. Only segments which were interpretable (no severe motion artifacts) with a diameter of ≥ 1.5mm were analyzed. Structures > 1mm^2 within and/or adjacent to the vessel lumen that could be discriminated from surrounding pericardial tissue, epicardial fat and the vessel lumen itself were defined as plaque.[15] The severity of coronary stenosis in each segment was classified by visual estimation in 5 categories: no stenosis, stenosis 1 to 29%, stenosis 30 to 49%, stenosis 50 to 70% and stenosis ≥70%. Coronary plaques were stratified into 3 groups: calcified (plaque containing ≥ 50% calcified tissue), mixed (plaque containing <50% calcified tissue) and non-calcified (plaque containing no calcified tissue). Importantly, 2 separate analyses were performed, based on 1) the presence of "any CAD" which was defined as at least one stenosis ≥30% in any vessel and 2) the presence of "obstructive CAD" which was defined as at least one stenosis ≥50% in any vessel.

Table 1. *Patient characteristics*

Variable	All Patients (n=425)
Men	243 (57%)
Age (years)	56 ± 11
Height (meter)	1.72 ± 0.10
Weight (kg)	86 ± 18
Diabetes mellitus (type 2)	346 (81%)
BMI ≥ 30 (kg/m²)	156 (37%)
Family history of CV disease	173 (41%)
Hypercholesterolemia†	244 (57%)
Hypertension‡	254 (60%)
Current smoker	98 (23%)
*Number of additional CV risk factors**	
1	131 (31%)
2	138 (32%)
3	109 (26%)
≥ 4	47 (11%)
Medication use	
Ace-inhibitor/AT II	219 (52%)
Statin	273 (64%)
Betablocker	71 (17%)
Calciumantagonist	50 (12%)
OAC/Clopidogrel/Persantin/Aspirin	118 (28%)

BMI = body mass index; CV = cardiovascular; DM = diabetes mellitus; OAC = oral anticoagulation. Definitions:

† *Defined as self-reported history of hypercholesterolemia and/or therapeutic treatment with lipid lowering drugs;*

‡ *Defined as self-reported history of hypertension, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication;*

* *Additional CV risk factors consisted of family history of CV disease, hypercholesterolemia, hypertension, obesity and current smoker.*

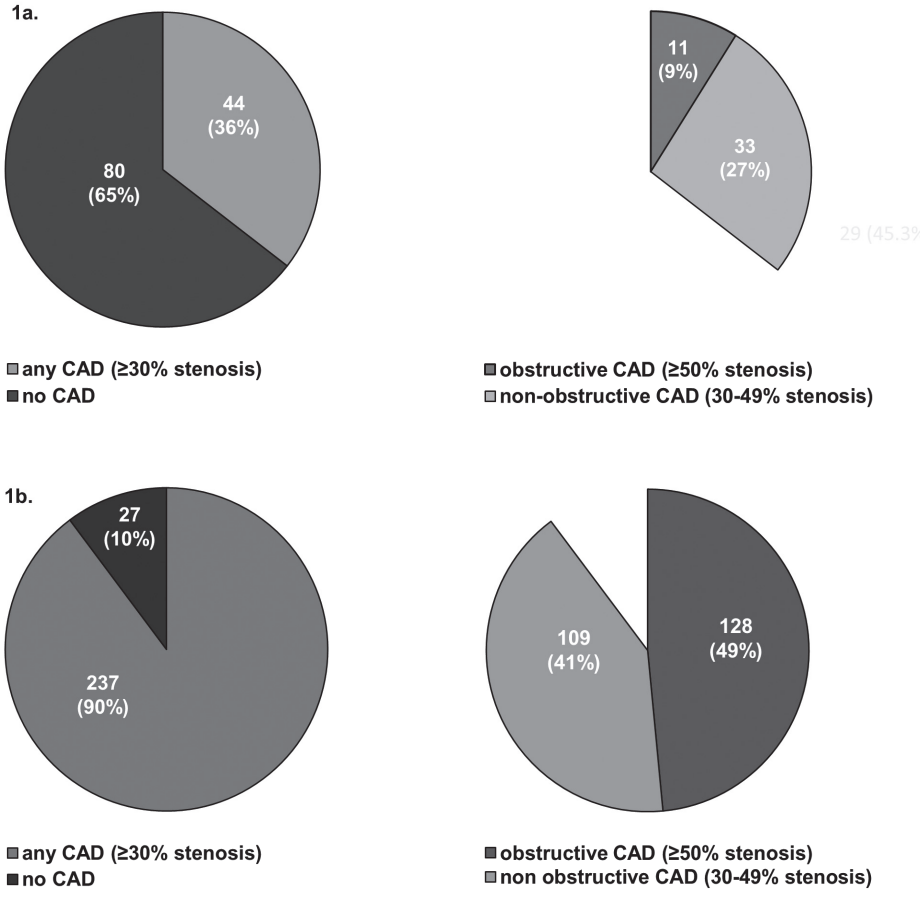
Normally distributed variables were expressed as mean ± SD and nonnormally distributed variables as median and interquartile range. Categorical variables were expressed as frequencies. First, the distribution of any CAD (≥30% stenosis) in patients with a CAC score of 0 and above 0 was assessed. Second, the association between the number of CV risk factors and the presence of any CAD (≥30% stenosis) was evaluated. Patients were stratified into 1, 2, 3, and ≥ 4 traditional CV risk factors. The prevalence of any CAD (≥30% stenosis) in each category was investigated with the Fisher's exact Test. The effect of the number of traditional CV risk factors on the presence of any CAD (≥30% stenosis) was assessed with logistic regression analysis. Third, the association between the several traditional CV risk factors and the presence of any CAD (≥30% stenosis) was investigated. Patients were stratified according to the presence of several traditional CV risk factors: hypertension, hypercholesterolemia, family history of CAD, current smoker and obesity. The prevalence of any CAD (≥30% stenosis) in each CV risk factor was assessed. The association between the several traditional CV risk factors and the presence of any CAD (≥30% stenosis) was assessed with the Fisher's exact Test. Similarly, the analyses were repeated for the presence of obstructive CAD (≥50% stenosis). A two-sided P-value <0.05 was considered statistically significant. All analyses were performed with SPSS software (Version 22.0, IBM Corp., Armonk, New York, USA).

Results

The clinical characteristics of the patients are provided in Table 1; 23 patients (5%) were excluded because of poor coronary CTA quality. The final population consisted of 425 patients at high-risk with DM without chest pain syndrome (mean age 56 ± 11 years, 57% men). Referral for coronary CTA included nonspecific chest pain/symptoms (16%), high-risk profile (81%), abnormal electrocardiogram (2%), and preoperative screening (1%).

A CAC score was performed in 388 patients (91%). The median CAC score was 29 (interquartile range 0-298). As depicted in Figure 1a, a CAC score of 0 was observed in 124 patients(32%). Of these patients, 44 patients (35.5%) had any CAD (≥30% stenosis), of which 11 (9%) had obstructive CAD (≥50% stenosis). In the 264 patients (68%) with a CAC score >0, any CAD (≥30% stenosis) was observed in 237 patients (90%), of which 128 (48.5%) were obstructive CAD (≥50% stenosis; Figure 1b).

Figure 1. *Distribution of any CAD (≥30% stenosis) and obstructive CAD (≥50% stenosis; (1a.) within patients with a CAC score of 0 and (1b.) within patients with a CAC score above 0.*



CAD = coronary artery disease; CV = cardiovascular; no = number.

Coronary CTA results are presented in Table 2; the prevalence of any CAD (≥30% stenosis) was 73%. A coronary artery stenosis of 30 to 49% was observed in 160 (38%) patients and a coronary artery stenosis ≥ 50% in 149 (35%) patients. Importantly, 116 patients (27%) presented with a normal coronary CTA. The mean number of calcified segments was 1 ± 2, the mean number of segments with mixed plaque was 2 ± 2 and on average 1 ± 2 segments had noncalcified plaque.

Table 2. *Coronary artery calcium score and coronary CT angiography*

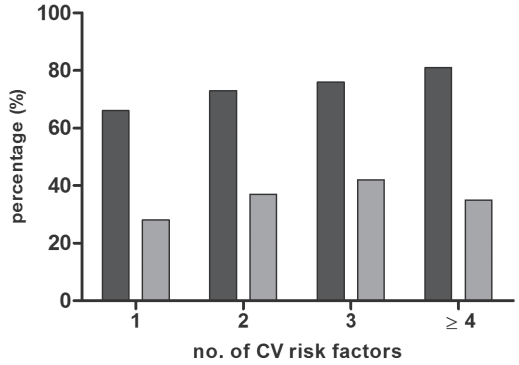
Variable		**Patients**
CAC scoring		*(n=388)*
CAC score, Agatston		29 (0-298)
CAC classification		
	0	124 (32%)
	1-100	118 (31%)
	101-400	63 (16%)
	> 400	83 (21%)
Coronary computed tomography angiography findings		*(n=425)*
Coronary stenosis		
	no stenosis	54 (13%)
	stenosis <30%	62 (14.5%)
	stenosis 30-49%	160 (37.5%)
	stenosis 50%-69	119 (28%)
	Stenosis ≥ 70%	30 (7%)
Coronary plaques composition		
	No. of calcified plaques	1 ± 2 0 (IQR 0-1)
	No. of mixed plaques	2 ± 2 0 (IQR 0-2)
	No. of non-calcified plaques	1 ± 2 0 (IQR 0-1)

CAC = coronary artery calcium, CAD = coronary artery disease; coronary CTA = coronary computed tomography coronary angiography; IQR = interquartile range.

In Figure 2, the distribution of any CAD (defined as ≥30% stenosis) according to the number of traditional CV risk factors is shown. In patients with 1 CV risk factor, the prevalence of any CAD (≥30% stenosis) was 66%. In patients with 2, 3 or ≥ 4 CV risk factors, the prevalence of any CAD (≥30% stenosis) was 73%, 76% and 81%, respectively. Overall, there was no significant association between the number of traditional CV risk factors and the presence of any CAD (≥30% stenosis) (P=0.18; Figure 3a). However, there was a significant trend for increasing numbers of traditional CV risk factors and the presence of any CAD (≥30% stenosis; P-value for trend 0.03).

Within the various traditional CV risk factors the prevalence of any CAD (≥30% stenosis) was 73% in patients with hypercholesterolemia compared to 79%, 71%, 80% and 71% for patients with hypertension, a family history of CAD, current smoker or obesity, respectively (Figure 4). Only hypertension was correlated with a higher frequency of any CAD (≥30% stenosis; OR 2.21 [95% CI 1.43;3.41], P<0.001; Figure 3b).

Figure 2. *Prevalence of any CAD (≥30% stenosis) and obstructive CAD (≥50% stenosis) according to the number of CV risk factors.*

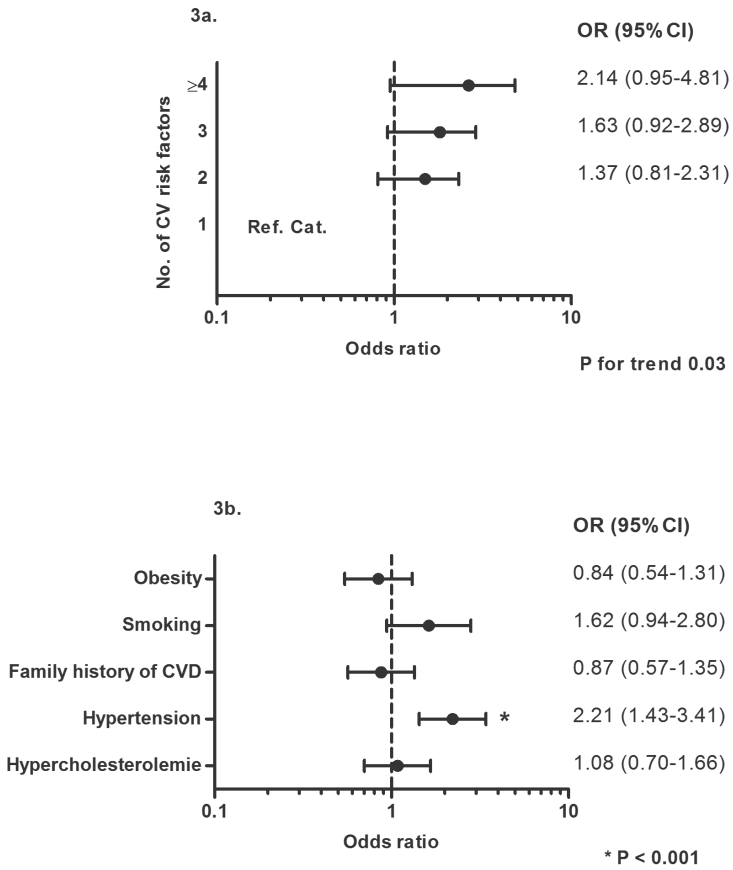


Number of patients	131	137	110	47
Any CAD (≥ 30% stenosis)	87 (66%)	100 (73%)	84 (76%)	38 (81%)
Obstructive CAD (≥ 50% stenosis)	36 (28%)	50 (37%)	46 (42%)	17 (36%)

CI = confidence interval, CV = cardiovascular, CVD = cardiovascular disease; No = number; OR = odds ratio; Ref. Cat. = referential category.

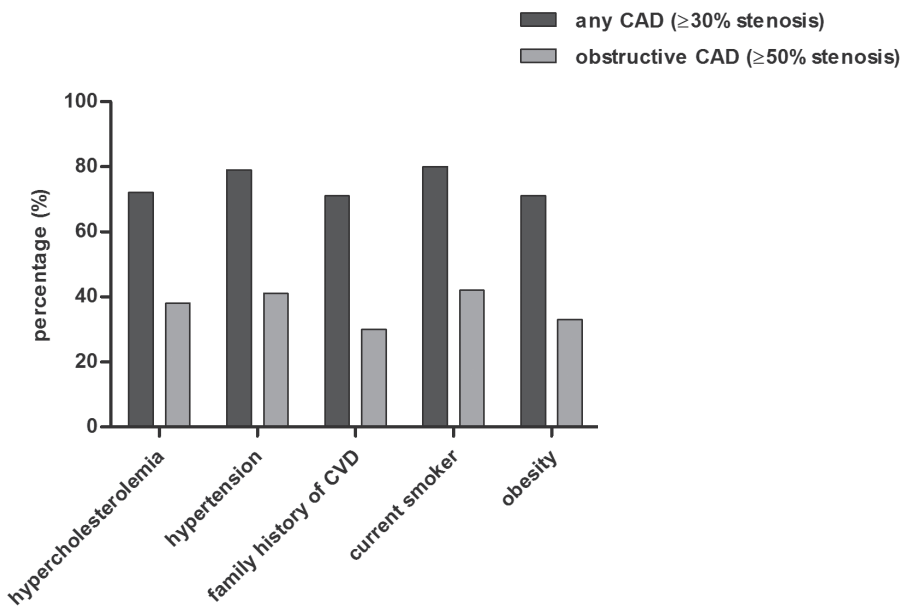
Definitions: as in Table 1.

Figure 3. *Association between the number (3a.) and presence (3b.) of CV risk factors and the presence of any CAD (≥30% stenosis).*



In Figure 2, also the distribution of obstructive CAD (≥50% stenosis) according to the number of traditional CV risk factors is shown. In patients with 1 CV risk factor the prevalence of obstructive CAD (≥50% stenosis) was 27% compared to 36%, 42% and 36% for patients with 2, 3 or ≥ 4 CV risk factors. Overall, there was no significant association between the number of CV risk factors and the presence of obstructive CAD (≥50% stenosis) (P=0.13, P-value for trend 0.06). However, compared to 1 CV risk factor, patients with 3 CV risk factors presented significantly more often with obstructive

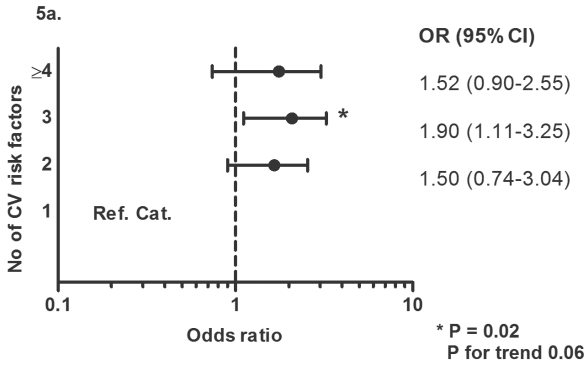
Figure 4. *Prevalence of any CAD (≥30% stenosis) and obstructive CAD (≥50% stenosis) in diabetic patients with a different extra CV risk factor.*

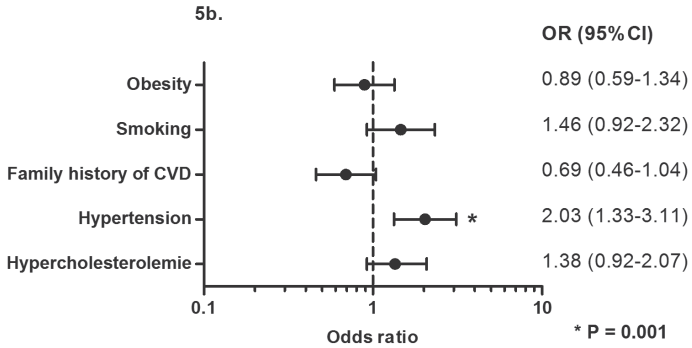


CVD = cardiovascular disease.
Definitions: as in Table 1.

CAD (≥50% stenosis) (OR 1.90 [95% CI 1.11;3.25], P=0.02) (Figure 5a). Within the different traditional CV risk factors the prevalence of obstructive CAD (≥50% stenosis) in patients with diabetes was 38% in patients with hypercholesterolemia compared to 41%, 30%, 42% and 33% for patients with hypertension, a family history of CAD, current smoker and obesity, respectively (Figure 4). Comparable to patients with any CAD (≥30%), only hypertension was correlated with a higher frequency of obstructive CAD (≥50 stenosis) (OR 2.03 [95% CI 1.33;3.11], P=0.001) (Figure 5b).

Figure 5. *Association between the number (5a.) and presence (5b.) of CV risk factors and the presence of obstructive CAD (≥50% stenosis).*





CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; No = number; OR = odds ratio; Ref. Cat. = referential category.

Discussion

This present study assessed the prevalence of CAD on coronary CTA in a large prospective registry of patients at high-risk with DM without chest pain syndrome. On coronary CTA, 27% of these patients at high-risk had no CAD. Of the patients with any CAD (≥30% stenosis), nearly half had obstructive CAD (≥50% stenosis). Moreover, the present study demonstrated that the number and presence of traditional CV risk factors was not associated with a higher frequency of CAD, except for hypertension.

The cardioprotective benefit of aspirin results from its ability to inhibit platelet aggregation and prevent platelet plug formation in atherosclerotic arteries in case of plaque rupture.[16] Inspite the fact that the exact mechanism of aspirin has yet to be fully elucidated, it is accepted that aspirin is only useful if coronary atherosclerosis is present and acts in case of a thrombotic event.[16,17] Contrary to lipid-lowering agents, aspirin has no influence on progression of atherosclerosis or plaque stability.[18]

The increased prevalence of atherosclerosis and thrombosis in patients with DM justifies the need of primary prevention with aspirin therapy. However, the results of several trials aiming at establishing the beneficial effect of aspirin therapy in patients with DM have been controversial.[11,19] Particularly, 2 randomized trials have shown that aspirin was not associated with significant reductions in CV events in patients with DM.[11,19] Conversely, a recent meta-analysis showed a modest-size reduction in MI and stroke in patients with DM treated with aspirin for primary prevention.[12] These results are counterbalanced by a relatively increased risk of gastrointestinal bleeding (1 to 5/1,000 per year) with aspirin use. In a population-based cohort study of 186,425 patients treated with aspirin (of which 29,030 had DM) compared with 186,425 matched controls (of which 27,066 had DM), patients with DM had an increased risk of major bleeding compared to patients without DM.[20] However, in patients with DM, there was no significant difference in risk of bleeding between patients with aspirin and without aspirin use.

Despite the inconclusive results regarding the efficacy and safety of aspirin in patients with DM, current guidelines may recommend aspirin to protect patients with DM from CV events.[1,21,22] The ESC guidelines state that aspirin should be considered in patients at high-risk with DM.[1] However, the definition of patients at low-risk with DM is not entirely clear. The Endocrine Society Clinical Practice Guidelines recommend aspirin in patients with DM aged >40 years and whose 10-year CV disease risk is > 10%.[22] The American

Diabetes Association, American Heart Association and American College of Cardiology Foundation recommend low-dose aspirin in patients with DM with an increased 10-year CV disease risk of 10%, who are not at increased risk for bleeding.[21] In patients with DM with an intermediate CV risk (defined as a 10-year risk score between 5-10%) aspirin can be considered.

The differences between guidelines and conflicting evidence highlight the importance of identifying which patients can be expected to benefit most from primary prevention with aspirin. Importantly, in the aforementioned trials patients were treated with aspirin without previous demonstration of the presence or absence of CAD. It has previously been stated that DM is a CAD-equivalent, and the risk for CV mortality of patients with DM is as high as patients without DM with previous MI or known coronary heart disease (CHD),[23] assuming that all patients with DM have CAD. However, more recent literature questioned this concept.[24] Nevertheless, current guidelines and risk classifications do not include CAD status as assessed by non-invasive testing. As addressed in the present analysis, coronary CTA could be important in identifying which patients will benefit most from primary prevention with aspirin.

The present study demonstrated that 27% of high-risk patients with DM without chest pain syndrome did not have any CAD (≥30% stenosis) on coronary CTA, and aspirin is not needed. Moreover, if obstructive CAD (≥50% stenosis) would have been selected as a cut-off for stratification of patients, in 65% of patients aspirin use could have been avoided. This percentage is consistent with previous studies where the absence of obstructive CAD (≥50% stenosis) in asymptomatic patients with DM varied between 63% and 74%.[13,25] Perhaps the greatest benefit of coronary CTA for tailoring prophylactic aspirin will be reached by using the cut-off value of obstructive CAD (≥50% stenosis) instead of any CAD. Especially since recently a sub-analysis of the Coronary CT Angiography EvaluatioN For Clinical Outcomes (CONFIRM) registry demonstrated in 4,706 patients with nonobstructive CAD (defined as 1%-49%) stenosis that aspirin therapy was not associated with an improvement in all-cause mortality (1.04% versus 1.22%; P=0.473).[26]

As an alternative of coronary CTA, screening patients at high-risk with DM by assessing the CAC score would result in lower radiation exposure and reduced costs. Silverman et al. demonstrated in 2,384 subjects with DM that CAC effectively stratifies across age, gender and risk factor burden: diabetic patients aged below 60 years with a CAC of 0 had a low near-term risk of 0.5 deaths per 1,000 person-years. In contrast, subjects with CAC above 100 had

a mortality rate of more than 10 deaths per 1,000 person-years [27]. However, in the present study 36% of the patients with a CAC of 0 in the present study population had any CAD(≥30% stenosis) and, of these a quarter of the patients had obstructive CAD (≥50% stenosis). This is in line with the results reported by Leem et al. who showed that in 157 asymptomatic patients with type 2 DM with a CAC score of 0, 28% had CAD (≥ 1% stenosis) on angiography, of which 11% were obstructive CAD.[28] Taking into account the results of present study, screening patients according to their CAC score instead of investigating CAD on coronary CTA would result in under-treatment of 9% (with obstructive CAD) to 36% (with any CAD) patients at high-risk with DM who may benefit from aspirin.

Some limitations need to be addressed. First, patients with DM were clinically referred for coronary CTA and may already constitute a higher risk group of patients. Second, the present study focused on the relation between CV risk factors and the presence of CAD, but the duration of DM was not taken into account. In addition, the effects of medical therapy (e.g. statins) on the presence of CAD might have reduced the impact of risk factors on the presence of CAD. Moreover, the age at which screening of patients with DM could be performed with coronary CTA to guide aspirin use remains to be established. Also, it is unclear whether coronary CTA should be repeated, because both CAC score and CAD are progressive over time.[29,30]

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Chapter 3

Long-term Prognosis of Patients with Intramural Course of Coronary Arteries Assessed with Computed Tomography Angiography

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Abstract

Objectives. The aim of the present study was to evaluated, in low-to-intermediate pre-test probability patients who were referred for coronary computed tomography angiography (CTA) and did not show obstructive coronary artery disease (CAD), whether an intramural course of a coronary artery is associated with worse outcome compared with patients without an intramural course of the coronary arteries.

Background. The prognostic value of an intramural course of the coronary arteries on coronary CTA in patients without obstructive CAD is not well-known.

Methods. The study population consisted of 947 patients with a low-to-intermediate pre-test probability who were referred for coronary CTA and who did not have obstructive CAD. During follow-up, the occurrence of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction and all-cause mortality was evaluated.

Results. On coronary CTA, 210 (22%) patients had an intramural course of a coronary artery. The median depth of the intramural course was 1.9 mm (IQR 1.4-2.6 mm). In 84 patients (40%) the depth of the intramural course was considered deep (>2 mm surrounding myocardium). During a median follow-up of 4.9 years (interquartile range (IQR) 3.2-6.9 years) a total of 43 events occurred: hospitalization due to unstable angina pectoris in 13 patients (1.4%), 7 patients (0.7%) had a nonfatal myocardial infarction and 23 patients died (2.4%). The 6-year cumulative event rate of unstable angina pectoris requiring hospitalization (0.0% vs. 1.1%), nonfatal myocardial infarction (0.5% vs. 0.4%), all-cause mortality (1.9% vs. 2.2%) as well as the combined endpoint of all 3 events (2.4% vs. 3.7%) was similar in patients with and without an intramural course of a coronary artery.

Conclusion. In patients without obstructive CAD on coronary CTA, the presence of an intramural course of a coronary artery was not associated with worse outcome.

Introduction

Coronary computed tomography angiography (CTA) is increasingly used to assess or exclude coronary artery disease (CAD) in patients with low-to-intermediate pre-test probability.[1,2] When analysing the coronary arteries for stenosis, variations in coronary anatomy are frequently observed. One of the most common findings on coronary CTA is an intramural course of the epicardial coronary arteries. The intramural course of a coronary artery is defined as any epicardial segment that runs intramurally through the myocardium that completely surrounds the vessel.[3] The reported prevalence of the intramural course of coronary arteries on coronary CTA ranges from 6% to 58%.[4] This large variation may be explained by the use of different imaging techniques and recent improvements in computed tomography (CT) technology that provide high spatial resolution and permit more precise analyses. In addition, the definition of the intramural course of the coronary artery (depth and length) differs among studies.[4]

Although an intramural course of a coronary artery is considered a benign anomaly, small case series have linked the presence of an intramural course of the coronary artery to myocardial infarction[5,6], arrhythmias[7] and sudden cardiac death[8]. However, prognostic data in a large population with an intramural course on coronary CTA are nonexistent. Accordingly, the present study evaluated, in patients with a low-to-intermediate pre-test probability who were referred for coronary CTA and without obstructive CAD, whether an intramural course of a coronary artery was associated with worse outcome compared with patients without an intramural course of the coronary arteries.

Methods

Patients

A total of 1,000 patients (from the Leiden University Medical Centre, the Netherlands and the Turku University Hospital, Turku, Finland) with cardiac complaints and/or an increased cardiovascular risk profile and low-to-intermediate pre-test probability[2] who were clinically referred for coronary CTA were included in the present analysis. Patients with a history of CAD (previous myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery), heart failure, valvular heart disease, arrhythmia or congenital heart disease were excluded. In addition, patients with obstructive

CAD on coronary CTA (defined as any coronary artery stenosis ≥50%), a nondiagnostic coronary CTA study, and patients lost to follow-up were not included in this analysis.

Clinical and coronary CTA data were prospectively entered into the database and analyzed retrospectively. For retrospective analysis of clinically acquired data, the Institutional Review Board of the Leiden University Medical Centre waived the need for written informed consent. Similarly, the Ethics Committee of the Hospital District of Southwest Finland approved the study protocol and waived the need for written informed consent. All clinically acquired data were handled anonymously.

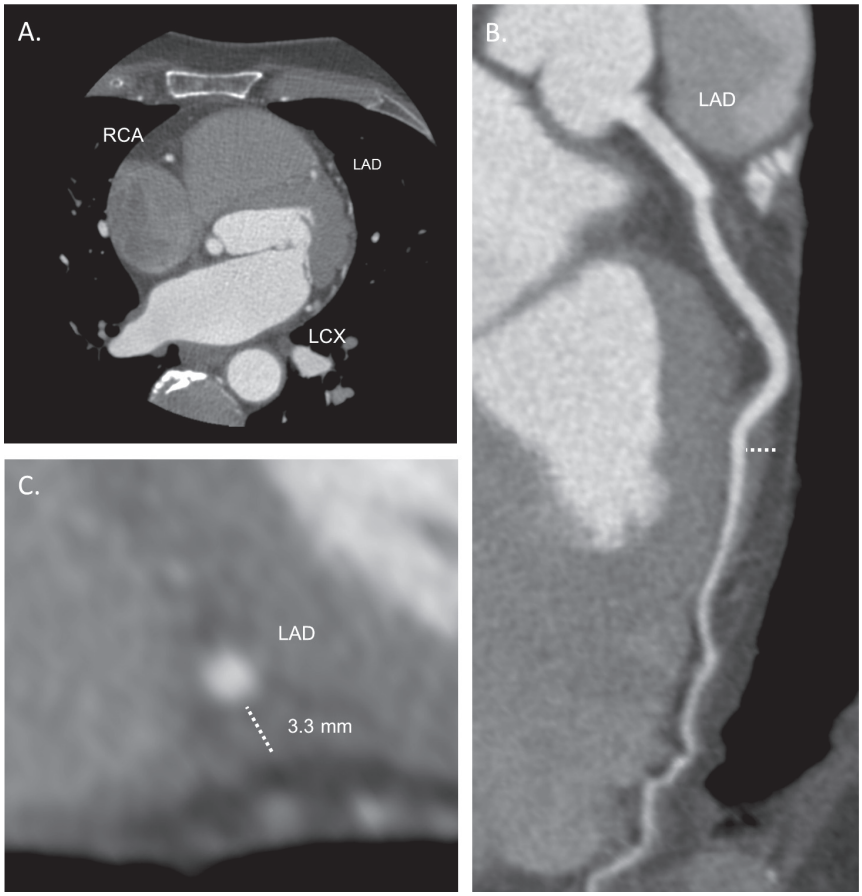
Coronary computed tomography

All coronary CT scans were performed using a 64- or 320-detector row CT scanner (64-slice: Aquillon 64, Toshiba Medical Systems, Otawara, Japan; 320-slice: Aquillon ONE, Toshiba Medical System, Otawara, Japan) in the Netherlands and a 64-detector row scanner (GE Discovery VCT, General Electric Medical Systems, Waukesha, Wisconsin, USA) in Finland. A nonenhanced CT scan (for the assessment of the coronary artery calcium [CAC] score) and a contrast-enhanced CT scan (for noninvasive coronary angiography) were performed. Coronary CTA was performed as previously described.[9,10] For the 64-slice scanner, a collimation of 64 x 0.5 mm, rotation time of 400 ms, and tube voltages and currents (adjusted to the body mass index) of 120 to 135 kV and 250 to 500 mA, respectively, were used. For the 320-slice scanner, a collimation of 320 x 0.5 mm, rotation time of 350 ms, and tube voltages and currents of 100 to 135 kV and 200 to 580 mA, respectively, were used. Advanced iterative reconstruction algorithms were applied. The average contrast dose was 76 ± 14 ml. For the coronary CTA data acquired in Finland, a collimation of 64 x 0.625 mm, a gantry rotation time of 350 ms, tube current between 600 and 750 mA, and voltage between 100 to 120 kV, depending on patient size, were used. The average contrast volume used was 60 to 80 ml.[11] If not contraindicated, beta-blockers were administered orally (25 to 125 mg metoprolol) 1 hour or intravenously (5 to 30 mg metoprolol) a few minutes before the coronary CTA in patients with a heart rate of > 60 beats/min. The mean heart rate at the time of image acquisition was 57 ± 8 beats/min. Sublingual nitroglycerine (0.4 to 0.8 mg) was administered before the coronary CTA acquisition in the absence of contraindications.

Post-processing of the scans was performed with dedicated software (Vitrea FX 1.0, Vital Images, Minnetonka, [in the Netherlands] and General Electric, GE ADW 4.5, Piscataway, New Jersey [in Finland]).

As previously described,[9] the CAC score was calculated according to the algorithm of Agatston.[12] All coronary CTAs were analyzed according to the modified 17-segment American Heart Association classification.[13] Coronary artery segments with a diameter of ≥ 1.5 mm were included for analysis. The severity of coronary stenosis in each segment was stratified into three categories: 1) normal if no plaques were present; 2) non-obstructive CAD if the plaque covered 1-49% of the lumen; and 3) obstructive CAD if the plaque covered ≥ 50%.

Figure 1. *Assessment of Intramural Course of Coronary Artery With Coronary Computed Tomography Angiography.*



Coronary computed tomography angiography images of a patient with an intramural course of the mid LAD coronary artery demonstrated on the axial image (A.), multiplanar reconstructed image (B.), and cross-section image (C.) at the side of the intramural course demonstrating the measurement of the depth (3.3mm). LAD: left anterior descending coronary artery; mm: millimeter; RCA: right coronary artery; LCX: left circumflex coronary artery.

Supplemental table 1. *Comparison of baseline characteristics of the patients excluded for analysis due to lost at follow-up in comparison with the patients included for analysis.*

Variable	Patients excluded N=53	Patients included N=947	P-value
Clinical characteristics			
Age (years)	47±13	53±12	**0.001**
Men (%)	46	44	0.78
Risk factors			
BMI >30 (%)	23	19	0.52
Hypercholesterolemia* (%)	26	35	0.18
Hypertension† (%)	26	40	0.06
Current smoking (%)	17	15	0.70
Family history of CAD (%)	54	48	0.41
Diabetes mellitus (%)	28	27	0.88
Coronary CTA			
Vessel dominance			0.22
Right (%)	75	84	
Left (%)	17	12	
Balanced (%)	8	4	
Intramural course of a coronary artery	23	22	0.94
Coronary artery calcium score (IQR) n=811	0 (IQR 0-11)	0 (IQR 0-12)	0.44
Non-obstructive CAD (%)	64	58	0.41
Coronary plaques (composition)			
No. of calcified lesions	0.2 ± 0.5	0.3 ± 1.0	0.51
No. of mixed lesions	0.8 ± 0.3	0.4 ± 1.1	0.52
No. of non-calcified lesions	0.8 ± 2.3	0.5 ± 1.4	0.37

Definitions and abbreviations as in tabel 1.

Coronary plaques were stratified into 3 groups: calcified (plaque containing ≥ 50% calcification); mixed (plaque containing <50% calcification) and non-calcified (plaque containing no calcification). To evaluate the presence of an intramural course of the coronary artery, multiplanar reconstruction images and cross sectional views of the coronary arteries were created and interpreted (Figure 1). Intramural course was defined as any epicardial artery segment that ran intramurally, surrounded by at least 1 mm of myocardium.[3] The intramural course was classified as superficial when the course was covered with 1 to 2 mm myocardium or as deep when covered with >2 mm myocardium.[14, 15]

Follow-up data

Follow-up data for the Dutch group of patients were obtained from hospital's files review, municipal civil registry and contacting the patients. For the Finnish group of patients, follow-up data were obtained from the national health statistics and patients' electronic medical records. The combined endpoint consisted of time to unstable angina pectoris that required hospitalization, nonfatal myocardial infarction or all-cause mortality. Both, unstable angina pectoris that required hospitalization[13] and nonfatal myocardial infarction[14] were defined according to standard definitions. Coronary CTA data analysis was performed blinded to the clinical follow-up data.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation and as median with 25-75 interquartile range (IQR) if not normally distributed. Categorical variables were presented as frequencies and percentages. Continuous variables were compared between groups with the independent samples t-test (if normally distributed) or with the Mann-Whitney U test (for non-Gaussian variables). Categorical variables were compared between groups using the Chi-Square test. Cumulative event rates for the endpoints of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction and all-cause mortality and the combined endpoint comprising of the first time of all 3 events were estimated with the Kaplan-Meier method and compared among groups using the Log-Rank test. Cox proportional hazard models were used to assess the association between clinical characteristics and coronary CTA results with the combined endpoint of unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction and all-cause mortality. Hazard ratios (HR) and their respective 95% confidence intervals (CI) were reported. Statistical analysis was performed using the SPSS software Version 22.0 (IBM Corp., Armonk, New York, USA). A 2-sided P-value of <0.05 was considered statistically significant.

Table 1. *Baseline characteristics of the patients stratified according to the presence or absence of an intramural course on coronary CTA.*

Variable	All patients N=947	Patients with intramural course N=210	Patients without intramural course N=737	P-value
Clinical characteristics				
Age (years)	53±12	54±11	53±12	0.19
Men (%)	44	40	45	0.21
Risk factors				
BMI >30 (%)	19	11	21	**0.004**
Hypercholesterolemia* (%)	35	36	35	0.74
Hypertension† (%)	40	40	39	0.82
Current smoking (%)	15	16	15	0.62
Family history of CAD (%)	48	52	47	0.21
Diabetes mellitus (%)	27	29	26	0.35
Chest pain	57	53	58	0.37
Typical angina pectoris (%)	11	9	11	0.36
Non-anginal chest pain or atypical angina pectoris (%)	46	44	47	0.41
Early invasive diagnostic tests and treatment	*(<6 months)*			
Coronary angiography (< 6 months) (%)	6.5	5.2	6.9	0.39
Revascularization (< 6 months) (%)	0.8	0.5	0.9	0.51
PCI (%)	0.7	0.5	0.8	0.61
CABG (%)	0.1	0	0.1	0.59
Coronary CTA				
Vessel dominance				0.45
Right (%)	84	87	83	
Left (%)	12	9	12	
Balanced (%)	4	4	5	
Coronary artery calcium score (IQR) n=811	0 (0-12)	0 (0-27)	0 (0-8)	**0.04**
Non-obstructive CAD (%)	58	62	57	0.24
Coronary plaques (composition)				
No. of calcified lesions	0.3±1.0	0.3±0.8	0.3±1.0	0.27
No. of mixed lesions	0.4±1.1	0.5±1.1	0.4±1.1	0.64
No. of non-calcified lesions	0.5±1.4	0.5±1.3	0.5±1.4	0.76

* *Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid lowering drugs,*

† *Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.*

BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; IQR: interquartile range; No: number; PCI: percutaneous coronary intervention.

Table 2. *Distribution of segments on CTA among 210 patients with an intramural course.*

Distribution of segments with an intramural course	N=210
LAD coronary artery	*99 (47)*
Proximal	4 (2)
Mid	56 (27)
Distal	22 (10)
Diagonal branch	17 (8)
LCX coronary artery	*109 (52)*
Intermediate / anterolateral	98 (47)
Proximal or Distal	9 (4)
OM	2 (1)
Right coronary artery	*2 (1)*
Distal	1 (0.5)
RDP	1 (0.5)

Values are N (%). LAD: left anterior descending; OM: obtuse marginal branches; LCX: left circumflex; RDP: right descending posterior.

Table 3. *Events stratified to the presence of an intramural course on coronary CTA.*

Events	Total N=947	Intramural course N=210	No intramural course N=737	P-value
Follow-up period in years	4.9 (3.2;6.9)	4.6 (3.2;6.6)	5.0 (3.3;7.0)	0.15
Unstable angina pectoris requiring hospitalization	13 (1.4)	2 (1)	11 (1.5)	0.64
Nonfatal myocardial infarction	7 (0.7)	2 (1.0)	5 (0.7)	0.57
All-cause mortality	23 (2.4)	4 (1.9)	19 (2.6)	0.69
Combined endpoint*	43 (4.5)	8 (3.8)	35 (4.7)	0.73

Values are median (IQR) or N (%).

* *Including unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction or all-cause mortality.*

Results

Patients

Of the 1,000 patients initially included, 53 patients (5%) were lost to follow-up and excluded from the analysis. All baseline characteristics of the patients excluded for analysis were similar to the patients included in the present analysis, except for age which was lower in the exclusion group (47±13 years versus 53±12 years, P=0.001) as demonstrated in supplemental Table 1. The clinical characteristics of the remaining 947 patients without obstructive CAD on coronary CTA (56% women, mean age 53±12 years) are presented in Table 1.

Coronary computed tomography

CAC score analysis was feasible in 811 (86%) patients. The median CAC score was 0 (IQR: 0 to 12). Most of the patients (63%) had a CAC score of 0, and 74 patients (9%) had a CAC score >100. The results of the coronary CTA are presented in Table 1. Non-obstructive CAD was observed in 553 (58%) patients whereas the remaining patients (42%) had no coronary artery stenosis. The mean number of calcified segments and segments with mixed plaque were 0.3 ± 1.0 and 0.4 ± 1.1, respectively, and, on average, 0.5 ± 1.4 segments had noncalcified plaque.

Presence of an intramural course

On coronary CTA, 210 (22%) patients had an intramural course of a coronary artery. The median depth of the intramural course was 1.9 mm (IQR: 1.4 to 2.6 mm). In 84 (40%) patients the depth of the intramural course was considered deep (>2 mm surrounding myocardium).

Table 2 describes the segmental location of the intramural course. The most frequent segments that shows an intramural course were the mid / distal left anterior descending (LAD) coronary artery (37%) and the intermediate / anterolateral coronary artery (47%).

Table 1 shows the differences in clinical characteristics between patients with versus without an intramural course of the coronary artery. Patients without an intramural course of the coronary artery were more frequently obese in comparison with patients with an intramural course of the coronary artery (21% versus 11%, respectively; P=0.004). On coronary CT scan, the median CAC score was significantly higher in patients with an intramural course compared with patients without an intramural course (0; IQR: 0 to 27 versus 0; IQR: 0

to 8, respectively; P=0.04). There were no differences in the presence of non-obstructive CAD or the number of calcified / mixed and non-calcified plaques between both groups.

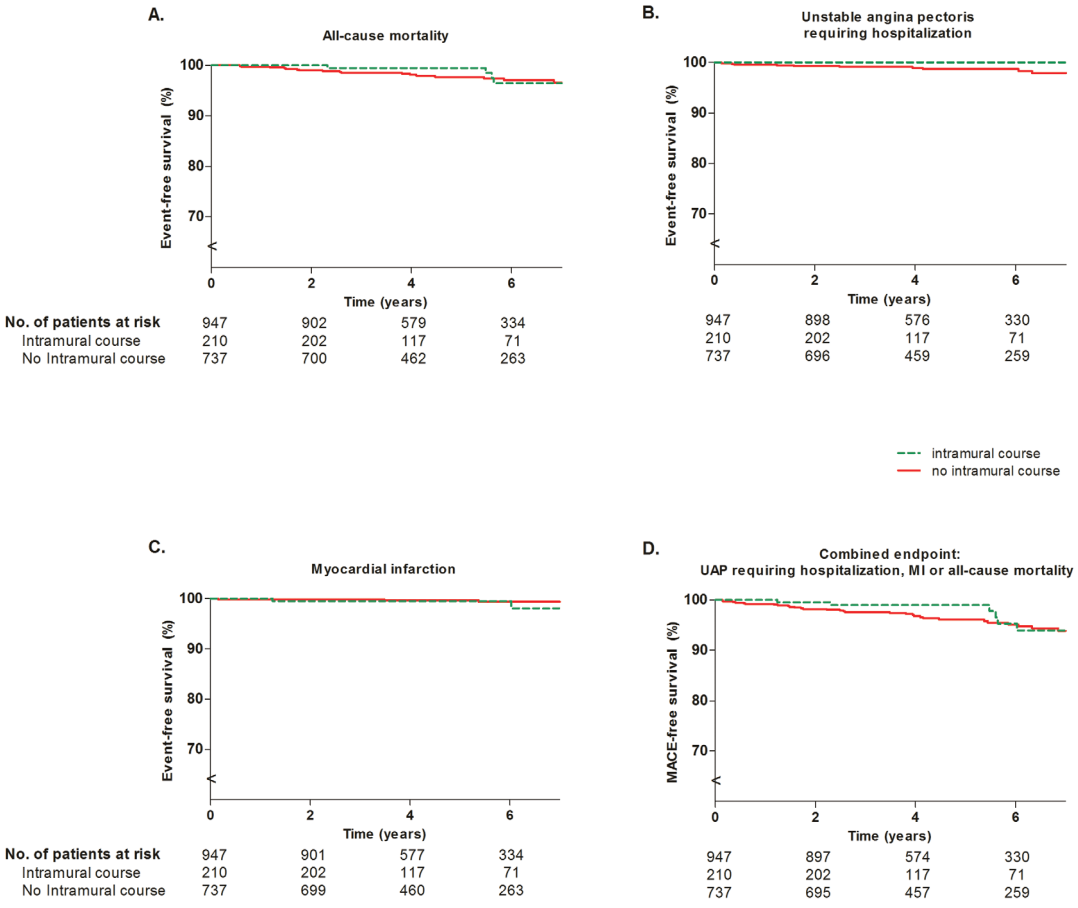
Patient outcome

As shown in Table 3, the median follow-up was 4.9 years (IQR: 3.2 to 6.9 years) and was similar in patients with and without an intramural course on coronary CTA (4.6; IQR: 3.2 to 6.6 versus 5.0; IQR: 3.3 to 7.0 years respectively, P=0.15). During follow-up, 43 events occurred; hospitalization due to unstable angina pectoris in 13 patients (1.4%), 7 patients (0.7%) had a nonfatal myocardial infarction and 23 patients died (2.4%). No patient experienced > 1 event. As shown in Figure 2A-2C, unstable angina pectoris that required hospitalization, nonfatal myocardial infarction and all-cause mortality occurred similarly in patients with and patients without an intramural course of a coronary artery. At 6-year follow-up, the cumulative event rates for unstable angina pectoris that required hospitalization were 0.0% versus 1.1%; for nonfatal myocardial infarction 0.5% versus 0.4%; and for all-cause mortality 1.9% versus 2.2%.

The Kaplan-Meier event-free survival for the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality stratified according to the presence of an intramural course of a coronary artery is shown in Figure 2D. Patients with an intramural course of the coronary artery had similar 6-year cumulative event rates of the combined endpoint compared with patients without an intramural course (the cumulative event rates were 2.4% vs. 3.7%, respectively; Log Rank P=0.73).

Associates for the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction and all-cause mortality are presented in Table 4. The intramural course of coronary arteries was not significantly associated with the combined endpoint (HR 0.87; 95%CI 0.40 to 1.88, P=0.73). In contrast, age, CAC score and the number of calcified and mixed plaques were associated with the combined endpoint of unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction and all-cause mortality during long-term follow-up.

Figure 2. *Kaplan-Meier Event-Free Survival Curves for Patients With and Without Intramural Course of the Coronary Artery.*



Kaplan-Meier curves for the endpoint (A.) all-cause mortality, (B.) unstable angina pectoris requiring hospitalization, (C.) nonfatal myocardial infarction and (D.) the combined endpoint.
MI: myocardial infarction; No.: number; UAP: unstable angina pectoris.

Table 4. *The association of clinical and coronary CTA characteristics with the combined endpoint: unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction or all-cause mortality.*

Variable	Event*	No event*	Univariate analysis		
	N=43	N=904	HR	95% CI	P-value
Clinical characteristics					
Age (years)	60±12	53±12	1.06	1.03-1.09	**<0.001**
Women (%)	54	56	1.04	0.57-1.90	0.90
Risk factors					
BMI >30 (%)	24	18	1.54	0.75-3.13	0.24
Hypercholesterolemia†(%)	24	36	0.61	0.3-1.24	0.17
Hypertension‡ (%)	44	39	1.07	0.58-1.98	0.83
Current smoking (%)	14	15	0.88	0.37-2.07	0.76
Family history of CAD (%)	37	49	0.61	0.33-1.13	0.11
Diabetes mellitus (%)	24	27	0.88	0.43-1.79	0.72
Coronary CTA					
Calcium score (IQR) (n=811)	8 (0-247)	0 (0-11)	1.002	1.001-1.002	**<0.001**
Non-obstructive CAD (%)	70	58	1.57	0.82-3.00	0.18
Intramural course of the coronary arteries (%)	19	22	0.87	0.40-1.88	0.73
Coronary plaques (composition)					
No. of calcified lesions	0.98±1.68	0.26±0.90	1.34	1.16-1.56	**<0.001**
No. of mixed lesions	1.07±1.97	0.39±1.05	1.26	1.09-1.45	**0.002**
No of non-calcified lesions	0.42±0.76	0.49±1.40	0.95	0.72-1.24	0.69

* *Including unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction or all-cause mortality.*

† *Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid lowering drugs.*

‡ *Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.*

BMI: body mass index; CAD: coronary artery disease; IQR: interquartile range.

Discussion

The present study evaluated, in a large cohort of patients without obstructive CAD, the prognostic implications of an intramural course of a coronary artery assessed on coronary CTA. An intramural course of a coronary artery was observed in 22% of patients. Patients with and without an intramural course of the coronary artery had similar low cumulative event rates for the combined endpoint of nonfatal myocardial infarction, unstable angina pectoris that required hospitalization or all-cause mortality during long-term follow-up.

Presence of intramural course of a coronary artery

Intramural course of the coronary artery was for the first time described on invasive coronary angiography by Porstmann et al. in 1960.[18] Coronary CTA is a more sensitive imaging tool than invasive coronary angiography to characterizes the course of the coronary arteries, and, accordingly, studies have reported a prevalence of intramural course of coronary arteries on coronary CTA that is more than twice as high as observed on invasive angiography (0.5 to 11.8%).[19, 20] Among 100 patients who underwent coronary CTA and invasive angiography, Leschka et al. observed an intramural course of the coronary artery in 26 patients on coronary CTA compared with only 12 patients on invasive angiography.[21] The lower prevalence of an intramural course on invasive angiography compared with coronary CTA can be partially explained by the fact that these 2 techniques detect different phenomena. Coronary CTA visualizes the anatomical relationship of the coronary artery to the surrounding myocardium. Conversely, invasive angiography can only detect systolic compression of the artery, which can be the consequence of an intramural course (also referred to as myocardial bridging[22]), but occurs only in a minority of patients with intramural course of the coronary artery. Uusitalo et al. demonstrated that only approximately one-third of the patients with an intramural course on coronary CTA showed systolic compression during invasive coronary angiography.[11]

The prevalence of an intramural course of a coronary artery on coronary CTA in the current study was 22%. This is in accordance with studies using 64-slice and 128-slice CT scanners, who have reported prevalences of 26% and 21%, respectively.[23, 24] Similarly to the present study, the LAD coronary artery is the coronary artery more frequently showing an intramural course, regardless of the methodology used.[15, 21] In addition, the present study also demonstrated that the intermediate / anterolateral coronary artery was frequently involved.

Intramural course of the coronary artery and long-term outcome

Some case reports have suggested that the presence of an intramural course of a coronary artery is associated with sudden cardiac death.[7, 23] The present study revealed similar survival rates for both groups during long-term follow-up. In addition, the occurence of the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, or all-cause mortality during long-term follow-up was similar in patients with and without an intramural course of a coronary artery. Rubinshtein et al. demonstrated in 334 patients that the presence of an intramural course of a coronary artery assessed with coronary CTA did not have a prognostic impact for the composite endpoint cardiovascular death or nonfatal myocardial infarction.[26] In their study, during a mean follow-up duration of 6 years, there was no significant difference in cumulative event rates between both groups (5.1% in patients with versus 3.2% in patients without an intramural course of a coronary artery; P=0.40). The reason that the frequently present intramural course of the coronary artery on coronary CTA was not associated with adverse events was probably because an intramural course only in the minority of the cases is associated with systolic compression ("bridging").[11]

Study limitations

The present study visualized the anatomical relationship of the coronary artery to the surrounding myocardium, and therefore, cyclic changes in coronary artery flow nor dynamic compression could be evaluated. Because the study was retrospective, no assessment of the required sample size was performed.

Conclusion

In patients without obstructive CAD on coronary CTA, an intramural course of a coronary artery is not associated with worse outcome.

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PART II

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION


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Chapter 4

Prognosis of Complete versus Incomplete Revascularisation of STEMI Patients with Multivessel Coronary Artery Disease: an Observational Study

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Abstract

Objectives. The best strategy in patients with acute ST-segment elevation myocardial infarction (STEMI) with multivessel coronary artery disease (CAD) regarding completeness of revascularisation of the non-culprit lesion(s) is still unclear. To establish which strategy should be followed, survival rates over a longer period should be evaluated. The aim of this study was to investigate whether complete revascularisation, compared with incomplete revascularisation, is associated with reduced short-term and long-term all-cause mortality in patients with first STEMI and multivessel CAD.

Methods. This retrospective study consisted of 518 patients with first STEMI with multivessel CAD. Complete revascularisation (45%) was defined as the treatment of any significant coronary artery stenosis (≥70% luminal narrowing) during primary or staged percutaneous coronary intervention (PCI) prior to discharge. The primary end point was all-cause mortality.

Results. Incomplete revascularisation was not independently associated with 30-day all-cause mortality in patients with acute first STEMI and multivessel CAD (OR 1.98; 95% CI 0.62-6.37; P=0.25). During a median long-term follow-up of 6.7 years, patients with STEMI with multivessel CAD and incomplete revascularisation showed higher mortality rates compared with patients who received complete revascularisation (24% versus 12%, P<0.001), and these differences remained after excluding the first 30 days. However, in multivariate analysis, incomplete revascularisation was not independently associated with increased all-cause mortality during long-term follow-up in the group of patients with STEMI who survived the first 30 days post-STEMI (HR 1.53 95%CI 0.89-2.61, P=0.12).

Conclusion. In patients with an acute first STEMI and multivessel CAD, incomplete revascularisation compared with complete revascularisation was not independently associated with increased short-term and long-term all-cause mortality.

Introduction

Primary percutaneous coronary intervention (PCI) of the culprit vessel in patients with ST-segment elevation myocardial infarction (STEMI) is a standard clinical practice.[1] However, in patients with STEMI and multivessel coronary artery disease (CAD), the best revascularisation strategy (complete versus incomplete revascularisation) remains debated. While primary PCI of the infarct-related artery (IRA) should be performed systematically, immediate revascularisation of the non-culprit vessel(s) is/are only recommended in patients with cardiogenic shock or persisting large areas of ischemia.[2] Recent landmark randomised trials such as the CvLPRIT (Complete versus Lesion-only Primary PCI trial), DANAMI-3-PRIMULTI (The Third Danish Study of Optimal Acute treatment of Patients with STEMI: Primary PCI in Multivessel disease) and the PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) trials demonstrated reduced risk of adverse cardiovascular events in patients undergoing immediate complete revascularisation compared with patients with incomplete revascularisation.[3-5] In contrast, large observational studies did not show differences in adverse cardiovascular event rates between the two revascularisation strategies.[6-8] Furthermore, the effect of complete versus incomplete revascularisation on clinical outcomes has not been evaluated at long-term follow-up (> 5 years).[9, 10]

Therefore, the aim of the current retrospective, observational study was to investigate whether incomplete revascularisation, compared with complete revascularisation, is associated with increased short-term and long-term all-cause mortality in patients with acute first STEMI and multivessel CAD.

Methods

Patients

The analysis concerns a retrospective analysis of patients who presented with a first acute STEMI and multivessel CAD at the Leiden University Medical Center (The Netherlands) between 2004 and 2008. The inclusion criteria were: 1) diagnosis of first acute STEMI that was defined as typical chest pain complaints <12 hours, elevated cardiac enzyme levels and significant ST-segment elevation or left bundle branch block on the ECG; 2) multivessel CAD on emergency coronary angiography (CAG); and 3) no history of CAD as defined by previous myocardial infarction, PCI or coronary artery bypass graft. All patients were treated according to the MISSION! protocol as

described earlier[11], which was based on the most recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for patients with acute myocardial infarction at that moment. The interventional cardiologist determined whether immediate or staged revascularisation of the non-culprit vessel(s) occurred. Patients with 1) emergent or staged revascularisation with coronary artery bypass graft surgery before discharge and 2) incomplete or uninterpretable CAG images were excluded. The primary endpoint was all-cause mortality. Mortality data were obtained from hospital's files review or municipal civil registries. Demographic, clinical and angiographic data were prospectively entered in the departmental Cardiology Information System (EPD-Vision©, Leiden University Medical Center, the Netherlands) and analysed retrospectively. The Institutional Review Board of the Leiden University Medical Centre approved the retrospective, observational study and waived the need for written informed consent for retrospective analysis of clinically acquired data.

Primary percutaneous coronary intervention and angiographic data analysis

CAG data were acquired from standardized angiographic projections according to the guidelines of the American College of Cardiology/American Heart Association and were stored digitally.[12] CAG data were reviewed retrospectively by two experienced observers. During image analysis the following information was reported: (in)complete revascularisation, coronary vessel dominance, culprit vessel, severity of CAD and the results of primary PCI. IRA was determined by the evaluation of acute electrocardiographic changes on the ECG at admission.[13] Complete revascularisation was defined as PCI of any significant coronary artery stenosis (≥70% luminal narrowing) of any vessel during the primary or staged PCI prior to discharge.

Statistical analysis

Normally distributed variables were expressed as mean ± SD and non-normally distributed variables as median and IQR. Categorical variables were presented as frequencies and percentages. Differences in baseline characteristics between patients with complete revascularisation and patients with incomplete revascularisation were evaluated with the independent samples t-test, the Mann-Whitney U test or the Chi-Square test when appropriate. Survival analyses were performed using Kaplan-Meier analysis. Cumulative event rates for the end point of all-cause mortality were compared between patients with complete revascularisation and patients with incomplete revascularisation,

using the Log-Rank test. The influence of differences in baseline characteristics on 30-day mortality post-STEMI was assessed by performing univariate and multivariate logistic regression analysis. To avoid any overfitting of the model, only a selection of variables with significant P-values (<0.05) at univariate analysis were entered in the multivariate model: age, three-vessel CAD, culprit vessel left main, Killip class≥2 and incomplete revascularisation. The results of the multivariate analysis were reported as adjusted odds ratios (OR) with 95% confidence interval (CI). The independent associates of all-cause mortality at long-term follow-up were investigated using univariate and multivariate Cox regression analysis for those patients who survived the first 30 days. Only variables with significant P-values (<0.05) at univariate analysis were included in the multivariate model: age, diabetes mellitus, family history of CAD, three-vessel CAD, renal dysfunction (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2), culprit vessel left main and incomplete revascularisation. The results of the multivariate Cox regression analysis were reported as hazard ratio (HR) and their respective 95% CI. Statistical analysis was performed using SPSS software (Version 22.0, SPSS IBM Corp., Armonk, New York, USA). A two-sided P-value of <0.05 was considered statistically significant.

Results

Patients

Of 1,133 patients with acute first STEMI, 542 had multivessel CAD on CAG. Additionally, 24 patients (4%) were excluded because of revascularisation with coronary artery bypass graft surgery before discharge (n=8) or incomplete or uninterpretable CAG data (n=16). The clinical baseline characteristics of the remaining 518 patients are shown in Table 1. The majority of patients were male (76%), with a mean age of 63±12 years and in one third of the patients emergent CAG showed three-vessel CAD. At presentation, 36 patients (7%) were in Killip class≥2. Complete revascularisation was performed in 231 patients (45%): in 197 patients (85%) during primary PCI and in 34 patients (15%) during staged revascularisation before discharge. Differences in baseline characteristics between patients with incomplete and complete revascularisation are presented in Table 1. Patients who received complete revascularisation before discharge were younger, presented less often with Killip class≥2, had the left anterior descending coronary artery less often as culprit vessel, had more often two-vessel CAD and had more often preserved renal function as compared with patients who received incomplete revascularisation.

Table 1. *Patient characteristics and angiographic data.*

	Total N=518	Incomplete revascularisation‡ N=287	Complete revascularisation‡ N=231	P-value
Gender (male)	76%	74%	78%	0.24
Age (years)	63 ± 12	64 ± 13	62 ± 12	**0.02**
Obesity (BMI ≥ 30kg/m^2)	16%	17%	15%	0.41
Diabetes	12%	14%	10%	0.15
Hypercholesterolemia*	17%	19%	15%	0.30
Hypertension†	37%	40%	34%	0.17
Current smoker	44%	43%	45%	0.58
Family history of CAD	38%	38%	38%	0.90
Presenting in Killip class ≥ 2	7%	10%	4%	**0.006**
Culprit vessel				
Left main	1%	1%	2%	0.50
RCA	42%	39%	45%	0.20
LAD	41%	46%	35%	**0.02**
LCx	16%	14%	18%	0.19
Three-vessel CAD	33%	42%	22%	**<0.001**
eGFR ≤ 60 mL/min/1.73m²	13%	15%	9%	**0.04**
Troponin T level	4.57 (IQR 1.77-8.93)	4.91 (IQR 1.86-9.22)	4.40 (IQR 1.58-8.60)	0.28
Peak cardiac troponin T level ≥3.5 µg/L	59%	61%	56%	0.18
LV ejection fraction	47±10	46±10	47±10	0.07
LV ejection fraction ≤40%	28%	31%	25%	0.13
Blood pressure at discharge				
Systolic	116 ± 17	115 ± 16	118 ± 18	0.10
Diastolic	70 ± 11	69 ± 10	71 ± 12	0.12
Medication at discharge				
Beta-blocker	93%	92%	94%	0.36
Aspirin	96%	96%	97%	0.75
Clopidogrel	99%	99%	99%	0.80
ACE-inhibitor/ ARB	96%	96%	97%	0.55
Statin	98%	98%	98%	0.71

* *Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid lowering drugs.*

† *Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.*

‡ *Complete revascularisation was defined as treating all present significant coronary artery stenosis ≥ 70% during primary PCI or before discharge.*

ACE-inhibitor: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers; BMI: body mass index; CAD: coronary artery disease; eGFR: glomerular filtration rate estimated using the Cockroft-Gault formula; IQR: interquartile range; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LV: left ventricle; RCA: right coronary artery; STEMI: ST segment elevation myocardial infarction.

Table 2. *Differences in baseline characteristics between patients who died within the first 30 days post-STEMI and those who survived.*

	Deceased within the first 30 days post-STEMI N=31	Survived the first 30 days post-STEMI N=487	P-value
Gender (male)	55%	77%	**0.005**
Age (years)	74 ± 12	62 ± 12	**<0.001**
Obesity (BMI ≥ 30kg/m^2)	29%	16%	0.13
Diabetes	10%	12%	0.8
Hypercholesterolemia*	14%	17%	0.63
Hypertension†	31%	37%	0.49
Current smoker	32%	45%	0.20
Family history of CAD	11%	40%	**0.003**
Presenting in Killip class ≥ 2	61%	4%	**<0.001**
Culprit vessel			
Left main	16%	0.4%	**<0.001**
RCA	29%	43%	0.13
LAD	42%	41%	0.91
LCx	13%	16%	0.65
Three-vessel CAD	55%	32%	**0.008**
Incomplete revascularisation‡	77%	54%	**0.01**
eGFR ≤ 60 mL/min/1.73m^2	48%	11%	**<0.001**
Peak cardiac troponin T level ≥3.5 µg/L	83%	58%	**0.01**
LV ejection fraction ≤40%	70%	27%	**<0.001**

For definitions and abbreviations: see Table 1.

30-day mortality

In the first 30 days post-STEMI, 31 patients (6%) died (28 during index hospitalisation). The cause of death was cardiac in 27 patients (87%), terminal postanoxic encephalopathy in 1 patient (3%) and unknown reason in 3 patients (10%). The cardiac causes of death were cardiogenic shock (17 patients, 63%), ventricular fibrillation (1 patient, 4%), left ventricular free wall rupture (1 patient, 4%), terminal heart failure (6 patients, 22%) and reinfarction due to intrastent thrombosis (2 patients, 7%). Table 2 shows the differences in baseline characteristics between the deceased patients and those who survived the first 30 days post-STEMI. The variables (independently) associated with the endpoint 30-day mortality are shown in Table 3. In the multivariate analysis age, Killip class≥2 and left main coronary artery as the culprit vessel were independently associated with increased 30-day mortality post-STEMI. However, incomplete revascularisation was not independently associated with increased 30-day mortality post-STEMI (OR 1.98 [95%CI 0.62-6.37], P=0.25).

Long-term follow-up

Long-term follow-up was complete in all patients with a median follow-up of 6.7 years (IQR 5.6-7.9 years). Ninety-eight patients died, 67 of them (68%) died after 30 days post-STEMI. The Kaplan-Meier survival curves stratified according to complete versus incomplete revascularisation are presented in Figure 1. Patients with STEMI with multivessel CAD and incomplete revascularisation showed higher mortality rates compared with patients who received complete revascularisation (24% versus 12%, P<0.001).

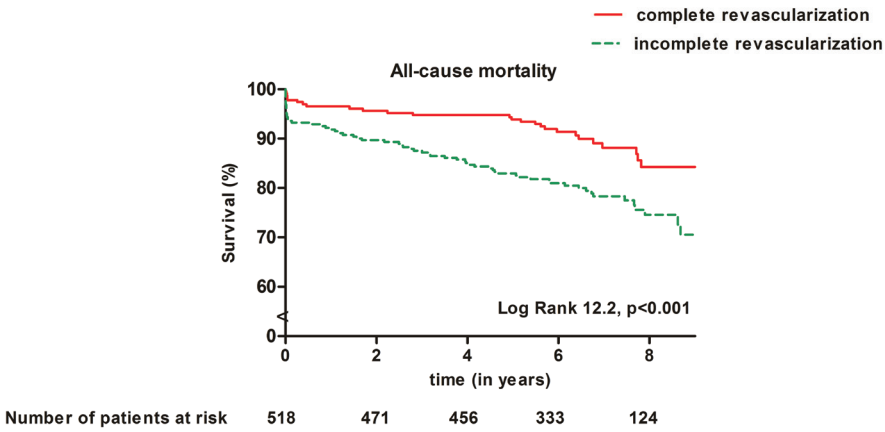
The cumulative mortality rates at 1, 2 and 5 years of follow-up were significantly higher for patients who were treated with incomplete revascularisation compared with patients who underwent complete revascularisation (9.8%,12.2% and 18.8% versus 4.3%, 5.2% and 6.9% respectively, P=0.02, P=0.006 and P<0.001 respectively). After excluding the patients who died within the first 30 days from the analysis, incomplete revascularisation was associated with worse long-term survival compared with complete revascularisation (P=0.012; Figure 2). However, multivariate Cox regression analysis showed that incomplete revascularisation was not independently associated with increased all-cause mortality (Table 4). Age and left main coronary artery as the culprit vessel were independently associated with the endpoint of all-cause mortality. After excluding patients presenting in cardiogenic shock (Killip class 4) on the day of admission (n=7), incomplete revascularisation was not independently associated with increased all-cause mortality (HR 1.56 [95%CI 0.91-2.69], P=0.11, supplemental Table 1).

Table 3. *Influence of baseline characteristics on 30-day mortality post-STEMI*

	Univariate			Multivariate		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Gender (male)	0.36	0.17-0.75	**0.006**			
Age (years)	1.09	1.05-1.13	**<0.001**	1.10	1.05-1.15	**<0.001**
Diabetes	0.85	0.25-2.91	0.80			
Hypercholesterolemia*	0.77	0.26-2.26	0.63			
Hypertension†	0.75	0.34-1.69	0.49			
Current smoker	0.59	0.26-1.33	0.20			
Family history of CAD	0.19	0.06-0.64	0.007			
Presenting in Killip class ≥2	38.42	16.32-90.43	**<0.001**	29.00	10.78-77.99	**<0.001**
Culprit vessel						
Left main	46.64	8.63-251.88	**<0.001**	48.16	4.43-523.47	**0.001**
RCA	0.55	0.25-1.12	0.14			
LAD	1.05	0.50-2.18	0.91			
LCx	0.78	0.26-2.28	0.65			
Three-vessel CAD	2.63	1.26-5.46	**0.01**	0.90	0.33-2.44	0.84
Incomplete revascularisation‡	2.92	1.24-6.91	**0.02**	1.98	0.62-6.37	0.25
eGFR ≤ 60 mL/min/1.73m^2	7.31	2.96-18.02	**<0.001**			
Peak cardiac troponin T level ≥3.5 µg/L	3.69	1.24-10.95	**0.02**			
LV ejection fraction ≤40%	6.43	2.42-17.11	**<0.001**			

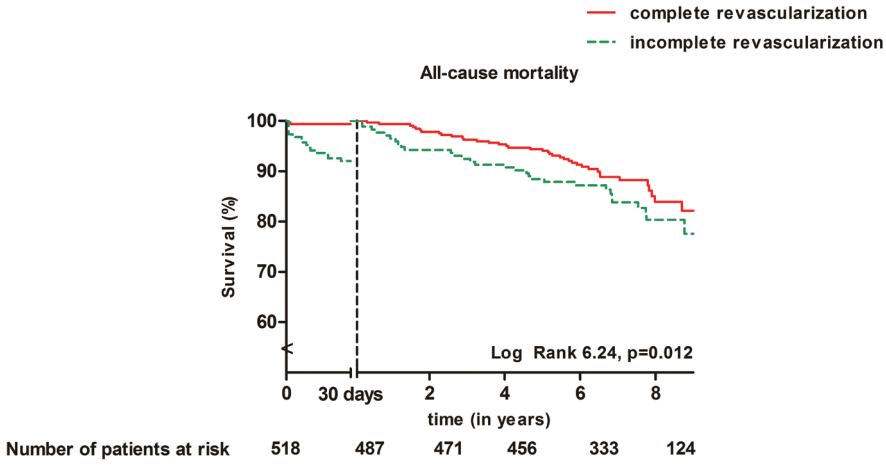
For definitions: see Table 1.

Figure 1. *Kaplan-Meier curves for the endpoint all-cause mortality in the total patient population stratified according to complete / incomplete revascularisation.*



Patients with incomplete revascularisation had a statistically significant higher cumulative incidence of all-cause mortality (P [Log Rank] < 0.001) during long-term follow-up after STEMI in comparison with patients with complete revascularisation.

Figure 2. *Kaplan-Meier curve for all-cause mortality in the subgroup of survivors of the first 30 days after STEMI stratified according to complete / incomplete revascularisation*



The survivors of the first 30 days post-STEMI with incomplete revascularisation compared with patients with complete revascularisation had a statistically significant higher cumulative incidence of all-cause mortality (P [Log Rank]=0.012) during long-term follow-up after STEMI.

Table 4. *Cox regression analysis for all-cause mortality during long-term follow-up in the group of STEMI patients who survived the first 30 days post-STEMI.*

	Univariate			Multivariate		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Gender (male)	0.99	0.56-1.73	0.96			
Age (years)	1.07	1.04-1.09	**<0.001**	1.05	1.03-1.08	**<0.001**
Diabetes	2.28	1.27-4.12	**0.006**	1.82	0.99-3.34	0.054
Hypercholesterolemia*	0.46	0.20-1.06	0.07			
Hypertension†	1.20	0.74-1.96	0.46			
Current smoker	0.91	0.56-1.48	0.71			
Family history of CAD	0.57	0.33-0.97	**0.04**	0.75	0.43-1.32	0.32
Presenting in Killip class ≥ 2	1.47	0.53-4.05	0.46			
Culprit vessel						
Left main	9.49	2.31-38.94	**0.002**	8.40	1.89-37.39	**0.005**
RCA	0.86	0.52-1.40	0.54			
LAD	1.24	0.77-2.00	0.39			
LCx	0.71	0.34-1.48	0.35			
Three-vessel CAD	1.95	1.21-3.16	**0.006**	1.34	0.80-2.23	0.26
eGFR ≤ 60 mL/min/1.73m^2	2.50	1.40-4.44	**0.002**	0.93	0.48-1.80	0.83
Peak cardiac troponin T level ≥3.5 µg/L	1.31	0.79-2.17	0.30			
LV ejection fraction ≤40%	1.43	0.85-2.41	0.18			
Medication at discharge						
Beta-blocker	0.75	0.30-1.87	0.54			
Aspirin	0.50	0.18-1.37	0.18			
Clopidogrel	20.28	0.00-4,6·10^7	0.69			
ACE-inhibitor / ARB	0.76	0.24-2.42	0.64			
Statin	0.81	0.11-5.86	0.84			
Incomplete revascularisation‡	1.91	1.14-3.20	**0.01**	1.53	0.89-2.61	0.12

For definitions and abbreviations: see Table 1.

Supplemental table 1. *Cox regression analysis for all-cause mortality during long-term follow-up in the subgroup of patients surviving the first 30 days and who were not in cardiogenic shock at admission.*

	Multivariate		
	HR	**95% CI**	**P-value**
Age (years)	1.07	1.04-1.09	**<0.001**
Presenting in Killip class ≥ 2	0.85	0.21-3.49	0.86
Culprit vessel left main	5.56	0.74-41.8	0.096
Three-vessel CAD	1.24	0.74-2.09	0.41
Incomplete revascularisation*	1.56	0.91-2.69	0.11

** Complete revascularisation was defined as treating all present significant coronary artery stenosis ≥ 70% during primary PCI or before discharge.*
CAD: coronary artery disease

Discussion

This study showed that patients with first acute STEMI and multivessel CAD who were treated with incomplete revascularisation had higher mortality rates at 30-day and long-term follow-up compared with patients who underwent complete revascularisation. However, after correcting for relevant clinical variables, incomplete revascularisation was not independently associated with increased all-cause mortality.

Prevalence of multivessel CAD and percutaneous revascularisation strategies

Multivessel CAD is present in 45%-55% of patients presenting with acute STEMI and is associated with 1.5-fold higher 30-day mortality rate compared with patients with STEMI with single vessel CAD.[8, 14-17] It has been hypothesised that complete revascularisation may improve the outcomes of STEMI patients with multivessel CAD. However, the results of various registries and randomised trials are conflicting.[3, 4, 7, 9] The randomised CvLPRIT trial demonstrated in 296 patients with STEMI with multivessel CAD a significant reduction of the combined endpoint consisting of all-cause mortality, recurrent myocardial infarction or heart failure in the complete revascularisation group compared with the IRA-only PCI group (4.7% and 13%; P=0.025).[4] However, data of the large National CV Data Registry from the United States, that involved 28,936 STEMI patients with multivessel CAD, demonstrated a

significantly higher mortality rate in patients with multivessel PCI (n=3,134) in comparison with IRA-only PCI (n=25,802) (7.9% and 5.1%, respectively; P<0.01).[7] After adjusting for potential confounders, complete revascularisation was not independently associated with increased risk of all-cause mortality.

Current guidelines recommend to consider complete revascularisation in selected patients with STEMI and multivessel CAD (class IIb, level of evidence B).[2] In this study, 45% of the patients with STEMI and multivessel CAD underwent complete revascularisation (85% during primary PCI) before hospital discharge. In other registries, the rates of complete revascularisation varied between 11% and 30%.[7, 18, 19] The disparities in complete revascularisation rates across the several studies may be explained by differences in patient populations and operator decision making. In this study, patients with complete revascularisation before discharge were younger, presented less often with Killip class≥2, had the left anterior descending coronary artery less often as culprit vessel, had more often two-vessel CAD and had more often preserved renal function. This is in agreement with the National CV Data Registry where patients with complete revascularisation were more likely to be younger or presenting with cardiogenic shock.[7]

Incomplete revascularisation and 30-day mortality

In the current study, independent associates for the endpoint of 30-day mortality in first patients with STEMI with multivessel CAD were higher age, Killip class≥2 and left main as culprit vessel. These observations are in line with the SHOCK trial, which demonstrated a high mortality rate in patients with acute myocardial infarction complicated by cardiogenic shock and lower prevalence of left main disease for in-hospital survivors.[20] However, similar to other large registries, incomplete revascularisation was not independently associated with the endpoint of 30-day mortality in patients with first STEMI and multivessel CAD.[7, 8, 18, 20] The EUROTRANSFER Registry (European Registry on STEMI Patients Transferred for PCI with Upstream Use of Abciximab), including 777 patients with STEMI and multivessel CAD, showed that multivessel PCI (n=70) compared with IRA-only PCI (n=707) was associated with a higher risk of death at 30-day follow-up (5.9% vs 12.9%, respectively, P=0.04).[8] However, this difference in mortality rate was no longer statistically significant after adjustment for covariates (adjusted OR 2.42 [95%CI 0.96 to 6.06]). Similar findings were reported by the large National CV Data Registry from the United States.[7]

These findings contrast with the results of two recent randomised trials demonstrating short-term benefit of complete revascularisation in comparison with incomplete revascularisation in patients with acute STEMI with

multivessel CAD.[3, 4] The PRAMI trial enrolled 465 patients with STEMI with multivessel CAD randomly assigned to multivessel PCI (n=234) or IRA-only PCI (n=231) and compared the groups for the occurrence of combined endpoint of cardiac death, nonfatal myocardial infarction, or refractory angina.[3] This study was prematurely terminated because of a highly statistically significant difference (P<0.001) in the primary outcome, favouring multivessel PCI. Complete revascularisation was associated with risk reduction within 6 months after the procedure in comparison with the IRA-only PCI. These findings were similar to those reported by the CvLPRIT trial investigators.[4] In this open-labelled randomised study, the impact of complete revascularisation at index admission (n=150) on short-term outcomes was compared with IRA-only PCI (n=146). At 30-day follow-up, patients allocated to the complete revascularisation arm showed lower rates of all-cause mortality, recurrent myocardial infarction, heart failure, and ischemic driven revascularisation compared with patients treated with PCI of the IRA-only (HR 0.45 [95%CI 0.19-1.04]; P=0.055). These conflicting results may be explained by patient characteristics and selection bias. Patients included in the registries showed higher risk (older age, associated co-morbidities and higher frequency of cardiogenic shock) compared with those included in the randomised trials.

A large meta-analysis by Moretti et al. demonstrated that the only benefit of complete revascularisation in patients with STEMI with multivessel CAD during short-term follow-up (1 year) related to less repeated revascularisation compared to patients with IRA-only revascularisation. [21]

Incomplete revascularisation and long-term follow-up

Data on the impact of complete revascularisation in patients with STEMI with multivessel CAD on long-term outcome are limited. The PRAMI trial showed a non-significant risk reduction of cardiac death in the multivessel PCI group (n=234) in comparison with the IRA-only PCI (n=231) during a mean follow-up of 23 months (HR 0.34; 95%CI 0.11-1.08; P=0.07).[3] Similar findings were reported by the DANAMI-3-PRIMULTI which showed no significant difference in all-cause mortality in 627 patients randomly allocated to no further invasive treatment or to complete FFR-guided revascularisation before discharge (HR 1.40; 95%CI 0.63-3.00, P=0.43).[5] Furthermore, in a study including 214 patients with STEMI with multivessel CAD, there were no differences in mortality rates at 2.5 years follow-up between IRA-only PCI, staged complete revascularisation and complete revascularisation during primary PCI (15.5%, 6.2% and 9.2% respectively, P=0.17).[10] In addition, Hannan et al. showed comparable 12-, 24- and 42-month mortality rates in

patients with IRA-only PCI (n=503) and multivessel PCI (n=503).[9] After exclusion of patients with hemodynamic instability, left ventricular ejection fraction ≤20% and malignant ventricular arrhythmia, there were no differences in mortality rates between the two groups.

The results of the present study are in line with the above mentioned studies. Patients with STEMI with multivessel CAD who received incomplete revascularisation showed an increased long-term mortality rate compared with patients who underwent complete revascularisation (24% vs.12%, P<0.001). However, multivariate analysis showed that incomplete revascularisation was not independently associated with increased all-cause mortality.

The results of the COMPLETE trial (ClinicalTrials.gov Identifier NCT01740479), including more than 3,900 patients who will be randomised and followed-up during a mean of 4 years, may shed light on this clinically relevant question.

Limitations

This study has some limitations that need to be addressed. First, this is a retrospective study. Second, patients with cardiogenic shock were not all completely revascularized. Following current guidelines, in this subgroup of patients, if there were truly critical (≥90%) stenoses or highly unstable lesions and if there was persistent ischemia after PCI of the culprit lesion, complete revascularisation was performed.[2] However, non-culprit lesions without critical stenoses were not routinely stented.[2] Additional analysis after excluding patients in cardiogenic shock at the time of admission demonstrated similar results: incomplete revascularisation was not independently associated with increased all-cause mortality during long-term follow-up. Third, the characteristics of the stents used during PCI in the current study were not taken into account. Furthermore, the presence of chronic total occlusions of the coronary arteries was not recorded. In addition, to avoid misclassification of the cause of death, this study investigated only all-cause mortality.[22] Moreover, although patients are advised to follow a cardiac rehabilitation program after hospital discharge, data on adherence to these programs were not available, and this could have influenced the survival rate.

Conclusion

Incomplete revascularisation in patients with acute first STEMI and multivessel CAD was not independently associated with increased short-term and long-term all-cause mortality.

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Chapter 5

Gender-Specific Differences in All-Cause Mortality Between Incomplete Versus Complete Revascularization in Patients With ST-elevation Myocardial Infarction and Multivessel Coronary Artery Disease

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Abstract

The best revascularization strategy (complete versus incomplete revascularization) in patients with ST-elevation myocardial infarction (STEMI) is still debated. The interaction between gender and revascularization strategy in STEMI patients on all-cause mortality is uncertain. The aim of the present study was to evaluate gender-specific difference in all-cause mortality between incomplete versus complete revascularization in patients with ST-elevation myocardial infarction (STEMI) and multivessel coronary artery disease (CAD). The study population consisted of 375 men and 115 women with a first STEMI and multivessel CAD without cardiogenic shock at admission or left main (LM) stenosis. The 30-day and 5-year all-cause mortality was examined in patients categorized according to gender and revascularization strategy (incomplete and complete revascularization). Within the first 30 days men and women with incomplete revascularization were associated with higher mortality rates compared to men with complete revascularization. However, the gender-strategy interaction variable was not independently associated with 30-day mortality after STEMI when corrected for baseline characteristics and angiographic features. Within the survivors of the first 30 days, men with incomplete revascularization (compared with men with complete revascularization) were independently associated with all-cause mortality during 5 years follow-up (HR 3.07 [95%CI 1.24;7.61], P=0.016). In contrast, women with incomplete revascularization were not independently associated with 5-year all-cause mortality (HR 0.60 [95%CI 0.14;2.51], P=0.48). In conclusion, no gender-strategy differences occurred in all-cause mortality within 30 days post-STEMI. However, in the survivors of the first 30 days, incomplete revascularization in men was independently associated with all-cause mortality during 5-years follow-up, but this was not the case in women.

Introduction

The long-term mortality risk in patients after ST-elevation myocardial infarction (STEMI) is between 5 and 15%.[1] Women tend to have a higher mortality rate compared to men post-STEMI.[2-4] It has been suggested that part of this difference can be explained by higher age and multi-morbidity in women presenting with STEMI.[2] Furthermore, gender-related disparities in revascularization strategy (complete versus incomplete revascularization) may contribute to differences in mortality rate.[5-7] Hence, evaluation of the interaction between gender and revascularization strategy in STEMI patients on all-cause mortality, independent of known confounders, is of interest, especially since the best revascularization strategy (complete versus incomplete revascularization) in STEMI patients is still debated.[8, 9] Current guidelines of the European Society of Cardiology recommend to consider immediate revascularization of significant non-culprit lesions during the same procedure in selected patients.[10] Therefore, the aim of the present study was to investigate gender-related differences between incomplete and complete revascularization on all-cause mortality in a large cohort of patients presenting with a first acute STEMI and multivessel coronary artery disease (CAD) without cardiogenic shock at admission or left main (LM) stenosis.

Methods

The study population consisted of 490 patients with a diagnosis of acute first STEMI and multivessel CAD on emergency coronary angiography (CAG) between 2004 and 2008. The diagnosis of first acute STEMI was defined as typical chest pain complaints <12 hours, elevated cardiac enzyme levels and significant ST-segment elevation or left bundle branch block on the electrocardiogram. Exclusion criteria were: (1) history of CAD, (2) cardiogenic shock at admission (defined as a Killip class of 4) and (3) LM stenosis. The study population consisted mostly of patients included in a previous study focusing on the all-cause mortality during short- and long-term follow-up.[11] The current evaluation will focus on differences between men and women in all-cause mortality during 30-days and 5-years follow-up, excluding patients with a cardiogenic shock at admission or LM stenosis. All patients were treated according to the MISSION! protocol as described earlier,[12] which was based on the most recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for patients

with AMI at that moment. The interventional cardiologist decided whether immediate or staged revascularization of the non-culprit vessel(s) occurred before discharge.

The endpoint was all-cause mortality. Mortality data were gained from the municipal civil registry or hospital files review. Demographic, clinical and angiographic data were prospectively entered in the departmental Cardiology Information System (EPD-Vision©, Leiden University Medical Center, the Netherlands) and analyzed retrospectively. According to the Dutch law, approval from The Medical Ethical Committee is not required for this retrospective analysis of clinically collected data. Likewise, no formal patient consent is required for this type of study.

The protocol of the angiographic projections and analysis have been described in detail.[11] In brief, the following information was reported during image analysis: culprit vessel, (in)complete revascularization, coronary vessel dominance, severity of CAD and the results of the primary and/or staged PCI prior to discharge. Infarct-related artery was determined by the evaluation of acute electrocardiographic changes on the electrocardiogram at admission. The definition of complete revascularization was PCI of any significant coronary artery stenosis (≥70% luminal narrowing) of any vessel during the primary or staged PCI prior to discharge.

Normally distributed variables are presented as mean ± standard deviation and non-normally distributed variables as median and 25-75 interquartile range (IQR). Categorical variables are expressed as frequencies and percentages (%). Differences in baseline characteristics between men and women were evaluated using the independent samples t-test, the Mann-Whitney U test, or the Chi-Square test, when appropriate. Survival analyses were performed using Kaplan-Meier analysis. For men and women the cumulative event rates for the endpoint all-cause mortality were compared between patients with complete revascularization and incomplete revascularization, using the Log-Rank test.

A 4-modality variable was used to test the effect of the gender-strategy interaction on 30-day and 5-year mortality: men with complete revascularization, men with incomplete revascularization, women with complete revascularization, and women with incomplete revascularization. Odds ratios (OR) for 30-day mortality and hazard ratios (HR) for 5-year mortality were calculated in reference to the group of men with complete revascularization.

The influence of differences in baseline characteristics on 30-day mortality post-STEMI was assessed by performing univariate and multivariate logistic

regression analysis. To avoid over-fitting of the model, only five variables were entered in the multivariate model: age, Killip class ≥ 2, left ventricular (LV) ejection fraction ≤ 40%, renal dysfunction (eGFR ≤ 60 mL/min/1.73m^2) and the 4-modality variable. The results of the univariate and multivariate analysis were reported as adjusted OR with 95% confidence interval (CI). The associates of all-cause mortality during 5-years follow-up were investigated using univariate and multivariate Cox regression analysis for those patients who survived the first 30 days. Only variables with P-values <0.10 at univariate analysis were included in the multivariate model: age, three-vessel CAD, LV ejection fraction ≤40%, a history of diabetes mellitus or hypertension and the 4-modality variable. The results of the univariate and multivariate Cox regression analysis were reported as HR with 95% CI. Statistical analysis was performed using SPSS software (Version 22.0, SPSS IBM Corp., Armonk, New York, USA). A two-sided P-value of <0.05 was considered statistically significant.

Results

The clinical baseline characteristics of the 490 patients with an acute first STEMI and multivessel CAD on CAG stratified according to gender (men [n=375] versus women [n=115]) are shown in Table 1. Women were older (69 ±12 vs. 61 ±12, P<0.001), had more often diabetes mellitus (DM), higher prevalence of hypertension and presented more often with Killip class ≥2, as compared to men. In addition, kidney function was worse in women. The medication at discharge between both groups were comparable. No difference existed in percentage of incomplete revascularization during admission, 53% in men versus 61% in women (P=0.16).

In the first 30 days post-STEMI, 21 patients (4%) died (18 during index hospitalization). There was no difference between men and women in all-cause mortality rate within 30 days, 8/115 (7%) versus 13/375 (3.5%; P=0.11). The variables associated with the endpoint 30-day mortality are shown in Table 2. In the multivariate analysis, age and Killip class ≥ 2 were independently associated with 30-day mortality post-STEMI. The gender-strategy interaction variable demonstrated no independent associate with 30-day all-cause mortality post-STEMI with as reference category men with complete revascularization.

Table 1. *Patient characteristics and angiographic data.*

	Men (N =375)	Women (N = 115)	P-value
Age (years)	61±12	69±12	**<0.001**
Obesity (body mass index ≥ 30kg/m^2)	14%	20%	0.20
Diabetes mellitus	10%	18%	**0.04**
Hypercholesterolemia*	15%	23%	0.06
Hypertension†	32%	53%	**<0.001**
Current smoker	47%	38%	0.09
Family history of cardiovascular disease	38%	42%	0.42
Presenting with Killip class ≥ 2	3.5%	8%	**0.04**
Culprit coronary artery			
Right	44%	38%	0.30
Left anterior descending	40%	49%	0.08
Left circumflex	17%	13%	0.37
Three-vessel coronary artery disease	31%	33%	0.63
Estimated glomerular filtration rate ≤ 60 mL/min/1.73m²	7%	26%	**<0.001**
Peak cardiac troponin T level ≥3.5 µg/L	58%	58%	0.97
Left ventricle ejection fraction ≤40%	28%	30%	0.70
Blood pressure at discharge			
Systolic (mmHg)	115±17	119±19	0.07
Diastolic (mmHg)	70±11	69±12	0.19
Medication at discharge			
Beta-blocker	93%	95%	0.36
Antiplatelet agent	100%	100%	-
Angiotensin converting enzyme inhibitor / angiotensin receptor blockers	97%	96%	0.60
Statin	99%	96%	0.06
Incomplete revascularization‡	53%	61%	0.16

Bold means significant P-values at <0.05 level.

* *Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid lowering drugs.*

† *Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.*

‡ *Complete revascularization was defined as treating all present significant coronary artery stenosis ≥ 70% during primary PCI or before discharge.*

Table 2. *Influence of baseline variables on 30-day mortality post-STEMI.*

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Men	0.48	0.19-1.19	0.11			
Gender / incomplete revascularization						
Men/complete		Reference category			Reference category	
Men/incomplete	11.11	1.43-86.31	**0.02**	4.08	0.44-37.87	0.22
Women/complete	8.093	0.72-91.34	0.09	2.72	0.20-37.38	0.46
Women/incomplete	16.31	1.93-138.14	**0.01**	3.27	0.28-38.87	0.35
Age (years)	1.12	1.07-1.17	**<0.001**	1.11	1.03-1.19	**0.009**
Diabetes mellitus	0.37	0.05-2.84	0.34			
Hypercholesterolemia*	0.53	0.12-2.34	0.40			
Hypertension†	0.73	0.27-1.93	0.52			
Current smoker	0.52	0.20-1.38	0.19			
Family history of cardiovascular disease	0.078	0.01-0.59	**0.01**	0.27	0.03-2.38	0.24
Presenting with Killip class ≥ 2	34.17	12.19-95.76	**<0.001**	10.72	2.36-48.68	**0.002**
Culprit coronary artery						
Right	0.53	0.20-1.39	0.20			
Left anterior descending	1.29	0.54-3.09	0.57			
Left circumflex	1.28	0.42-3.90	0.67			
Three-vessel coronary artery disease	2.07	0.86-4.99	0.10	0.70	0.18-2.73	0.60
Estimated glomerular filtration rate ≤ 60 mL/min/1.73m^2	4.94	1.72-14.18	**0.003**	0.85	0.17-4.17	0.84
Peak cardiac troponin T level ≥3.5 µg/L	3.81	1.09-13.33	**0.04**	1.95	0.44-8.52	0.38
Left ventricle ejection fraction ≤40%	5.40	1.81-16.12	**0.003**	3.23	0.89-11.74	0.07

Bold means significant P-values at <0.05 level.
CI: confidence interval; OR: odds ratio.
Definitions: see Table 1.

The 5-year follow-up was complete in all patients. In total 57 patients died, of which 43 (75%) were men. No significant difference occurred between 5-year mortality rates between women 14/115 (12%) and men 43/375 (11%; P =0.84). After excluding the first 30 days post-STEMI, the 5-year mortality rate in women was 6/107 (6%) and in men 30/362 (8%; P=0.36).

Table 3 summarizes the cumulative mortality rates at 1, 2 and 5 year follow-up in women and men stratified according to incomplete versus complete revascularization. There was no significant difference in the cumulative mortality rates between incomplete and complete revascularization in women at 1-, 2- and 5-year follow-up (9%, 10% and 13% versus 7%, 7%, 11%). However, the cumulative mortality rates at 1-, 2- and 5-year were significantly higher in the group of men with incomplete versus men with complete revascularization (8% versus 2% [P=0.017], 10% versus 3% [P=0.009] and 18% versus 4% [P<0.001], respectively).

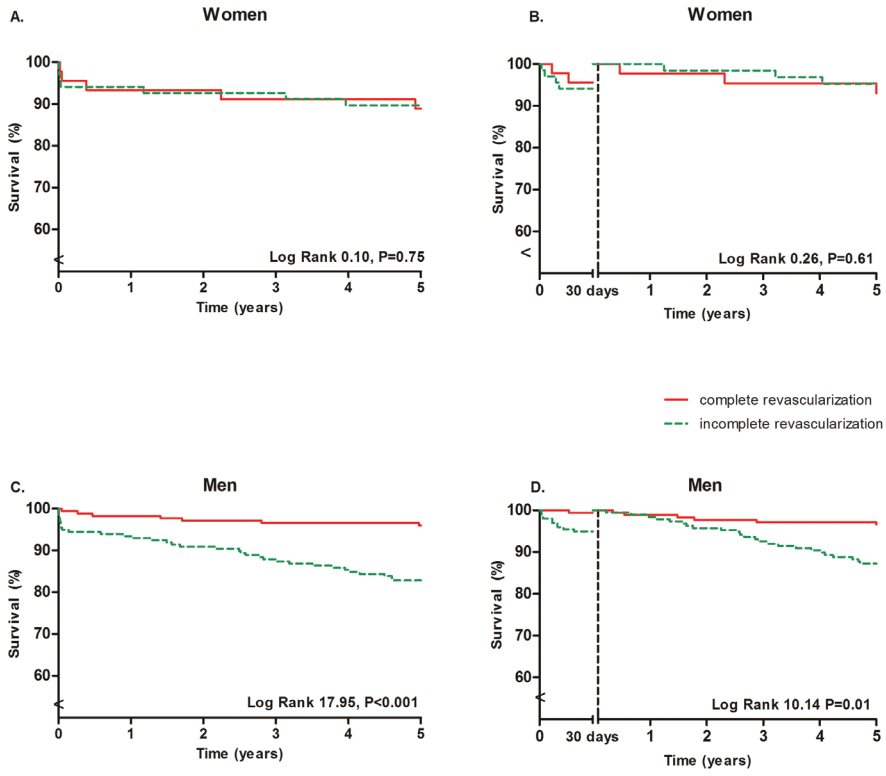
Figure 1 displays the Kaplan-Meier curves of 5-year follow-up in men (a, c) versus women (b, d) stratified according to incomplete versus complete revascularization. In men, the group with incomplete revascularization had worse long-term survival compared with the group of men with complete revascularization (Log Rank 17.95, P<0.001). This difference remained after excluding the first 30 days post-STEMI (Log Rank 10.14, P=0.01). In women, there was no significant difference in 5-year survival between both groups (Log Rank 0.10, P=0.75), even after excluding the first 30 days (Log Rank 0.26, P=0.61).

Table 3. *Mortality rates during 1-, 2- and 5-year follow-up of women and men with complete versus incomplete revascularization.*

	No./Total no. (%) of patients			
	Complete revascularization	**Incomplete revascularization**	**Hazard ratio (95% CI)**	**P-value**
Women				
One-year	3/45 (7%)	6/70 (9%)	1.33 (0.33-5.33)	0.68
Two-years	3/45 (7%)	7/70 (10%)	1.55 (0.40-6.01)	0.52
Five-years	5/45 (11%)	9/70 (13%)	1.20 (0.40-3.57)	0.75
Men				
One-year	3/175 (2%)	15/200 (8%)	4.53 (1.31-15.66)	**0.017**
Two-years	5/175 (3%)	20/200 (10%)	3.66 (1.37-9.76)	**0.009**
Five-years	7/175 (4%)	36/200 (18%)	4.86 (2.16-10.91)	**<0.001**

Bold means significant P values at <0.05 level.

Figure 1. *Five-year survival in men and women stratified according to complete versus incomplete revascularization.*



A. There was no difference in survival between complete and incomplete revascularization in women (P[Log Rank]=0.75). B. After excluding the first 30 days post-STEMI the outcome remained similar in women with incomplete revascularization compared with complete revascularization (P[Log Rank] =0.61). C. Men with incomplete revascularization in comparison with men with complete revascularization had a statistically higher cumulative incidence of all-cause mortality during 5-year follow-up after STEMI (P [Log Rank] < 0.001). D. After excluding the first 30 days post-STEMI, the outcome remained worse in men with incomplete revascularization compared with complete revascularization (P[Log Rank]=0.01).

Table 4. *Cox regression analysis for the survivors of the first 30 days post-STEMI(N=469) for all-cause mortality during 5 years follow-up.*

		Univariate			Multivariate	
	HR	**95% CI**	**P-Value**	**HR**	**95% CI**	**P-value**
Men	1.50	0.63-3.61	0.36			
Gender / incomplete revascularization‡						
Men/complete		Reference category			Reference category	
Men/incomplete	3.86	1.58-9.44	**0.003**	3.07	1.24-7.61	**0.016**
Women/complete	2.05	0.51-8.21	0.31	0.77	0.15-3.91	0.75
Women/incomplete	1.36	0.34-5.44	0.66	0.60	0.14-2.51	0.48
Age (years)	1.05	1.02-1.08	**0.001**	1.06	1.02-1.09	**0.001**
Three-vessel coronary artery disease	2.41	1.26-4.64	**0.008**	1.39	0.69-2.81	0.35
Left ventricle ejection fraction ≤40%	2.21	1.12-4.35	**0.02**	2.32	1.16-4.61	**0.017**
Diabetes mellitus	2.43	1.14-5.17	**0.02**	1.91	0.86-4.21	0.11
Hypercholesterolemia*	0.43	0.13-1.40	0.16			
Hypertension†	1.95	1.01-3.75	**0.046**	1.76	0.88-3.54	0.11
Current smoker	0.76	0.39-1.49	0.43			
Family history of cardiovascular disease	0.64	0.31-1.30	0.21			
Presenting with Killip class ≥ 2	2.49	0.60-10.38	0.21			
Culprit coronary artery						
Right	0.73	0.37-1.45	0.37			
Left anterior descending	1.63	0.85-3.14	0.14			
Left circumflex	0.66	0.24-1.88	0.44			
Estimated glomerular filtration rate ≤ 60 mL/min/1.73m^2	1.78	0.74-4.30	0.20			
Peak cardiac troponin T level ≥3.5 μg/L	1.57	0.79-3.14	0.20			
Medication at discharge						
Beta-blocker	1.07	0.26-4.44	0.93			
Angiotensin converting enzyme inhibitor / angiotensin receptor blockers	0.50	0.12-2.09	0.34			
Statin	0.47	0.06-3.43	0.46			

Bold means significant P-values at <0.05 level.
CI: confidence interval; HR: hazard ratio.
For definitions: see Table 1.

The variables of the survivors of the first 30-days post-STEMI associated with all-cause mortality within 5 year follow-up are shown in Table 4. After correction for significant univariate associates, men with incomplete revascularization remained independently associated with 5-year all-cause mortality (HR 3.07 [95%CI 1.24;7.61], P=0.016). In contrast, women with incomplete revascularization were not independently associated with 5-year all-cause mortality (HR 0.60 [95%CI 0.14;2.51], P=0.48). In addition, age and LV ejection fraction below 40% were independently associated with all-cause mortality during 5-year follow-up.

Discussion

The present study assessed gender-related differences on all-cause mortality between incomplete and complete revascularization in first STEMI patients with multivessel CAD during short- and long-term follow-up. Within the first 30-days post-STEMI, no differences in all-cause mortality rate between incomplete and complete revascularization occurred among men and women. However, during 5 years of follow-up, men with incomplete revascularization who survived the first 30 days were at 3.1-fold higher mortality risk compared with men with complete revascularization (after adjusting for confounders). In contrast, women stratified to incomplete and complete revascularization who survived the first 30 days had both similar mortality risk as men with complete revascularization.

In STEMI patients there are disparities in clinical presentation and comorbidity between men and women.[2] In the present study, women compared with men were older, presented with more comorbidity (higher percentage of DM and hypertension) and more frequently presented with Killip class ≥2. In addition, the kidney function was more often impaired in women. These findings are in line with large registries evaluating the clinical characteristics at presentation.[2-4] The National Registry of Myocardial Infarction (NRMI) demonstrated that women were significantly older than men at the time of the first myocardial infarction: 73.9 versus 66.5 years, respectively (P<0.001).2 In addition, in this registry the proportion of patients presenting without chest pain / discomfort was significantly higher for women than men, which leads to longer ischemic time and worse outcomes.

However, in the above mentioned registries the interaction of revascularization strategy and gender on all-cause mortality was not taken into account. This is of importance since the best revascularization strategy (incomplete or complete revascularization) is still debated in STEMI patients with multivessel CAD, as results of several studies are inconsistent.[8, 9, 13-16] Furthermore, differences in revascularization benefit may exist between women and men. Ghauharali-Imami et al. analyzed gender differences in mortality in a prospective consecutive cohort of STEMI patients with multivessel CAD, with respect to complete versus incomplete revascularization with an intermediate follow up of 3.3 ±1.2 years.[17] The results demonstrated that women underwent less frequently complete revascularization compared with men, being 30% vs 38%, respectively (P=0.04). However, the mortality rate in women was not significantly different between both revascularization strategies (complete and incomplete revascularization) during in-hospital, 1-year and intermediate follow-up. In contrast, men with complete revascularization had lower mortality rates than men with incomplete revascularization during in-hospital and 1-year follow-up (0% versus 3%; P<0.001 and 1% versus 5%; P=0.02). Conversely, no difference was observed for intermediate follow-up between men with complete revascularization and men with incomplete revascularization (6% versus 8%; P=0.30).

The present study demonstrated no differences in all-cause mortality within 30-days post-STEMI between both revascularization strategies among women and men. However, when analysing the survivors of the first 30 days, men with incomplete revascularization showed a higher mortality rate during 5-year follow-up compared with men with complete revascularization (18% versus 4%, P<0.001). In women, in both strategy groups (incomplete and complete revascularization) no significant difference were found in mortality rate during 5-year follow-up. Yet, the long-term benefit of complete revascularization compared with incomplete revascularization in men was not noted in the previous mentioned study by Ghauharali-Imami et al.[17] However, the current study differed in duration and completeness of follow-up. Additionally, in the present study, the first 30 days were excluded from the long-term follow-up analysis. This is relevant since the mortality rate in the first 30 days is high and long-term results will be largely influenced by the outcome of the first 30 days.

It is hypothesized that men have more benefit from complete revascularization compared with women, since women tend to have fewer non-culprit lesions, with more often focal lesions with smaller minimal lumen area. In the present study stenosis characteristics were not taken into account. However,

the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study validates that despites the fact that women have more comorbid risk factors than men, women have less extensive coronary artery disease both by angiographic and intravascular ultrasound (IVUS) measures.[18] The lesions in women compared with men have less plaque rupture, similar plaque burden and smaller lumens. In addition, in comparison with men, angiographic lesions of similar severity by angiography are less likely to be ischemia-producing in women.[19] Moreover, Kim et al. demonstrated in 2-year data from the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study that the proportion of functionally significant lesions (FFR ≤ 0.80) was lower in women than in men for lesions with 70% to 90% stenosis (71.9% vs. 82.0%, P = 0.019).[19]

The present study has some limitations that need to be addressed. First, this is a retrospective observational study with all its inherits. Furthermore, stenosis and stent-characteristics were not taken into account. In addition, to avoid misclassification of the cause of death, the present study investigated only all-cause mortality.

Conclusion

The first 30-days post-STEMI, gender-strategy interaction variable was not independently associated with all-cause mortality. However, in the survivors of the first 30 days, incomplete revascularization in men with a first STEMI and multivessel CAD, in contrast to women, was independently associated with all-cause mortality during 5-years follow-up.

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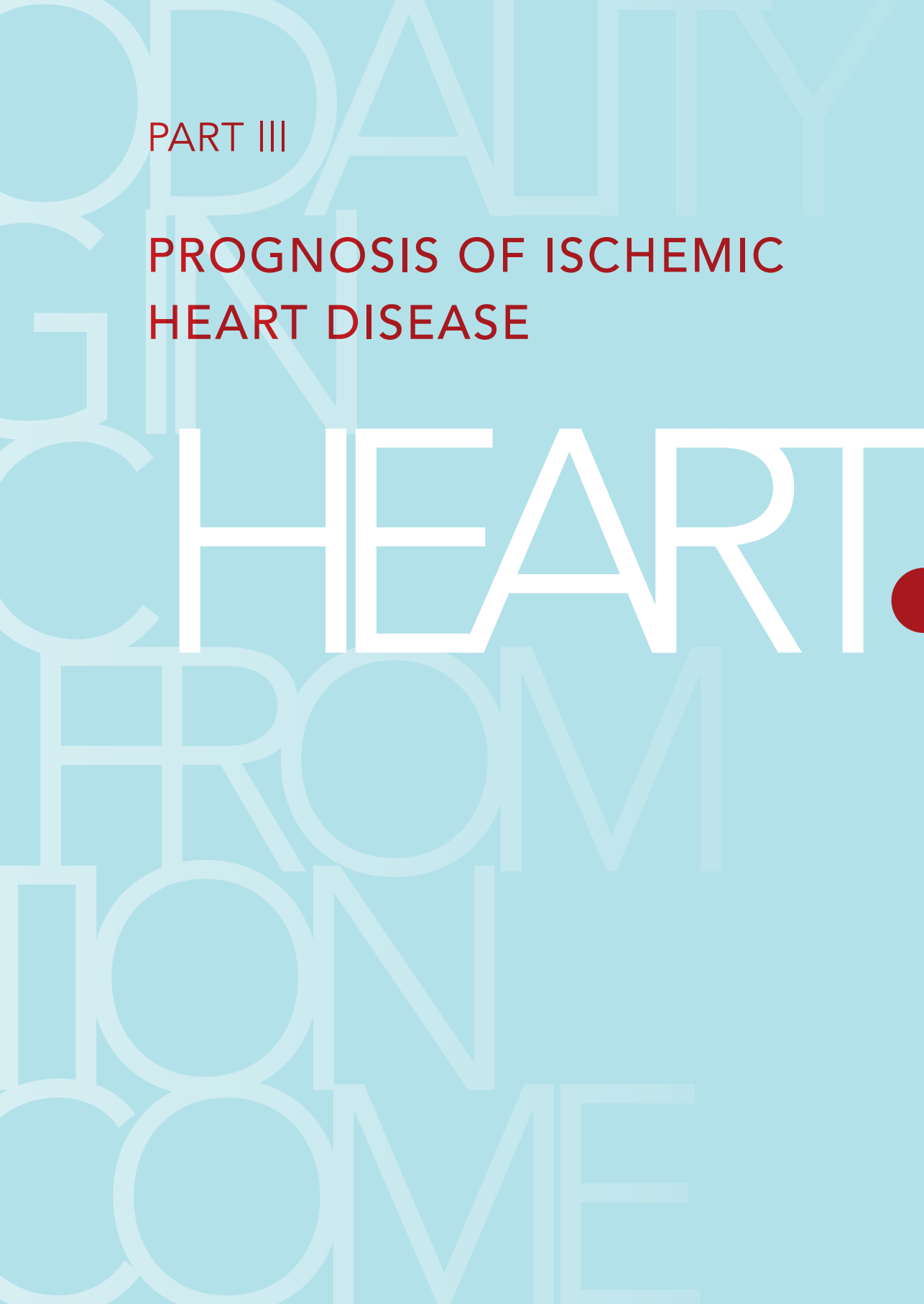
PART III

PROGNOSIS OF ISCHEMIC HEART DISEASE

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Chapter 6

Influence of Myocardial Ischemia Extent on Left Ventricular Global Longitudinal Strain in Patients after ST-segment Elevation Myocardial Infarction

Am J Card 2017;119:1-6

Dimitriu-Leen AC, Scholte AJHA, Katsanos S, Hoogslag GE, van Rosendael AR, van Zwet EW, Bax JJ, Delgado V.

Abstract

Two-dimensional echocardiographic left ventricular (LV) global longitudinal strain (GLS) after ST-segment elevation myocardial infarction (STEMI) is moderately correlated with infarct size and reflects the residual LV systolic function. This correlation may be influenced by the presence of myocardial ischemia. The present study investigated how myocardial ischemia modulates the correlation between LV GLS and infarct size determined with single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in patients with first STEMI treated with primary coronary intervention. A total of 1,128 patients (age 60±11 years) who underwent SPECT MPI for the evaluation of infarct size and residual ischemia were evaluated. LV GLS was measured on transthoracic echocardiography. The time interval between echocardiography and SPECT MPI was 1±1 month. A moderate correlation between echocardiographic LV GLS and infarct size on SPECT MPI was observed (r=0.58, P<0.001). This correlation was weakened by the presence or extent of ischemia; in the group of patients without ischemia, the correlation between LV GLS and infarct size on SPECT MPI was r=0.66 (P<0.001), whereas in patients with mild or moderate to severe ischemia, the correlations were r=0.56 and r=0.38, respectively (both P<0.001). Moderate to severe myocardial ischemia was independently associated with more impaired LV GLS after adjusting for infarct size, age, diabetes mellitus and hypertension (ß 0.60, 95%CI 013-1.06). In conclusion, the presence of myocardial ischemia after STEMI impacts on the correlation between echocardiographic LV GLS and infarct size measured on SPECT MPI. Residual ischemia is independently associated with more impaired LV GLS.

Introduction

Left ventricular ejection fraction (LVEF) is the most widely used parameter for risk stratification of patients with ST-segment elevation myocardial infarction (STEMI).[1] However, left ventricular global longitudinal strain (LV GLS) measured with speckle tracking echocardiography may better reflect the extent of myocardial infarction and the residual LV systolic function.[2-4] A strong correlation between LV GLS and infarct size assessed with late gadolinium contrastenhanced magnetic resonance imaging (LGE-MRI) or single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has been shown.[5-10] However, this correlation is not straightforward because regional LV dysfunction may extend beyond the region of scar resulting in more impaired LV GLS. Factors that may negatively impact on LV GLS include burden of coronary artery disease, diabetes mellitus, age, hypertension and associated valvular heart disease among others.[7, 11-14]

In addition, the presence of myocardial ischemia may further impair LV GLS and weaken the correlation between LV GLS and infarct size. The present study evaluated the influence of myocardial ischemia on the correlation between LV GLS and infarct size in patients with STEMI who were clinically referred to SPECT MPI. Moreover, the independent association between myocardial ischemia and LV GLS was investigated.

Methods

A total of 1,224 patients with a previous first STEMI treated with primary coronary intervention at the Leiden University Medical Centre (The Netherlands) between 2004 and 2010 who were clinically referred for SPECT MPI were included (to evaluate infarct size and residual ischemia).[15] The echocardiographic study closest to the date of SPECT MPI was selected to assess LV GLS.

Demographic, clinical, nuclear imaging, and echocardiographic data were prospectively entered in the departmental Cardiology Information System (EPD-Vision©, Leiden University Medical Center, the Netherlands) and retrospectively analyzed. The Institutional Review Board of the Leiden University Medical Center approved the study and waived the need for written informed consent for retrospective analysis of clinically acquired data.

Echocardiographic images were obtained with the patient lying in the left lateral decubitus position. The data were acquired with commercially available

ultrasound systems (Vivid 7 and E9; General Electric-Vingmed, Horten, Norway) with 3.5-MHz or M5S transducers. Two-dimensional, color, continuous, and pulsed wave Doppler data were acquired from the parasternal (long- and short-axis) and apical (2-, 3-, and 4-chamber) views. Data were digitally stored for subsequent offline analysis with EchoPac 112.0.1 (GE Medical Systems, Horten, Norway). LVEF was calculated from the LV end-diastolic and end-systolic volumes measured from the apical 4- and 2-chamber views using the biplane Simpson method.[1] In addition, LV diastolic dysfunction was assessed measuring the peak velocity of early (E) and late (A) peak diastolic velocities from the pulsed wave Doppler transmitral flow recordings and the deceleration time (DT) of the early filling wave. In addition, tissue Doppler imaging data were acquired to measure the mitral annulus E' diastolic tissue velocity, and the E/E' ratio was calculated as a measure of LV filling pressures. An experienced observer measured LV GLS from the apical 4-chamber, 2-chamber, and long-axis views using 2-dimensional speckle-tracking analysis and blinded to the information from SPECT MPI.[4] The software calculated the LV GLS as the average of the peak systolic longitudinal strain of the 3 apical views and displayed in a 17-segment "bull's eye" plot.

SPECT MPI was performed using a 2-day stress–rest protocol starting on day 1 with a stress acquisition. The patients underwent a symptom-limited bicycle test with continuously blood pressure and 12-lead electrocardiographic recording or, when unable to exercise, a dobutamine stress test (5 to 40 μg/kg/min for 15 minutes with handgrip-exercise starting at 6 minutes supplemented with atropine when necessary) or an adenosine stress test (140 μg/kg/min for 6 minutes with additional bicycle riding on individual level) according to current recommendations.[16-18] At peak exercise, after 3.5 minutes of the adenosine infusion or at peak heart rate during dobutamine, 500 MBq of technetium-99m tetrofosmin was administrated intravenously. After 30 minutes, stress images were obtained with the patient lying on a supine position. On the second day, resting images were obtained 45 minutes after intravenously administration of 500 MBq technetium-99m tetrofosmin. The images were acquired with a triple-head SPECT camera (GCA 9300/HG; Toshiba Corporation, Tokyo, Japan) or a double-head SPECT camera (7200pi; Toshiba Corporation, Tokyo, Japan). All cameras were equipped with low-energy, high-resolution collimators. A 20% window was used with a 140-keV energy peak of technetium-99m, and data were stored in a 64x64 matrix.

Table 1. *Clinical characteristics*

Variable	Overall population N=1128
Age (years)	60±11
Men	858 (76%)
BMI>30kg/m²	186 (17%)
Hypercholesterolemia†	203 (18%)
Hypertension‡	381 (34%)
Current smoker	556 (49%)
Family history of CAD	499 (44%)
Diabetes mellitus	97 (9%)
LAD culprit vessel	516 (46%)
Multivessel CAD	591 (52%)
TIMI flow 2-3	1112 (99%)
Peak CPK level (U/L)	1531 (IQR 751-3,129)
Peak cTnT level (µg/L)	4.05 (IQR 1.6-7.9)
eGFR level (mL/min/1.73m²)	97 (IQR 77;118)
Medications at discharge	
ACE-inhibitors/ARBs	1105 (98%)
Antiplatelet therapy	1128 (100%)
Beta-blockers	1073 (95%)
Statins	1122 (99.5%)

ACE-I: ACE-inhibitor; AT-II: angiotensine-II receptor antagonist; BMI: body mass index; CAD: coronary artery disease; eGFR: glomerular filtration rate estimated with the Cockroft-Gault formula; IQR: interquartile range; LAD: left anterior descending; LCx: left circumflex; LM: left main; RCA: right coronary artery; STEMI: ST-segment elevation myocardial infarction.

† *Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or therapeutic treatment with lipid lowering drugs.*

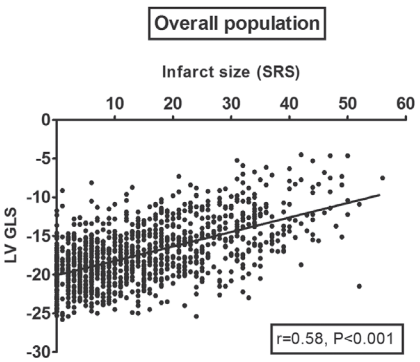
‡ *Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.*

Images were processed to obtain the short-axis, vertical long-axis and horizontal long-axis tomographic sections, and polar map formats, normalized to maximal activity.[16] The SPECT MPI data were scored semiquantitatively according to the 17-segment model.[19] Each segment was scored on a 5-point scale: 0: normal, 1: slight reduction of tracer uptake (not definitely abnormal), 2: moderate reduction of uptake (definitely abnormal), 3: severe reduction

Table 2. *Echocardiographic parameters.*

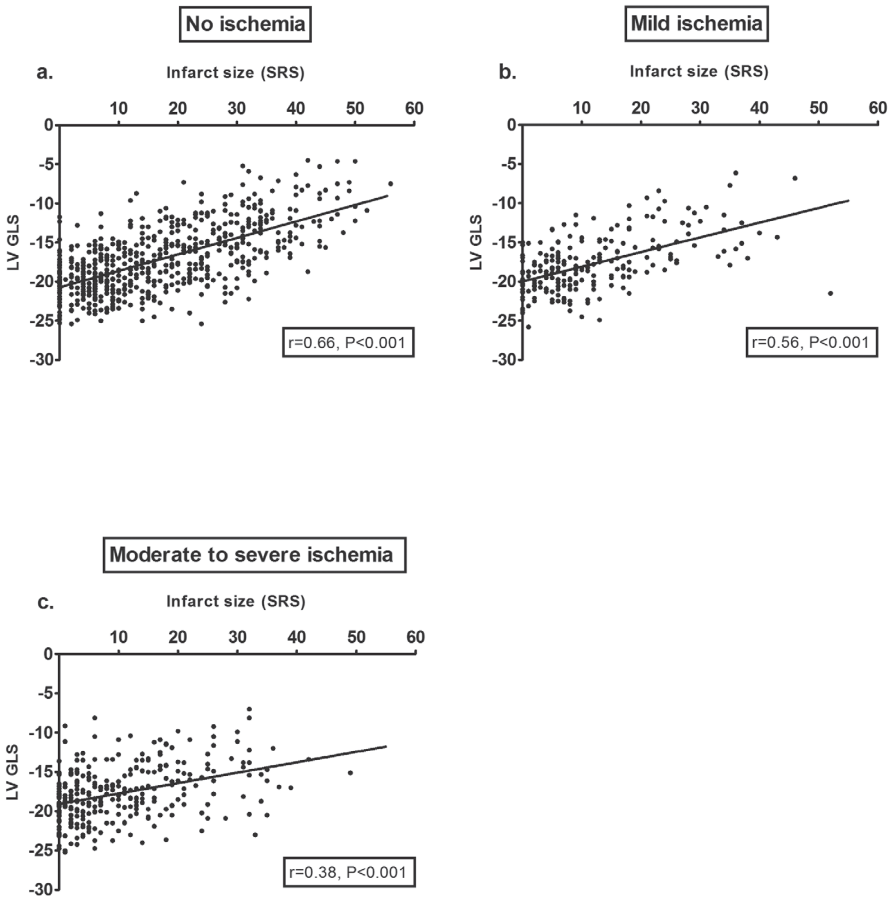
Echocardiography parameters	Overall population N=1128
Left ventricle end-systolic volume (mL)	58±28
Left ventricle end-diastolic volume (mL)	116±40
Left ventricle ejection fraction (%)	51±10
Left ventricle global longitudinal strain (%)	-17.4±3.9
E/A ratio	1.03±0.48
Deceleration time (ms)	244±83
E/E′ ratio	13±7
Mitral regurgitation ≥ grade 2 (moderate to severe)	107 (9%)

Figure 1. *Pearson's correlation between infarct size and LV GLS in the overall population.*



In the overall population there is a moderate correlation between infarct size on SPECT MPI and LV GLS ($r=0.58$, $P<0.001$).
LV GLS: left ventricular global longitudinal strain; SRS: summed rest score.

Figure 2. *Pearson's correlation between infarct size and LV GLS in patients without ischemia (SDS 0, Figure 2a), mild ischemia (SDS 1-3, Figure 2b) and moderate to severe ischemia on SPECT MPI (SDS ≥ 4, Figure 2c).*



Patients with no ischemia (SDS 0, Figure 2a) demonstrated a better correlation between infarct size and LV GLS (r=0.66, P<0.001) in comparison with patients with mild (SDS 1-3, Figure 2b: r=0.58, P<0.001) and moderate to severe ischemia on SPECT MPI (SDS ≥ 4, Figure 2c; r=0.38, P<0.001). LV GLS: left ventricular global longitudinal strain; SRS: summed rest score.

of uptake and 4: absence of uptake.[20] The summed stress score (SSS) and summed rest score (SRS) were calculated by the summation of the segmental scores at stress and rest, respectively. The summed difference score (SDS), reflecting the stress-inducible ischemia size, was calculated by subtracting the SRS of the SSS. Afterward, the SSS and the SRS were divided into tertiles. The SDS was categorized in three groups: SDS 0 (no ischemia), SDS 1-3 (mild-moderate ischemia) and SDS ≥4 (severe ischemia).

Normally distributed variables are expressed as mean ± standard deviation and non-normally distributed variables as median and interquartile range (IQR). Categorical variables are presented as frequencies and percentages. The correlation between LV GLS and infarct size on SPECT MPI was evaluated with Pearson's correlation. Afterward, the total population was divided into 3 groups according to the presence of no (SDS =0), mild (SDS 1-3) or moderate to severe ischemia (SDS ≥4). Subsequently, the correlation between LV GLS and infarct size was assessed in each subgroup using Pearson correlation. The association between (mild or moderate to severe) ischemia and LV GLS was corrected for factors known to affect LV GLS (age, hypertension, diabetes mellitus and infarct size) using a multivariate linear regression analysis. The beta-coefficients and the 95% confidence interval (CI) were reported. A 2-sided P-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (Version 22.0, SPSS IBM Corp., Armonk, NewYork, USA).

Results

Measurement of LV GLS was not feasible in 96 patients (8%), whereas SPECT MPI examination was incomplete or uninterpretable in 19 patients (2%), leaving 1,128 patients who were considered in the analysis (Table 1). Most patients were men (76%), and the mean age was 60±11 years. Left anterior descending coronary artery myocardial infarction was present in 46% of patients, and 52% had multivessel coronary artery disease.

Table 2 summarizes the echocardiographic parameters. Mean LVEF was 51±10%, and mean LV GLS was -17.4±3.9%. Table 3 presents the SPECT MPI results. The time elapsed between index STEMI and echocardiography was 3±0.9 months, between index STEMI and SPECT MPI 3±1.6 months and between the echocardiography and the SPECT MPI 33±43 days. In most patients, the stress test consisted of a symptom-limited bicycle test (75%). Fifty-one patients (4.5%) experienced cardiac symptoms during the stress test.

Table 3. *Single-photon Emission Computed Tomography Myocardial Perfusion Imaging parameters.*

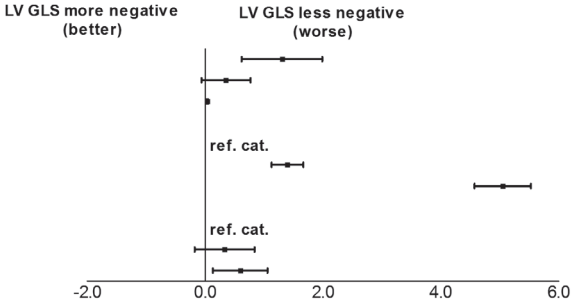
SPECT parameters	Overall population N=1128
Stress test	
Exercise	850 (75%)
Adenosine	271 (24%)
Dobutamine	7 (0.6%)
Maximal exercise (Watt)	155±43
Validity (%)	106±19
Symptoms during exercise	51 (5%)
ECG during exercise	
Positive	154 (14%)
Negative	944 (84%)
Non-diagnostic	30 (2%)
Heart rate rest (/min)	79±15
Maximum heart rate during exercise (/min)	138±29
Systolic blood pressure rest (mmHg)	145±24
Systolic blood pressure exercise (mmHg)	186±35
Diastolic blood pressure rest (mmHg)	84±13
Diastolic blood pressure exercise (mmHg)	91±17
Infarct size / summed rest score	
median	11 (IQR 4;22)
1^{e} tertile SRS ≤ 6	404 (36%)
2^{e} tertile SRS 7-18	371 (33%)
3^{e} tertile SRS ≥ 19	353 (31%)
Ischemia size / summed difference score	
median	0 (IQR 0;4)
no ischemia / SDS 0	611 (54%)
mild ischemia / SDS 1-3	219 (12%)
moderate to severe ischemia / SDS ≥ 4	298 (26%)
Infarct + Ischemia size / summed stress score	
median	14 (IQR 7;24)
1^{e} tertile SSS ≤ 9	405 (36%)
2^{e} tertile SSS 10-20	354 (31%)
3^{e} tertile SSS ≥ 21	369 (33%)

IQR: interquartile range; LVEF: left ventricle ejection fraction; SDS: summed difference score; SRS: summed rest score; SSS: summed stress score.

Based on electrocardiography, 154 patients (14%) were considered as having inducible ischemia. In addition, 46% of patients showed ischemia (SDS >0), of which 298 (26%) had moderate to severe ischemia (SDS ≥4).

In the overall population, there was a moderate correlation between LV GLS and infarct size (r=0.58, 95% CI 0.54;0.62, P<0.001) (Figure 1). After dichotomization of the patients according to the absence or presence of ischemia, the subgroup of patients without ischemia (r=0.66, 95% CI 0.61;0.70, P<0.001; Figure 2a) showed stronger correlation between LV GLS and infarct size than in patients with mild ischemia (r=0.56, 95% CI 0.45;0.66, P<0.001; Figure 2b) and patients with moderate to severe ischemia (r=0.38, 95% CI 0.27;0.47, P<0.001; Figure 2c). After correcting for age, diabetes mellitus, infarct size, and hypertension, moderate to severe ischemia was independently associated with worse (less negative) LV GLS after STEMI (Figure 3). Figure 4 illustrates the difference in LV GLS between 2 patients with similar infarct size, but 1 patient shows ischemia, whereas the other patient does not have ischemia.

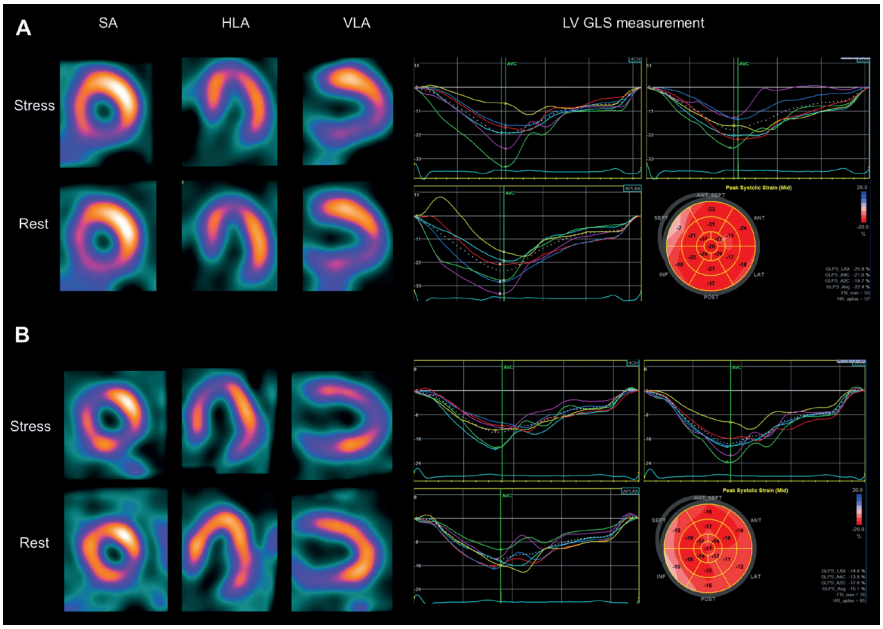
Figure 3. *Multivariate linear regression analysis*



Variables	ß (95%CI)*	P-value
Diabetes Mellitus	1.31 (0.62;1.99)	**<0.001**
Hypertension	0.35 (0.77;2.83)	0.09
Age	0.04 (0.02;0.05)	**<0.001**
Infarct size		**<0.001**
small infarct	ref. cat	
moderate infarct	1.40 (0.93;1.86)	**<0.001**
large infarct	5.05 (4.57;5.53)	**<0.001**
Ischemia size		**0.04**
no ischemia	ref. cat.	
mild ischemia	0.33 (-0.18;0.84)	0.20
Moderate to severe ischemia	0.60 (0.13;1.06)	**0.012**

After correction for infarct size, diabetes mellitus, age and hypertension, moderate to severe ischemia (SDS ≥ 4) was independently associated with worse LV GLS (β 0.60, 95%CI 0.13-1.06).
**Increasing values represents worsening of LV function (less negative LV GLS)*
CI: confidence interval; LV GLS: left ventricular global longitudinal strain.

Figure 4. *Example of a difference between GLS measurements in two patients with similar infarct size, but different ischemia size.*



In this example, both patients demonstrate on SPECT MPI similar infarct size (SRS=22). However, patient A has no ischemia on SPECT MPI with a LV GLS of -22 in contrast to patient B, which has severe ischemia (SDS=19) with a worse LV GLS of -15. HLA: horizontal-long axis, SA: short axis, vertical-long axis, LV GLS: left ventricular global longitudinal strain.

Discussion

The present study demonstrated a modest correlation between LV GLS and infarct size determined on SPECT MPI in patients after STEMI. This correlation was influenced by ischemia extent: the group of patients without ischemia showed a stronger correlation between LV GLS and infarct size compared to patients with residual myocardial ischemia. The presence of myocardial ischemia was independently associated with more impaired LV GLS after adjusting for infarct size, age, diabetes mellitus, and hypertension.

Two-dimensional speckle tracking echocardiography has emerged as a quantitative method to assess LV systolic function and has shown good correlations with infarct size using LGE-MRI and SPECT MPI as reference standard (Table 4).[5-10] For example, Gjesdal et al. showed that LV GLS impaired in parallel with increasing infarct size assessed with LGE-MRI 8.5 months after

STEMI.[6] The correlation between LV GLS and infarct size based on LGE-MRI was 0.84 ($p<0.001$). The presence of ongoing edema may overestimate the infarct size and the presence of stunned myocardium may lead to more impaired LV GLS at early stages after STEMI, whereas at midterm follow-up, infarct size decreases and its correlation with LV GLS may change.[21] The present study is the largest so far comparing LV GLS and infarct size based on SPECT MPI and provides further insight by evaluating the influence of residual ischemia on this correlation. The presence of residual myocardial ischemia or development of new coronary lesions that cause ischemia is an important question during follow-up of survivors after STEMI. In the present study the correlation between infarct size assessed with SPECT MPI and LV GLS was in line with previous studies (Table 4).[5-10] Importantly, infarct size was assessed at 3 months after STEMI, and in addition, the presence of myocardial ischemia was assessed, allowing to investigate whether this correlation may differ between patients with and without ischemia.

In patients with an acute infarction, the follow-up may be complicated by the presence of stress-induced ischemia which is associated with a two- to fourfold increase in cardiac events compared to those without ischemia.[22] In the present study, 46% of the population had ischemia on SPECT MPI of which 26% moderate to severe ischemia (SDS≥4). Repetitive episodes of ischemia might result in LV dysfunction (chronically stunned myocardium).[23] Biering-Sørensen et al. demonstrated in 293 patients with clinically suspected coronary artery disease and preserved LVEF that patients with significant coronary artery disease (area stenosis ≥70% in ≥1 vessel on coronary angiography) had more impaired LV GLS compared with patients without significant coronary artery disease (-17.1±2.5% versus -18.8±2.6%, $P<0.001$).[24] LV GLS remained an independent associate of coronary artery disease after multivariate adjustment for baseline characteristics, exercise test, and conventional echocardiography (OR 1.25; $P=0.016$ per 1% decrease). In post-STEMI patients, the assessment of myocardial ischemia may be challenged by the presence of preexistent wall motion abnormalities.[25] LV segments with impaired longitudinal strain due to the presence of scar may influence the function of surrounding segments resulting in reduced function or hyperkinesia in the remote segments.[26] Accordingly, the correlation between LV GLS and infarct size assessed with SPECT MPI may not be straight forward, particularly, if residual ischemia of the remote and peripheral areas of the myocardial infarction is present. Some limitations should be acknowledged. First, this was a single-center, retrospective, observational evaluation. Second, infarct size was assessed with SPECT MPI which has less spatial resolution than LGE-MRI.[25]

Table 4. *Studies evaluating the correlation between left ventricular global longitudinal strain and infarct size in post-ST-elevation myocardial infarction patients. Only studies with at least 25 patients were considered.*

	Zhu et al.[5]	Sjoli et al.[9]	Gjesdal et al.[6]	Bière et al.[8]	Wang et al.[10]	Munk et al.[7]
No. Patients	*26*	*39*	*40*	*41*	*57*	*227*
Characteristics						
Age (years)	56±11	62±9	58±10	57±12	64±13	62±11
Hypertension	-	33%	-	16%	-	33%
Diabetes Mellitus	-	8%	-	8%	-	8%
Echocardiography						
Time post-STEMI	4 days	10±5 days	8.5±5.4 months	3.9±1.2 days	3-6 months	1 and 30 days
2D/3D	3D	2D	2D	2D	3D	2D
Technique for determination of infarct size	LGE-MRI	LGE-MRI	LGE-MRI	LGE-MRI	99Tc-sestamibi SPECT	99Tc-sestamibi SPECT
Time post-STEMI	4 days	6-23 months	8.5±5.4 months	90 days	3-6 months	30 days
Mean LV GLS (%)	<10% MIS: -16.6±2.79 10-30% MIS:-13.7±2.9 >30% MIS: -10.3±2.4	-15.6±4.6 (acute phase) -16.4±2.7 (after PCI)	<30g: -17.9±1.7 30-50g: -15.3±1.9 ≥50g: -11.2±3.2	-13.9±3.4	<30% MIS: -16.4±2.9 ≥30% MIS: -10.7±4.3	-14.8±4.1 (day 1) -16.8±3.4 (day 30)
Correlation of LV GLS and infarct size	r=0.86, P<0.01	r=0.76, P<0.0001	r=0.84, p<0.001	r=0.60, P<0.001	r=0.79, P<0.001	r=0.61,P<0.0001 (day 1) r=0.66,P<0.0001 (day 30)

2D/3D: 2-dimensional / 3-dimensional; LV GLS: left ventricular global longitudinal strain; MIS: myocardial infarct size; No: number; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

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Chapter 7

^{123}I-MIBG SPECT for Evaluation of Patients with Heart Failure

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Abstract

Heart failure (HF) is characterized by activation of the sympathetic cardiac nerves. The condition of cardiac sympathetic nerves can be evaluated by ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) imaging. Most cardiac ^{123}I-MIBG studies have relied on measurements from anterior planar images of the chest. However, it has become progressively more common to include single-photon emission computed tomography (SPECT) imaging in clinical and research protocols. This review examines recent trends in ^{123}I-MIBG SPECT imaging and evidence that provides the basis for increased use of the procedure in clinical management of patients with heart failure (HF). A particular area where ^{123}I-MIBG SPECT has been shown to be complementary to planar imaging in patients with HF in studies of coronary artery disease (CAD) after an acute myocardial infarction (MI). Moreover, ^{123}I-MIBG SPECT has been used in numerous studies to document regional denervation for arrhythmic event risk assessment. For better quantification of the size and severity of innervation abnormalities in ^{123}I-MIBG SPECT, programs and protocols specifically for ^{123}I have been developed. Also, the introduction of new solid-state cameras has created the potential for more rapid SPECT acquisitions or a reduction in radiopharmaceutical activity. Although positron-emission tomography (PET) imaging has superior quantitative capabilities, ^{123}I-MIBG SPECT is, for the foreseeable future the only widely available nuclear imaging method for assessing regional myocardial sympathetic innervation.

Introduction

Heart failure (HF) is characterized by activation of the sympathetic cardiac nerves. The condition of cardiac sympathetic nerves can be evaluated with ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG), which is a norepinephrine analog and therefore a tracer for sympathetic neuron integrity and function.[1] Most of the literature on the use of ^{123}I-MIBG imaging for evaluating patients with HF is based on measurements from anterior planar images of the chest, with cardiac uptake quantified in terms of the heart-to-mediastinum ratio (HMR) and the washout rate (WR) between early and late images.[2,3] However, given the conversion from planar to single-photon emission computed tomography (SPECT) techniques in clinical nuclear myocardial perfusion imaging (MPI) beginning in the 1980s, it is not surprising that ^{123}I-MIBG SPECT was also performed by some early adopters of the radiopharmaceutical.[4,5] Despite the challenges associated with performing ^{123}I-MIBG SPECT and interpreting the images in patients with severely reduced cardiac ^{123}I-MIBG uptake, it has become progressively more common for ^{123}I-MIBG SPECT imaging to be included in clinical and research protocols; in such settings, it is usually performed as part of one or more of the imaging sessions when planar images are acquired.[2]

Both qualitative and quantitative image reviews of ^{123}I-MIBG SPECT studies may be performed, to identify of focal areas of reduced uptake (similar to schemas used for the interpretation of MPI SPECT). Unfortunately, only small amounts of data from ^{123}I-MIBG SPECT images in patients without heart disease are available; most often, segmental count density expressed as a percentage of total myocardial count density is used to compare affected areas with least affected areas in patients.[6-8] Changes in relative uptake and absolute uptake between early and late SPECT images can be used to calculate parameters comparable to the planar washout rate.[9] In general, SPECT results have been used in the same way as planar data namely, to investigate the relationship between the quantitative value of ^{123}I-MIBG uptake and a specific outcome event, such as worsening of chronic HF, the occurrence of an arrhythmic event or cardiac death, or another quantitative parameter, such as a change in the left ventricular ejection fraction or the MPI defect score. Consistent with findings on planar imaging, patients with larger or more severe regional ^{123}I-MIBG SPECT defects usually have poorer outcomes.[10]

This review examines recent trends in ^{123}I-MIBG SPECT imaging and evidence that provides the basis for the increased use of the procedure in the clinical management of patients with HF. The focus of the article is primarily on work that has been done in the past 10-15 y, considering specifically how the technique can complement the established value of planar ^{123}I-MIBG imaging and provide unique insight into the risk of arrhytmia and the need for advanced therapies. Recent advances in imaging technology and quantitation methods are also briefly reviewed, as these represent the future for the clinical use of cardiac ^{123}I-MIBG SPECT.

^{123}I-MIBG SPECT complements planar imaging

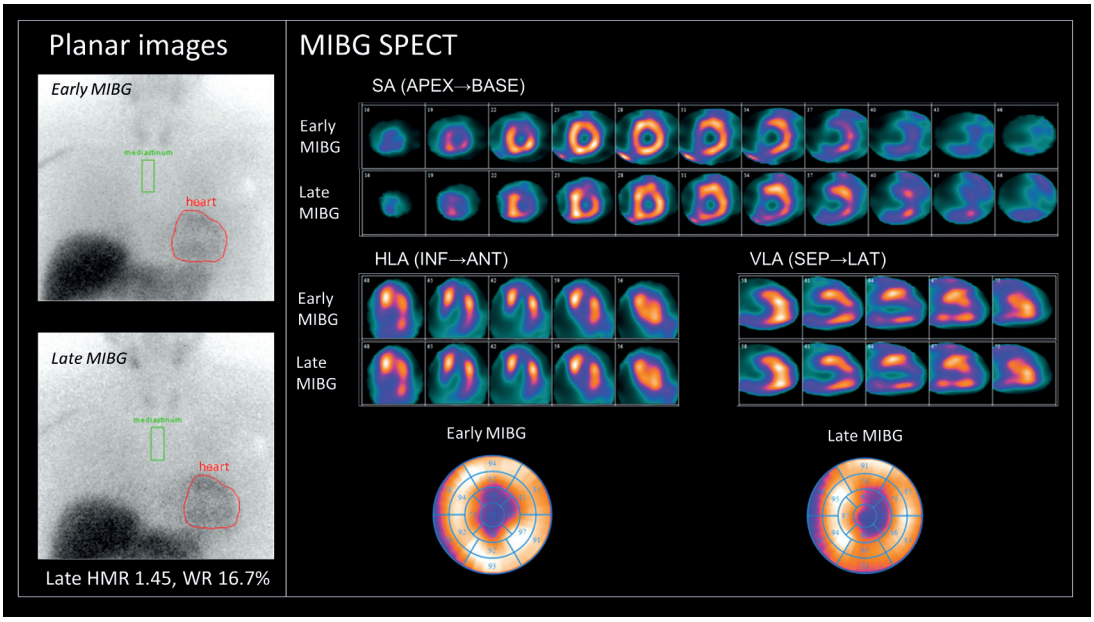
Several studies have examined the use of ^{123}I-MIBG imaging as a diagnostic and prognostic tool in patients with HF.[3,11] Although most of these studies relied primarily on planar imaging determinations of HMR and WR, some also included measurements from SPECT examinations because of the realization that SPECT may overcome the difficulties of planar imaging, including superposition of noncardiac structures and lack of segmental analysis (Figure 1). Many such ^{123}I-MIBG SPECT studies were performed by Kasama et al., who investigated the effects of a variety of HF medications on ^{123}I-MIBG cardiac uptake and clinical outcome, usually performing imaging before the initiation of a new medication and again after 6 months.[12-19] Early and late ^{123}I-MIBG SPECT images (acquired at 15 min and at 4 hours) were scored visually using 20- and 17-segment regional polar or bull's-eye maps. Additionally, segmental count data were used to calculate regional washout rates in some studies. The various randomized studies demonstrated statistically significant reductions in late ^{123}I-MIBG total defect scores after treatment with angiotensin-converting enzyme inhibitor (perindopril), angiotensin receptor blockers (valsartan, candesartan), a loop diuretic (torasemide) and aldosterone inhibitors (spironolactone). Similar results were obtained by other investigators, such as Somsen et al.[20] for enalapril, and Lotze et al.[21] and de Milliano et al.[22] for various beta blockers.

^{123}I-MIBG SPECT has been shown to be complementary to planar imaging in studies of coronary artery disease (CAD) after an acute myocardial infarction (MI).[23, 24] Viable but denervated myocardium has shown to be supersensitive to the effects of infused catecholamines,[25] which may provide a substrate for the genesis of ventricular arrhythmias. For this reason, results of ^{123}I-MIBG

SPECT and MPI SPECT are often compared to identifying segments with adrenergic/perfusion mismatch. As in MPI SPECT studies, the myocardium is usually subdivided into a number of segments (ranging from 5 to 20), and each location is scored for severity on scales from (0 to 3 or 0 to 4).

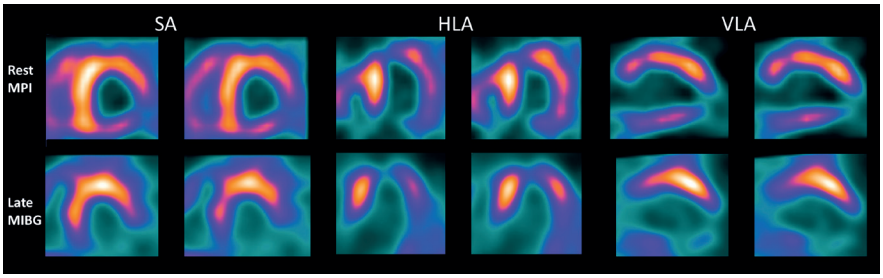
Three categories of ^{123}I-MIBG SPECT and MPI SPECT findings are commonly reported: both normal; both equivalently abnormal (matched defects); or ^{123}I-MIBG SPECT defect more severe than MPI defect (mismatched defect, as shown in Figure 2). A defect less severe on ^{123}I-MIBG SPECT than on MPI SPECT is rarely, if ever, observed. Mismatched defects may be subcategorized in terms of whether the area in question demonstrates ischemia on stress MPI or remains unchanged.

Figure 1. *^{123}I-MIBG SPECT complements planar imaging on segmental analysis.*



A 60 year old patient with planar and SPECT images in the short axis (SA), horizontal axis (HLA), vertical long axis (VLO) and bullseye of ^{123}I-metaiodobenzylguanidine (MIBG). There is a reduced late heart/mediastinum ratio (HMR) of 1.45, whereby MIBG SPECT demonstrates a fixed apical defect.

Figure 2. *Innervation/perfusion mismatch between ^{123}MIBG SPECT in comparison with rest myocardial perfusion imaging (MPI) with 99mTc-tetrofosmin.*



A 63 year old patient with ischemic cardiomyopathy with a large defect infero-postero-lateral expanding apical with on MIBG SPECT in comparison with rest MPI a more extended defect infero-lateral.

Most studies of ^{123}I-MIBG imaging in the patients after MI have compared defects on ^{123}I-MIBG SPECT with results on rest and stress MPI SPECT in order to assess the relationship between areas of infarction and denervation. Three small studies in which 58 patients were examined within 3 months after MI arrived at the joint conclusion that ^{123}I-MIBG defects were generally larger than those on MPI, whether determined from quantitative count-based assessments or semi-quantitative scoring of SPECT myocardial segments.[26-28] Given that sympathetic nerve fibers in the heart travel in the subepicardium parallel to the vascular structures and penetrate the underlying myocardium, it is conceivable that this difference in defect size, among others, is caused by the fact that neural tissue has a greater sensitivity to hypoxia than myocardial fibers and has longer recovery time.[29,30] More recent studies, such as those by Simoes et al.,[31] Marini et al.,[32] and Hayashi et al.,[33] confirmed the presence of denervated areas extending beyond the infarct borders and proposed associations with depolarization abnormalities, unappreciated myocardial necrosis, and long-term variability in induced ventricular tachyarrhythmias.

Interest has been shown in the potential for the global quantitation of ^{123}I-MIBG SPECT images to replace the planar HMR for diagnostic and prognostic purposes. An analysis of the ^{123}I-MIBG SPECT studies from the AdreView myocardial imaging for risk evaluation in heart failure (ADMIRE-HF) trial, which is a prospective trial evaluating ^{123}I-MIBG imaging for identifying patients who have HF and are most likely to experience cardiac

events, demonstrated that the SPECT HMR was equivalent to the planar HMR for discriminating between patients with HF and control subjects.[6,34] Additionally, the ability of ^{123}I-MIBG SPECT to provide regional information not available on planar images remains a driver for efforts to incorporate this procedure into assessments of patients with HF for arrhythmic risk.[35]

^{123}I-MIBG SPECT for arrhythmic event risk assesment

Better arrhythmic event risk assessment is necessary given that in the MADIT II trial only 23.5% of the 720 patients with HF and a prophylactic implantable cardioverter defibrillator (ICD) received antiarrhythmia device therapy for ventricular tachyarrhythmia.[36] Early research on experimentally denervated myocardium suggested that such regions were much more sensitive to norepinephrine infusion than normally innervated regions, a situation considered potentially proarrhythmic.[37] Over the subsequent decades, ^{123}I-MIBG SPECT was used in numerous studies to document such regional denervation and its association with naturally occurring or inducible ventricular arrhythmic events. The dominant observation was that the larger the extent of ^{123}I-MIBG SPECT abnormality, the higher the likelihood of ventricular tachyarrhythmia.[38-41]

Most investigators performing ^{123}I-MIBG SPECT studies had expected to find that arrhythmic event risk would increase with the size of the denervated area as well as the amount of innervation-perfusion mismatch, as reflected by paired ^{123}I-MIBG and MPI SPECT studies. Another expectation was that there would be a dividing point in ^{123}I-MIBG defect size between patients with "low risk" and patients with "high-risk" for arrhythmic events. In the small study by Arora et al.,[38] both mean ^{123}I-MIBG defect scores and the number of late mismatches were higher in the 10 patients who had experienced appropriate ICD discharges compared than in the 7 who had not. Patients who had ischemic heart disease and inducible ventricular tachycardia on electrophysiology testing had higher total ^{123}I-MIBG SPECT defect scores than patients who did not have inducible ventricular tachycardia, with a late total defect score threshold of 37, yielding a 77% sensitivity and a 75% specificity.[39] In the prospective study by Boogers et al.,[40] patients with an ICD and a late total defect score >26 were 10 times more likely to receive appropriate ICD therapy (cumulative 3-y event rate 52% vs. 5%, $p<0.01$). Interestingly, in the

latter 2 studies, ^{123}I-MIBG SPECT defect size was a significant predictor of arrhythmic events but not mismatch scores. In contrast, Marshall et al.[42] found differences in both the total ^{123}I-MIBG SPECT defect score (37.0 ± 9.4 versus 25.5 ± 7.7 ($p=0.001$)) and the mismatch score (18.5 ± 8.5 versus 8.4 ± 5.0 ($p<0.01$)) between patients with ICD firing and those without ICD firing. As in the study of Bax et al., a total ^{123}I-MIBG SPECT defect score ≥31 had a sensitivity of 78% and a specificity of 77%.

Recent evidence suggests that quantitative characterization of myocardial transition zones (between normal and infarcted or denervated myocardium) may supplement the more simple definition of innervation-perfusion mismatch. In a quantitative reanalysis of the MPI SPECT images that were interpreted visually in the study of Bax et al., [39] MPI scar extent, border zone extent, and ^{123}I-MIBG uptake in the border zone were analyzed; the best prediction accuracy for ventricular tachycardia (VT) inducibility was achieved with the last (area under the ROC = 0.78).[43] In a prospective study of 15 patients referred for ischemic VT ablation, 3D innervation models were derived from ^{123}I-MIBG SPECT examinations and registered to high-density voltage maps.[44] ^{123}I-MIBG innervation defects were ~2.5-fold larger than bipolar voltage-defined scars, all VT ablation sites were within areas of abnormal innervation, but 36% of successful ablation sites demonstrated normal voltages (>1.5mV). These studies strongly suggested that innovations in quantitative analysis techniques represent the future of ^{123}I-MIBG SPECT for identifying arrhythmic event risk and guiding therapy.

Studies have also raised questions about the relationship between ^{123}MIBG defect severity and arrhythmic event risk. Planar HMR data showed that the highest occurrence of arrhythmic events was seen in patients with HF and an intermediate reduction in uptake rather than the lowest values. In 2014, Verberne et al. presented the results of an informed interpretation of ^{123}I-MIBG and MPI SPECT studies from the ADMIRE-HF trial; the results showed that patients with HF and an intermediate severity of total defect scores (14-28 of a possible maximum of 68) had higher arrhythmic event rates than those with more severe defects.[45] As part of the same study, visual scoring of regions (anterior, inferior, septal, lateral, and apical) on ^{123}I-MIBG SPECT and MPI SPECT studies as normal, matched, or mismatched resulted in similar findings; patients with HF and 1 or 2 mismatched regions had the highest arrhythmic event rate.[46] In both of those analyses, the largest absolute number

of arrhythmic events was seen in patients with the most severe defects, but the highest proportion was seen in patients with intermediate-severity defects.

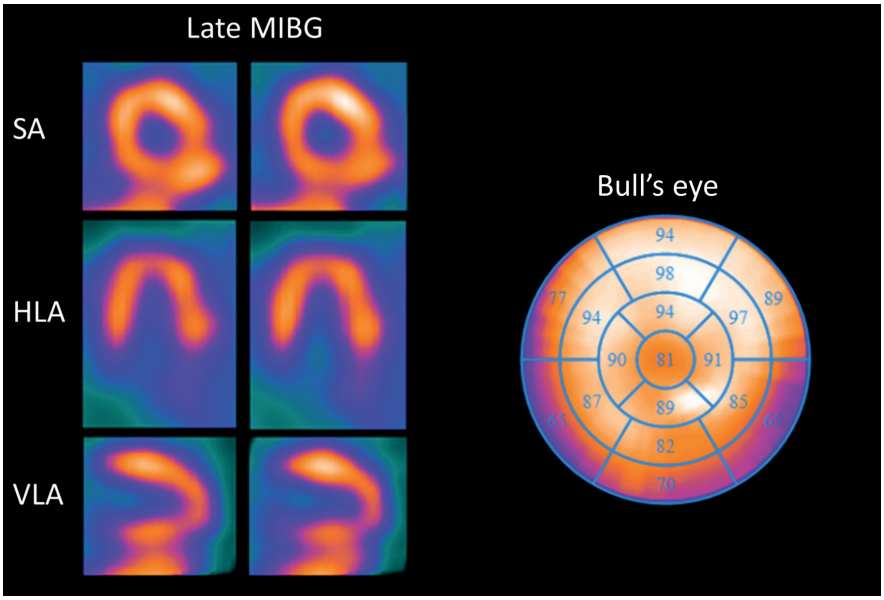
The aforementioned results attest to the mechanistic complexity of arrhythmia generation and support the conclusion that no single test can identify all at-risk patients with HF. Nevertheless, there is growing evidence that ^{123}I-MIBG SPECT imaging should be considered for the assessment of patients with HF for appropriate therapeutic interventions.

Advances in ^{123}MIBG SPECT quantitation

^{123}I-MIBG is internalized by neuroendocrine cells through the rapid energy-dependent uptake-1 mechanism,[47] reaching a relative plateau within a few minutes after injection. It is stored, unmetabolized, in the neurosecretory granules, resulting in a specific concentration unlike in cells of other tissues. Because of flow-limited uptake of the ^{123}I-MIBG tracer, retention measures are insensitive to low-to-moderate levels of regional denervation and decline only when nerve losses become fairly severe.[48]

Since the earliest investigations of ^{123}I-MIBG SPECT in cardiology, quantitation of the size and the severity of innervation abnormalities has been performed.[49] Initially, semiquantitative scoring from visual analysis, analogous to that used in MPI, was performed, as noted earlier for studies of patients after MI.[27,28] When quantitative bull's-eye mapping for MPI SPECT became readily available, it was also applied to ^{123}I-MIBG SPECT analysis.[23,50-52] However, because the quantitative programs were usually adapted from those developed for MPI SPECT, they did not take into account the unique physical properties of MIBG iodinated with ^{123}I, which affects image quality. These include the presence of a significant number of high-energy photons (1.1% yield of 529 keV g rays);[53] accumulation in the liver that overlaps the inferior wall (Figure 3); and scattering from the lung field to the lateral left ventricular wall,[54] as a result of which the normal cardiac ^{123}I-MIBG distribution includes relatively low uptake in the inferior wall,[55] which is more pronounced in the elderly. Therefore, in contrast to what is observed in PET examinations with ^{11}C-hydroxyephedrine and ^{18}F-fluoro-dopamine, the regional ^{123}I-MIBG uptake in the left ventricle is heterogeneous, in healthy subjects, as observed by Morozumi et al. and Yoshinaga et al.[56,57]

Figure 3. *^{123}I-MIBG SPECT image with accumulation in the liver which overlaps the inferior wall.*



^{123}MIBG SPECT images in the short axis (SA), horizontal axis (HLA), vertical long axis (VLO) and bull's eye with accumulation in the liver which overlaps the inferior wall and affects image quality.

More recently, programs and protocols have been developed specifically for ^{123}I-labeled compounds such as ^{123}I-MIBG. These have included the introduction of iterative reconstruction techniques with compensation for scatter and septal penetration[53,58,59] and use of volumetric analysis techniques.[60] The development of ^{123}I-MIBG databases of healthy subjects has also provided a more reliable means for quantifying the significance of reduced uptake in HF and other cardiology patients.[6]

The potential of improved ^{123}I-MIBG quantitation techniques has been explored in recent reevaluations of the large ^{123}I-MIBG SPECT imaging database from the ADMIRE-HF trial. Through the use of a variable reference threshold for pixel-based abnormalities based on the planar HMR, quantitative differences between ^{123}I-MIBG SPECT patterns in patients with ischemic and patients with non-ischemic HF could be reliably demonstrated with satisfactory reproducibility by both voxel- and region-based methods.[7,61] In a separate analysis, global denervation (≥9 abnormal ^{123}I-MIBG segments from the standard 17-segment map) was associated with the highest cardiac

mortality rates in both patients with ischemic and patients with non-ischemic HF patients, but further distinction was possible on the basis of MPI SPECT findings. In patients with ischemic HF, mortality risk was highest among those with 3-7 rest MPI segmental defects, whereas in patients with non-ischemic HF, the highest risk was associated with near normal rest MPI studies (0-3 segmental defects).[62]

Pellegrino et al. demonstrated excellent observer reproducibility of visual evaluation of ^{123}I-MIBG SPECT with a low-dose ^{123}I-MIBG protocol.[63] Nevertheless, it can be challenging to evaluate ^{123}I-MIBG SPECT studies visually, especially in patients with HF and a global reduction in uptake.[35] Automated quantitation of ^{123}I-MIBG SPECT studies offers the potential to overcome some of the limitations of visual image interpretation and improves the clinical utility of such studies for diagnosis and prognosis.

^{123}I-MIBG SPECT with solid-state cameras

The recent introduction of new solid-state cardiac nuclear cameras that provide 180-degree of imaging without the need for gantry rotation, improved collimator design, and optimized acquisition geometry with increased photon sensitivity and contrast resolution has created the potential for more rapid SPECT acquisitions or a reduction in radiopharmaceutical activity and thus a lower dose for patients.[64-66]

This technology also offers advantages for ^{123}I-MIBG SPECT imaging, including better energy discrimination and temporal resolution.[67] List-mode acquisition analogous to that used in PET presents an opportunity to obtain true dynamic SPECT data, which could provide new physiologic insights to enhance the information content of the examination.

Initial experiences with ^{123}I-MIBG SPECT imaging and solid-state cadmium-zinc-telluride (CZT) cameras have been promising. Patients with LV dysfunction were shown to have higher ^{123}I-MIBG summed defect scores than those with normal function.[68] Similar results were obtained when mechanical dyssynchrony on MPI SPECT was compared with ^{123}I-MIBG SPECT findings.[69]

Data on the in vivo myocardial kinetics of ^{123}I-MIBG are rare. Dynamic ^{123}I-MIBG SPECT has the potential for defining new quantitative parameters

as shown in early human experiments. Tinti et al. demonstrated the feasibility of dynamic 3-dimensional ^{123}I-MIBG kinetic analysis for providing additional information on cardiac innervation, particularly though the analysis of time-activity curves for ^{123}I-MIBG.[70] Also, in an experimental pig model myocardial peak uptake was observed earlier than had been previously described.[71]

Although the possibilities of dynamic ^{123}I-MIBG SPECT were initially explored with conventional rotating gamma cameras,[72] the clinical potential of this technique with CZT cameras likely will be established as the new solid-state camera technology matures and more users gain experience with it.

Comparison of SPECT and PET techniques

The superior quantitative capabilities of PET imaging make PET an attractive alternative to SPECT. However, unlike compounds such as ^{123}I-MIBG, which can be centrally manufactured and widely distributed commercially, most PET agents are labeled with short half-life isotopes such as ^{11}C and therefore are available only in facilities with an on-site cyclotron. Nevertheless, as a research tool, PET remains extremely valuable. The PET agent most analogous to ^{123}I-MIBG is meta-hydroxephedrine (mHED), as the uptake of both by sympathetic neurons is mediated by the norepinephrine transporter. However, in only a few studies has the cardiac uptake of ^{123}I-MIBG been directly compared with that of mHED.

In a study of rabbits injected with both ^{123}I-MIBG and mHED, similar reductions in uptake in denervated myocardium were observed.[73] However, pretreatment with the norepinephrine-depleting compound reserpine had a greater effect on mHED uptake than on ^{123}I-MIBG uptake, suggesting that the former might be more specific for intravesicular uptake than the latter. Luisi et al. showed that the relative retention of mHED was significantly greater than that of ^{123}I-MIBG in pigs, reflecting improved specificity as a result of less nonspecific uptake of the former tracer.[74] Rischpler et al. reported that the ^{131}I-MIBG uptake defect in rats matched the area of an earlier MI, whereas the mHED uptake defect was larger.[75] However, in a direct comparison of ^{123}I-MIBG SPECT and mHED PET in 21 patients with LV dysfunction, Matsunari et al. reported a high correlation between defect sizes in the 2 methods;[76] however, late ^{123}I-MIBG SPECT overestimated defect sizes in the inferior and septal regions, presumably because of image quality issues caused by adjacent liver activity.

Although the early development of an ^{18}F-labeled compound for PET imaging of sympathetic neurons is continuing,[77] for the foreseeable future ^{123}I-MIBG SPECT will remain the only widely available nuclear imaging method for assessing regional myocardial sympathetic innervation.

Conclusion

The shift from planar to SPECT techniques in ^{123}I-MIBG imaging has been slow in comparison with what occurred in clinical MPI 25-30 y ago. Nevertheless, the accumulation of evidence regarding the value of ^{123}I-MIBG SPECT results, along with improvements in imaging equipment and image processing techniques, should result in acceleration of the growth and clinical use of the technique in the coming years.

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MULTIMO
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DISEASE
PREVENT
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Chapter 8

Cardiac ^{123}I-MIBG imaging beyond Heart Failure: Potential Clinical Indications

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Dimitriu-Leen AC, Scholte AJHA.

Abstract

^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) imaging can visualize cardiac sympathetic innervation by providing (semi-)quantitative information on the myocardial sympathetic activity. Although there are lots of prognostic studies in patients with heart failure, clinical application of cardiac ^{123}I-MIBG outside Japan is still limited. However, the number of potential clinical indications for ^{123}I-MIBG imaging is growing as autonomic dysfunction is also present in other cardiac diseases.

The present review gives an overview of the potential clinical cardiac indications beyond heart failure of ^{123}I-MIBG imaging to evaluate the cardiac sympathetic activity. The focus of the manuscript is primarily based on studies that have been performed outside Japan.

Introduction

^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy enables visualization of cardiac sympathetic innervation by providing (semi-)quantitative information of the myocardial sympathetic activity.[1] From the early and late planar ^{123}I-MIBG images the heart-to-mediastinum (H/M) ratio can be obtained. This parameter represents the relative distribution of cardiac sympathetic nerve terminals and offers information about the neuronal function. In addition, the washout rate of the tracer between the early and late planar image can be gained providing information about the sympathetic drive. Furthermore, focal innervation defects can be detected with ^{123}I-MIBG single-photon emission computed tomography (SPECT).[2]

Cardiac ^{123}I-MIBG scintigraphy is a well-known technique for the determination of prognosis in patients with heart failure.[3] The late H/M ratio and washout rate appeared to be powerful predictors of survival and ventricular arrhythmias.[4] In addition, ^{123}I-MIBG imaging can be used to monitor the effect of medical therapy.[5] Therefore, the nuclear cardiology guidelines of the Japanese Circulation Society recommend cardiac ^{123}I-MIBG in heart failure patients for assessment of heart failure severity and prognosis.[6] Outside Japan the use of cardiac ^{123}I-MIBG scintigraphy is low in clinical practice since it has not been implemented in clinical guidelines.[7,8] In addition, there is a lack of standardization and validation of cardiac ^{123}I-MIBG imaging and post-processing procedures.[9] As well as the limited gains in cost-effectiveness and the long awaited FDA approval in the USA.[10] However, clinical research with ^{123}I-MIBG imaging is growing and the number of potential clinical indications is promising (as depicted in Table 1).[11,12] An obvious case whereby cardiac denervation is present and ^{123}I-MIBG imaging might give important information is after cardiac transplantation.[13] Moreover, autonomic dysfunction can also be present beyond heart failure for instance in patients after myocardial infarction,[14] with arrhythmias[15] and amyloidosis.[16] An area were ^{123}I-MIBG imaging provides additive information as well is for the evaluation of patients with cardiovascular risk factors such as diabetes mellitus (DM),[17] (resistant) hypertension,[18] and obesity.[19]

This review examines recent trends for potential clinical indications in the future for cardiac ^{123}I-MIBG imaging. The focus of the article is primarily on clinical studies that have been performed outside Japan.

Tabel 1. *List op (potential) clincial application of cardiac ^{123}I-MIBG imaging beyond heart failure.*

Clinical application of cardiac ^{123}I-MIBG imaging beyond heart failure	
Cardiac disease	
	Myocardial infarction
	Takotsubo cardiomyopathy
	Atrial fibrillation
	Post-heart transplantation
	Post-LVAD-implantation
Systemic disorders	
	Amyloidosis
	Diabetes mellitus
	Hypertension
Other	
	Obesity

Cardiac diseases beyond heart failure

Myocardial infarction

The autonomic function in patients after an acute myocardial infarction (AMI) can be disturbed since damaged myocardial tissue (scar) caused by prolonged ischemia and hypoxia results in denervated sympathetic fibers. Compared to normal innervated myocardium, denervated regions are more sensitive to norepinephrine and therefore of value in the risk assessment for arrhythmias.[20] The size of the denervated myocardium represented by the total ^{123}I-MIBG defect score correlates highly with the occurrence of ventricular arrhythmias resulting in appropriate ICD discharges.[21] Similarly, inducible ventricular arrhythmias during electrophysiology testing are correlated with larger total ^{123}I-MIBG defect scores.[22] In addition, the areas of myocardial autonomic denervation determined with ^{123}I-MIBG imaging often extent the infarct borders determined on myocardial perfusion imaging (MPI) SPECT.[14,23] This so called innervation / perfusion mismatch is due to the fact that neural tissue is more sensitive to hypoxia compared to myocardial fibers and the recovery time in neural tissue is increased.[24,25] The areas with innervation / perfusion mismatch are at increased risk of ventricular arrhythmias.[26] However, there is an on-going debate whether the size of ^{123}I-MIBG innerva-

tion / perfusion mismatch on top of the size of innervation defect is associated with more ventricular arrhythmias since results are conflicting.[26-28]

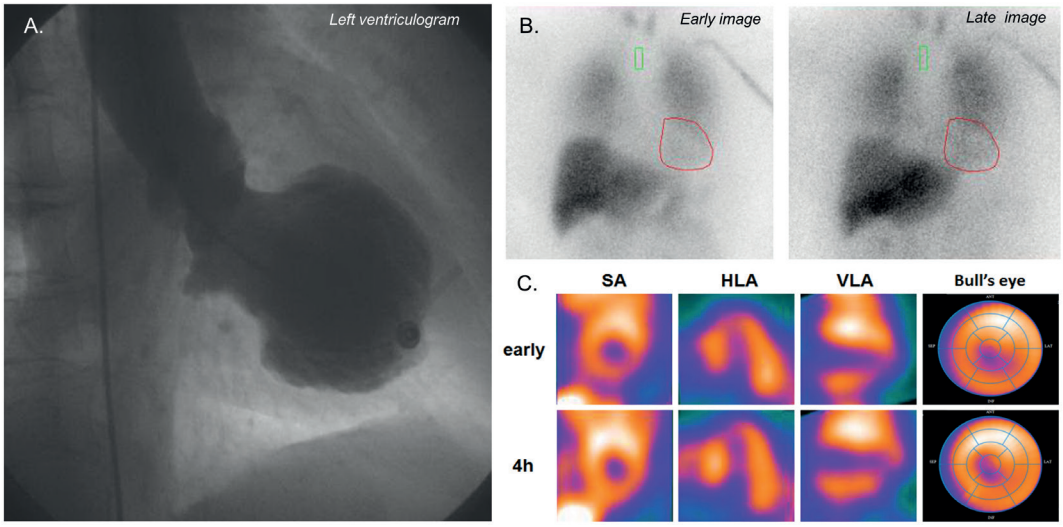
Another possible consequence of cardiac sympathetic denervation in post-AMI patients is a disturbance in the nocturnal blood pressure drop.[29] The exact underlying mechanism of this disturbance is not yet fully elucidated. However, acknowledged is the fact that the sympathetic activity is of importance as reports have demonstrated that the intrinsic catecholamine levels are strongly related to systemic blood pressure course.[30] Therefore, cardiac dysinnervation reflected by lower H/M ratio is associated with dysregulation of blood pressure variation with significantly worse prognosis in patients post-AMI evidenced by higher rates of all-cause death, myocardial infarction, coronary revascularization, and stroke.[31]

Takotsubo cardiomyopathy

The clinical presentation of patients with a Takotsubo cardiomyopathy resembles AMI. However, in contrast to an AMI, no significant coronary lesions or thrombi are found on invasive coronary angiography. There are different pathophysiological hypothesis explaining the exact mechanism of a Takotsubo cardiomyopathy.[32,33] The two main hypothesis are that Takotsubo cardiomyopathy is caused by a stress-induced neurohormonal event affecting the coronary microcirculation or by undetected spasm, and / or thrombotic epicardial artery occlusion.[32,33] To diagnose Takotsubo cardiomyopathy, ^{123}I-MIBG imaging might be helpful since regional myocardial uptake of the radiotracer is reduced in the hypokinetic / akinetic left ventricle segments (depicted in Figure 1).[34] However, summarized data from 22 reviewed reports of 112 patients with Takotsubo cardiomyopathy who underwent ^{123}I-MIBG scintigraphy demonstrated that the first ^{123}I-MIBG scan was usually performed 1 to 2 weeks after the admission suggesting that this technique did not contribute to the diagnostic process.[34] Though, investigation with ^{123}I-MIBG during the first day has to be performed to determine which abnormalities are already shown direct after admission and what the exact value of ^{123}I-MIBG scintigraphy will be in the diagnostic process.

In addition, Cimarelli et al. demonstrated in a case report that patients with a Takotsubo cardiomyopathy revealed a similar pattern of ^{123}I-MIBG and ^{18}F-FDG uptake underlying a relation between cardiac sympathetic function and insulin mediated glucose cellular intake and metabolism.[35]

Figure 1. *^{123}I-MIBG scintigraphy in a patient with Takotsubo cardiomyopathy.*



A female patient presenting with typical chest pain without significant coronary artery disease on coronary agiography with on left ventriculogram (A.) a typical contraction pattern of the left ventricle suspected for Takotsubo cardiomyopathy. Additionally, on early and late planar ^{123}I-MIBG image (B.) a decreased H/M ratio (1.68 and 1.46 respectively) and on SPECT ^{123}I-MIBG (C.) reduced accumulation apical expanded to the inferior wall.

Atrial fibrillation

Activation of the autonomic nervous system plays an important role in the initiation and maintenance of atrial tachycardia as it induces various atrial electrophysiological changes with as result increased risk for atrial tachyarrhythmias, such as atrial fibrillation and atrial tachycardia.[15]

In Japan, small studies have demonstrated the value of ^{123}I-MIBG imaging in patients with atrial fibrillation.[36-38] In patients with idiopathic paroxysmal atrial fibrillation a lower H/M ratio was associated with vascular events (36) and the occurrence of permanent atrial fibrillation.[37] In addition, in patients with atrial fibrillation treated with a Maze procedure an increase in denervation occurred in the early stage after the procedure.[38] However, after 1 year significant reinnervation of those areas occurred.

Additionally, Wenning et al. demonstrated in 16 patients who underwent pulmonary vein isolation that new innervation deficits demonstrated on ^{123}I-MIBG SPECT images were associated with atrial fibrillation relapses.[39]

Amyloidosis

In primary and familial amyloidosis, cardiac involvement is frequently manifest.[40] However, the diagnosis is often difficult.[41] To ease the diagnosis of cardiac amyloidosis ^{123}I-MIBG can be used, because it indirectly visualizes the effect of myocardial depositions of amyloid by evaluating the occurrence of sympathetic nerve destruction.[16,42] In patients with biopsy-proven systemic amyloidosis echocardiographic signs of amyloidosis are associated with a lower H/M ratio and higher washout rate.[43] Moreover, results suggest that ^{123}I-MIBG imaging detects cardiac amyloid earlier than echocardiography.[44] Therefore, it may play a pivotal role in the early detection of cardiac involvement of amyloidosis. This is of importance since current therapies (including liver transplantation) limit disease progression but not amyloid depositions. Consequently, the H/M ratio does not improve after liver transplantation in patients with cardiac amyloidosis.[45]

In addition, ^{123}I-MIBG imaging can be useful as a prognostic marker. In patients with amyloidosis with a V30M transthyretin mutation, Coutinho et al. demonstrated that the late H/M ratio was independent associated with all-cause mortality.[46] As a consequence, the five-year mortality risk in patients with a late H/M ratio <1.60 was 6-fold higher compared with patients with a late H/M ratio ≥ 1.60.

Cardiovascular risk factors

Diabetes Mellitus

The prevalence of DM is increasing in the western world, mainly consisting of type 2 DM.[47] Several studies have examined the use of ^{123}I-MIBG imaging as a diagnostic and prognostic tool in patients with type 1 and 2 DM.[17,48,49] DM is often complicated by diabetic neuropathy affecting different parts of the peripheral nervous system including the autonomic nerve fibres innervating the heart.[50] This so called cardiovascular autonomic neuropathy (CAN) is one of the most severe complications of DM; it causes abnormalities in heart rate regulation and impairs vascular dynamics resulting in an increased risk of silent ischemia, life-threatening arrhythmias and sudden cardiac death.[50] Hattori et al. demonstrated that in an early stage sympathetic impairment on ^{123}I-MIBG SPECT was mainly localized in the inferior wall, while global uptake determined on planar images remained within the normal range.[51] However, gradually in a more advanced stage of CAN the adjacent segments were as well affected. Given that CAN is reversible if treated in an early stage,

early evaluation to detect regional denervation areas with ^{123}I-MIBG SPECT might be of value to achieve a better prognosis.

Non-insulin dependent DM appears to be more frequently related with ^{123}I-MIBG uptake impairment compared with insulin dependent DM. However, sympathetic myocardial dysinnervation is more common in patients with insulin-dependent DM than initially thought.[49] Instead of measuring heart rate variability, ^{123}I-MIBG imaging is a more precise method to investigate the presence of CAN. This was demonstrated in a cohort of asymptomatic patients with type 2 DM with normal myocardial perfusion the prevalence of CAN diagnosed with ^{123}I-MIBG scintigraphy was much higher than by evaluation with heart rate variability, 58% versus 27%, respectively.[17]

In addition, in patients with heart failure and DM the H/M ratio is significantly lower than in patients without DM.[48,52] Furthermore, patients with heart failure and DM with a H/M ratio <1.6 are at 3-fold higher 2-years risk of heart failure progression compared with patients with a late H/M ratio ≥1.6.[52]

Resistant hypertension

If the blood pressure remains too high regardless of three antihypertensive medications of different classes or controlled with four or more agents, and secondary hypertension is excluded, resistant hypertension should be considered.[53] It is important to treat resistant hypertension since it is a powerful predictor for cardiovascular morbidity and mortality. The sympathetic innervation of the kidney plays an important role in the pathophysiology of hypertension since efferent renal sympathetic outflow stimulates renin release, increases tubular sodium reabsorption and reduces renal blood flow.[54] In addition, increased afferent renal signals stimulate central sympathetic outflow resulting in neurogenic hypertension. Investigations have suggested that renal artery sympathetic denervation might reduce the sympathetic overdrive and thereby lower the blood pressure.[55] The effect of renal artery sympathetic denervation on the cardiac sympathetic overdrive can be assessed with ^{123}I-MIBG imaging. Studies demonstrated an increase in H/M ratio and decrease in washout rate, independently of blood pressure changes.[18,56] This improvement in cardiac innervation is of importance since studies have demonstrated controversial results of the effect of renal denervation on the blood pressure. Therefore, ^{123}I-MIBG imaging has the potential to evaluate the effect of renal denervation on arrhythmias and heart failure.[18,56] However, in contrast to above studies van Brussel et al. demonstrated no reduction in sympathetic activity on cardiac level in 16 patients with resistance hypertension who underwent bilateral renal artery sympathetic denervation.[57]

Therefore, the precise role in renal denervation needs to be further evaluated in larger studies.

Obesity

Obese patients are at high risk for cardiovascular events. To fight obesity, activation of brown adipose tissue (BAT) is a new treatment target as it increases energy consumption and thereby inducement of weight loss. ^{18}F-FDG PET/CT is a common imaging tool to evaluate therapies targeting BAT activity.[58] However, ^{123}I-MIBG imaging might also be indicated since BAT is activated mainly by adrenergic receptors. The increased number of adrenergic receptors on BAT visualized by ^{123}I-MIBG allows discrimination between brown and white adipose tissue since white tissue has only a limited number of adrenergic receptors. Okuyama et al. demonstrated in rats that ^{123}I-MIBG and ^{125}I-MIBG accumulates in BAT and not in white adipose tissue.[19] In line with previous study, Admiraal et al. demonstrated in 10 healthy Caucasian men that ^{123}I-MIBG SPECT/CT compared with ^{18}F-FDG PET/CT classified the same anatomic regions as active BAT.[59] Therefore, ^{123}I-MIBG SPECT/CT is indicated to visualize and quantify sympathetic stimulation of BAT.

However, the activity of sympathetic drive and BAT visualized by ^{123}I-MIBG SPECT/CT is age-dependent.[60] In contrast, between lean and obese patients the visualized BAT volume did not differ in volume suggesting that ^{123}I-MIBG SPECT/CT is capable of detecting the sympathetic nervous system BAT activity in both patient groups.

Evaluation of chemotherapy related cardiotoxicity

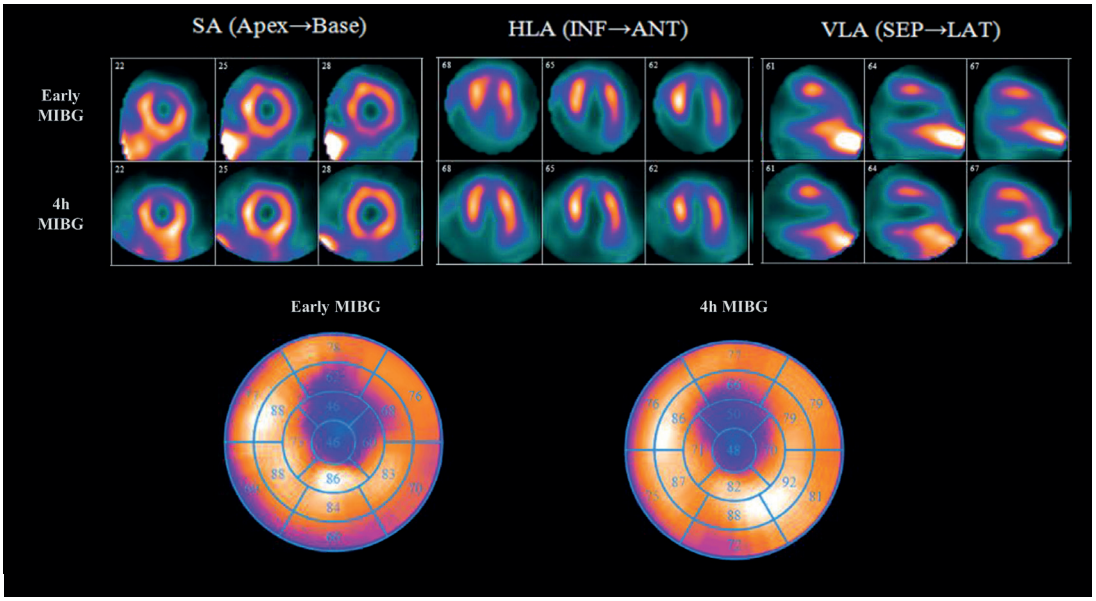
The survival rates in patients with cancer have increased tremendously over the last years because of improved therapeutic options. However, by prolonging life cardiologic side effects from treatments have become more clear.[61] One of the best known cardiotoxic agent is anthracycline which causes dose-dependent permanent damage at cellular level with as the most frequent and serious side effect the onset of heart failure by reducing left ventricular ejection fraction (LVEF). Although dose reduction limits the cardiotoxicity, cardiologic evaluation around cancer treatment is necessary since decline in LVEF still occurs. Experts state that evaluation of the LVEF is the cornerstone in the cardiac imaging assessment.[62] However, ^{123}I-MIBG imaging might be a novel approach in the early evaluation of cardiotoxicity.[63] Early investiga-

tion by Wagasugi et al. suggest that in the early phase after chemotherapy the evaluation of cardio toxic effects with ^{123}I-MIBG is more sensitive than LVEF since ^{123}I-MIBG accumulation in the heart shows a greater and more linear dose-dependent decrease than LVEF after doxorubicin therapy.[64]

However, not only patients treated with anthracyclines should be evaluated with ^{123}I-MIBG since the novel agent monoclonal antibody trastuzumab affects the heart as well by inducing transient reversible myocyte dysfunction independent of dose (as demonstrated in Figure 2).[65]

^{123}I-MIBG parameters might indicate in patients treated with trastuzumab with an affected LVEF whether recovery of the LVEF occurs during follow-up.[66] Stokkel et al. suggested in a pilot study that ^{123}I-MIBG scintigraphy might indicate whether recovery of LVEF will occur.[66]

Figure 2. *Effects of trastuzumab on sympathic activity.*



A 69-year old-patient treated with trastuzumab (Herceptin®) due to breast carcinoma with on ^{123}I-MIBG SPECT a innervation defect in the anterior and apical region.

Heart transplantation and left ventricular assist device implantation

Complete denervation of the allograft occurs after heart transplantation. In some patients the catecholamine storage capacity is regained which is associated with improved response of the heart rate and contractile function to exercise.[67] However, this is a slow process that takes often more than 1 year up to even 12 years and can be demonstrated by ^{123}I-MIBG imaging.[13,68] In addition, patients with idiopathic cardiomyopathy are less likely to re-gain innervation compared to other aetiologies of congestive heart failure, as well as in patients with DM.[69]

Patients pending on or non-eligible for a heart transplantation can nowadays be treated with a left ventricular assist device (LVAD) to reduce mortality and improve quality of life. To evaluate the effects of LVAD on cardiac sympathetic innervation ^{123}I-MIBG imaging has demonstrated that after LVAD implantation the early and late H/M ratio increases and the washout rate decreases.[70,71]

Conclusion

This review provides an overview of the potential increasing number of clinical indications of cardiac ^{123}I-MIBG imaging besides heart failure in the last few years.

However, first cardiac ^{123}I-MIBG has to be implemented in heart failure guidelines outside Japan, before other potential indications will. Until then other indications beyond heart failure will stay pre-clinical.

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MULTIM
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Chapter 9

The Impact of Acquisition Time of Planar Cardiac ^{123}I-MIBG Imaging on the Late Heart-To-Mediastinum Ratio

Eur J Nucl Med Mol Imaging 2016;43:326-332

Dimitriu-Leen AC, Gimelli A, al Younis I, Veltman CE, Verberne HJ, Wolterbeek R, Zandbergen-Harlaar S, Bax JJ, Scholte AJHA.

Abstract

Purpose. The aim of this study was to investigate whether performing the late cardiac ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) scan earlier than 4 hours post-injection (pi) has relevant impact on the late heart-to-mediastinum ratio (H/M ratio) in patients with heart failure (HF).

Methods. Forty-nine patients with HF (median left ventricular ejection fraction of 31%, 51% ischemic HF) referred for cardiac ^{123}I-MIBG scintigraphy were scanned at 15 minutes (early) pi and at 1, 2, 3 and 4 hours (late) pi of ^{123}I-MIBG. Late H/M ratios were calculated and evaluated using a linear mixed model with the mean late H/M ratio at 4 hours pi as a reference. A difference in late H/M ratios of more than 0.10 between the different acquisition times in comparison with the late H/M ratio at 4 hours pi was considered as clinically relevant.

Results. Statistically significant mean differences were observed between the late H/M ratios at 1, 2 and 3 hours pi compared with the late H/M ratio at 4 hours pi (0.09, 0.05 and 0.02, respectively). However, the mean differences did not exceed the cut-off value of 0.10. On an individual patient level, compared to the late H/M ratio at 4 hours pi, the late H/M ratios at 1, 2 and 3 hours pi differed more than 0.10 in 24 (50%), 9 (19%) and 2 (4%) patients, respectively.

Conclusions. Variation in acquisition time of ^{123}I-MIBG between 2 and 4 hours pi does not lead to a clinically significant change in the late H/M ratio. An earlier acquisition time seems to be justified and may warrant a more time-efficient cardiac ^{123}I-MIBG imaging protocol.

Introduction

Heart failure (HF) is an increasing healthcare problem in the Western world.[1] Among other features, the pathophysiology of HF is characterized by a deregulated sympathetic nervous system.[2] ^{123}Iodinemetaiodobenzylguanidine (^{123}I-MIBG) imaging is able to visualize cardiac sympathetic innervation by providing (semi-)quantitative information on the myocardial sympathetic activity.[3] Several studies have reported that cardiac ^{123}I-MIBG uptake provides unique information for predicting prognosis and evaluating therapeutic effects in patients with HF.[4-7] The semi-quantitative parameter that is most used to analyse cardiac ^{123}I-MIBG uptake is the heart-to-mediastinum ratio (H/M ratio) of the late planar image. The reported acquisition time for this so-called "late" scan varies considerably, but it is recommended 4 hours after injection of ^{123}I-MIBG.[8] A shorter time interval between the injection of ^{123}I-MIBG and the late scan reduces waiting time and may facilitate clinical use. However, only a few studies have investigated the impact of variation in acquisition time after ^{123}I-MIBG administration on the late H/M ratio.[9, 10] Therefore, the aim of this study was to investigate whether performing the late scan earlier than 4 hours post-injection (pi) has relevant impact on the late H/M ratio in patients with HF.

Materials and methods

Patients

Fifty patients with HF from 2 centres (Leiden, the Netherlands and Pisa, Italy), clinically referred for cardiac ^{123}I-MIBG scintigraphy between 2012 and 2015 were included. The inclusion criteria were symptoms of HF New York Heart Association functional class II-IV and age between 18 and 74 years. Patients with severe shortness of breath who were unable to lie flat for several times under a gamma camera were excluded from this study. All patients were treated according to the European Society of Cardiology guidelines for the diagnosis and management of HF and therefore received optimal pharmacological therapy, revascularization and implantable defibrillator with or without cardiac resynchronization therapy (CRT) device when appropriate.[11] The study complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Leiden University Medical Center. Written informed consent was obtained from all patients.

^{123}I-MIBG data acquisition

After thyroid blockade according to the local protocol and a resting period of 30 minutes, 185 MBq of ^{123}I-MIBG (AdreView; GE Healthcare, Princeton NJ, USA) was administrated as an intravenous bolus. Afterwards, ^{123}I-MIBG planar imaging was performed in the supine position five times pi; the early acquisition was performed 15 minutes pi and the late acquisitions were performed at 1, 2, 3 and 4 hours pi. Planar images were acquired in the anterior view for 10 minutes with dual head gamma cameras, a Siemens ECAM (Pisa, Italy) or a Toshiba GCA 7200/PI (Leiden, the Netherlands), and stored in a 256x256 matrix. All camera heads were provided with low-energy high-resolution collimators and the images were obtained with a 15% energy window centred at the 159 keV photopeak of ^{123}I.

Planar ^{123}I-MIBG image analysis

All planar ^{123}I-MIBG images were transferred to the Leiden University Medical Center for a centralized analysis. The images were semi-quantitatively analysed by calculating the H/M ratio using dedicated post-processing software on a Syngo-MI workstation (Siemens Medical Solutions, Malvern, PA). Manually a polygonal region-of-interest (ROI) was drawn over the myocardium including the left cavity and a rectangular ROI was placed upon the upper half of the mediastinum using the following anatomical landmarks: the lung apex as upper border, the upper cardiac border and the medial contours of the lungs. The H/M ratio was calculated by dividing the mean count density (i.e. counts/pixel) within the cardiac ROI by the mean count density in the mediastinal ROI. The washout rate was expressed as a percentage of decrease in myocardial counts between early and late planar images with correction for background and physical decay of ^{123}I. For this calculation the following formula was used: $WR_{BKG\ corrected} = [(H_e\text{-}M_e)\text{-}(H_l\text{-}M_l \times {}^{123}\text{I decay correction})]/(H_e\text{-}M_e) \times 100$.[8] In this formula H represents the mean count density in the cardiac ROI and M represents the mean count density in the mediastinal ROI in the early (e) and (l) late images.

Statistical analysis

Normally distributed variables were expressed as mean ± standard deviation, and non-normally distributed variables as median and interquartile range (IQR). Categorical variables were given as absolute values and percentages. Patient characteristics and ^{123}I-MIBG scintigraphy results of subgroup analyses were compared with the independent sample t-test, the Mann-Whit-

ney U test or the chi square test when appropriate. The late H/M ratios at 1, 2 and 3 hours pi were compared with the late H/M ratio at 4 hours pi with a linear mixed model with a given fixed factor time. A mean difference in late H/M ratio of more than 0.10 between the (mean) different H/M ratios at 1, 2 and 3 hours pi and the (mean) late H/M at 4 hours pi was considered clinically relevant. This was assessed by evaluating whether the 95%-confidence intervals (95% CI) for the real differences in means of the late H/M ratios at 1, 2 and 3 hours pi respectively compared with the late H/M ratio at 4 hours pi included the value 0.1. In the subgroup analysis, the influence of left ventricular ejection fraction on the differences in late H/M ratios between the ischemic and non-ischemic HF groups at 1, 2, 3 and 4 hours pi was assessed by performing multivariate logistic regression analyses including H/M ratio and left ventricular ejection fraction. The washout rates between 15 minutes and 1, 2 and 3 hours pi were compared with the washout rate between 15 minutes and 4 hours pi with a linear mixed model with a given fixed factor time. A paired t-test power analysis demonstrated that a sample size of 49 patients achieved 90% power to reject the null hypothesis that the test and standard are equivalent, thereby assuming an absolute difference of more than 0.10 with an estimated standard deviation of 0.20 with a significance level (alpha) of 0.01670. A two-sided P value <0.05 was considered statistically significant. All analyses were performed with SPSS software (Version 22.0, SPSS IBM Corp., Armonk, NY, USA).

Results

Patients

The study population comprised 49 patients with HF, because 1 patient withdrew his informed consent after the examination. The patient characteristics of the study population are depicted in Table 1. Seventy-six percent (37/49) of the total study population was male with a mean age of 64±9 years. The aetiology of HF was ischemic in 51% (25/49) of the patients. Patients with ischemic HF had a statistically significantly lower left ventricular ejection fraction compared with patients with non-ischemic HF, 28% (IQR 23-35) versus 33% (IQR 29-40) (P=0.04), respectively and antiplatelet or oral anticoagulant therapy was more frequent at 96% (24/25) versus 75% (18/24) (P=0.04), respectively.

Table 1. *Baseline characteristics of the study population (n=49)*

Patient characteristic	Total group (N=49)	Patient subgroup		
		Ischemic HF (N=25)	Non-ischemic HF (N=24)	P-value
Age (years)	64±9	66±9	62±8	0.08
Sex (male)	37 (76%)	21 (84%)	16 (67%)	0.16
Height (cm)	176±9	175±8	176±10	0.73
Weight (kg)	85±14	84±13	87±14	0.36
Cardiovascular risk factors				
Diabetes Mellitus*	8 (16%)	4 (16%)	4 (17%)	0.95
Obesity, BMI ≥ 30 (kg/m²)	7 (14%)	2 (8%)	5 (21%)	0.20
Family history of CVD†	19 (39%)	9 (36%)	10 (42%)	0.68
Hypercholesterolemia‡	27 (55%)	16 (64%)	11 (46%)	0.20
Hypertension§	30 (61%)	13 (52%)	17 (71%)	0.18
Current smoker	8 (16%)	4 (16%)	4 (17%)	0.95
Ejection fraction (%)	31 (IQR 25-38)	28 (IQR 23-35)	33 (IQR 29-40)	**0.04**
CRT-D / ICD therapy	31 (63%)	17 (68%)	14 (58%)	0.48
Medication				
ACE-/AT II-inhibitor	45 (92%)	23 (92%)	22 (92%)	0.97
Beta blocker	39 (80%)	20 (80%)	19 (79%)	0.94
Calcium antagonist	3 (6%)	2 (8%)	1 (4%)	0.58
Lipid-lowering agent	35 (71%)	20 (80%)	15 (63%)	0.18
Antiplatelet/OAC therapy	42 (86%)	24 (96%)	18 (75%)	**0.04**
Diuretics	38 (78%)	22 (88%)	16 (67%)	
Oral antidiabetics	8 (16%)	4 (16%)	4 (17%)	0.95
Insulin	3 (6%)	1 (4%)	2 (8%)	0.53
Nitrates	3 (6%)	3 (12%)	0 (0%)	0.08
NYHA class				0.28
I	11 (22.45%)	7 (28.0%)	4 (16.7%)	
II	27 (55.1%)	11 (44.0%)	16 (66.6%)	
III	11 (22.45%)	7 (28.0%)	4 (16.7%)	
NT-proBNP (pg/L)	771 (IQR 428-1264)	900 (IQR 451-1487)	716 (IQR 331-1244)	0.34

ACE: angiotensin converting enzyme inhibitor; AT-II: angiotensin-II; BMI: Body Mass Index, CRT-D: cardiac resynchronization therapy defibrillator; CVD: cardiovascular disease; HF: heart failure; ICD: implantable cardioverter defibrillator; IQR: interquartile range; NT-proBNP: N-terminal pro-brain natriuretic peptide; *NYHA: New York Heart Association; OAC: oral anticoagulant.*

* *Self-reported history of Diabetes Mellitus and/or treatment with antidiabetics,*

† *presence of coronary artery disease in first-degree family members at age <55 years in men and <65 years in women,*

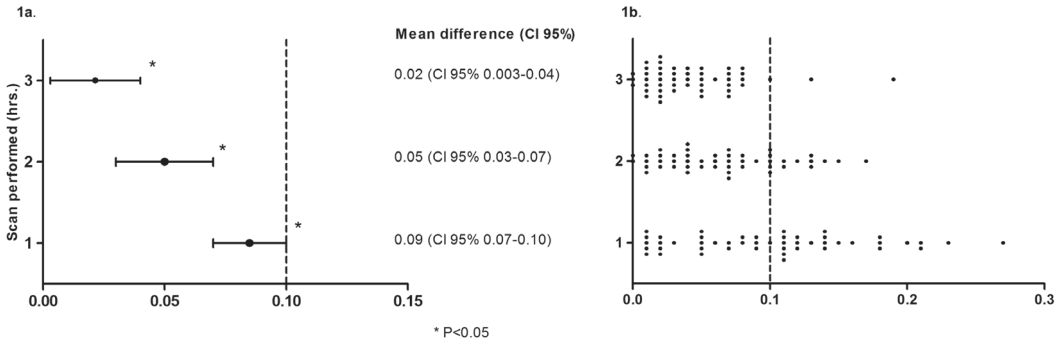
‡ *Self-reported history of hypercholesterolemia and/or treatment with lipid-lowering drugs,*

§ *Self-reported history of hypertension and/or use of antihypertensive medication, or a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.*

Planar ^{123}I-MIBG image analysis

The results of the planar ^{123}I-MIBG image analysis are shown in Table 2. Of the 49 patients, 1 patient did not have an acquisition 4 hours pi. In the total study population the late H/M ratio was 1.60±0.18 at 1 hour, 1.56±0.19 at 2 hours pi and 1.53±0.19 at 3 hours pi and differed all significantly from the late H/M ratio of 1.52±0.20 at 4 hours pi (P <0.001, P<0.001 and P=0.02, respectively). However, none of the mean differences between the late H/M ratios at 1, 2 and 3 hours pi exceeded the predefined clinically relevant 0.10 difference with the late H/M ratio at 4 hours pi (Figure 1a). An example of a patient with only small differences between the late H/M ratios at 1, 2 and 3 hours pi compared with the late H/M ratio at 4 hours pi is depicted in Figure 2. On an individual patient level, compared to the late H/M ratio at 4 hours pi, the late H/M ratios at 1, 2 and 3 hours pi differed more than 0.10 in 24 (50%), 9 (19%) and 2 (4%) patients, respectively (Figure 1b).

Figure 1. *Mean differences (1a.) and absolute differences of each individual patient in the H/M ratios at 1, 2 and 3 hours pi in comparison with H/M ratio at 4 hours pi.*



1. The mean difference with 95% CI of H/M ratios of late ^{123}I-MIBG images with acquisition at 1, 2 and 3 hours pi in comparison with the H/M ratio of the late ^{123}I-MIBG image at 4 hours pi analysed with a linear mixed model (1a.). Each dot represents an absolute difference of each individual patient in the late H/M ratios at 1, 2 and 3 hours pi compared with H/M ratio at 4 hours pi (1b.). A mean difference in H/M ratio of more than 0.10 between the different acquisition times in comparison with the late H/M ratio at 4 hours pi was considered clinically relevant.
CI: confidence interval; hrs: hours; H/M ratio: heart-to-mediastinum ratio; pi: post-injection.

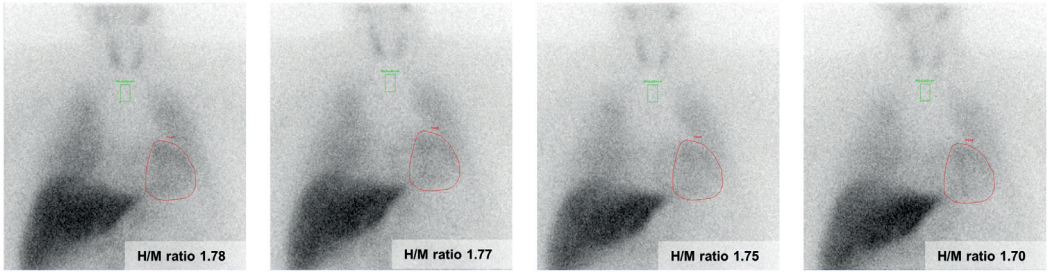
Table 2. *^{123}I-MIBG scintigraphy results*

MIBG scintigraphy	Total group (n=49)	Patient subgroup		
		Ischemic HF (n=25)	Non-ischemic HF (n=24)	P-value
Actual acquisition time after injection (in minutes)				
Early scan	15 (IQR 13-19)	15 (IQR 13-22)	14 (IQR12-17)	0.08
Late scan 1H	66 (IQR 62-71)	69 (IQR 64-73)	64 (IQR 59-67)	0.01
Late scan 2H	118 (IQR 115-123)	119 (IQR 116-123)	117 (IQR 114-122)	0.26
Late scan 3H	178 (IQR 176-182)	179 (IQR 176-182)	177 (IQR 174-181)	0.17
Late scan 4H	239 (IQR 236-245)	238 (IQR 236-246)	240 (IQR 236-245)	0.70
Heart/mediastinum ratio				
Early scan	1.60±0.15	1.55±0.15	1.64±0.14	0.03
Late scan 1H	1.60±0.18	1.54±0.16	1.66±0.18	0.02
Late scan 2H	1.56±0.19	1.51±0.17	1.61±0.21	0.09
Late scan 3H	1.53±0.19	1.47±0.16	1.59±0.20	0.03
Late scan 4H	1.52±0.20	1.46±0.17	1.58±0.21	0.03
Washout rate (%)				
Late scan 1H	11±12	13±12	9±11	0.23
Late scan 2H	21±16	21±16	21±16	0.96
Late scan 3H	29±17	32±17	26±17	0.29
Late scan 4H	34±17	36±17	33±17	0.50

H: hour(s); HF: heart failure; IQR: interquartile range.

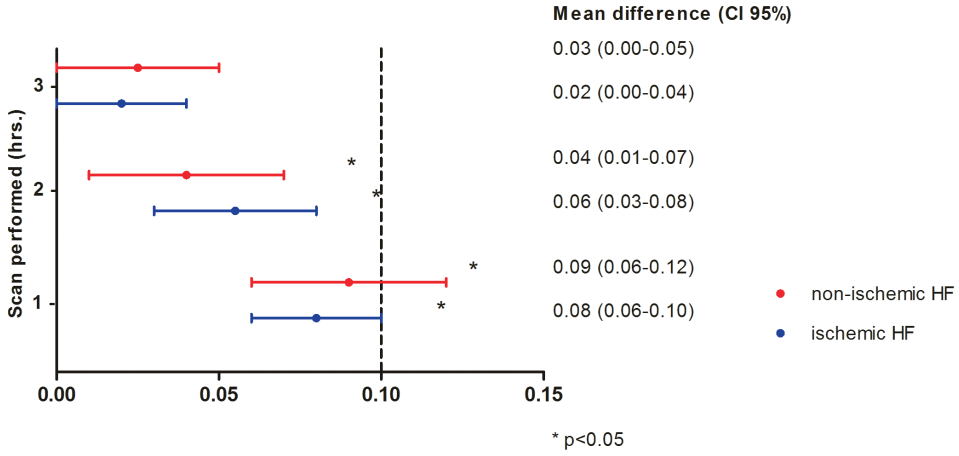
The H/M ratios of the early scan and the late scan performed at 1, 3 and 4 hours pi were significantly higher in the non-ischemic HF group in comparison with the ischemic HF group (P=0.03, P=0.02, P=0.03 and P=0.03, respectively). When corrected for the left ventricular ejection fraction there was no independent association between the late H/M ratio at 1, 3 and 4 hours pi and type of HF (OR 0.09 [95%CI 0.006-0.18], P=0.07; OR 0.07 [95% CI -0.027;0.17], P=0.16 and OR 0.06 [95%CI-0.03-0.16], P=0.16, respectively). Figure 3 shows the mean differences in late H/M ratios at 1, 2 and 3

Figure 2. *Example of a patient with ischemic HF and planar acquisitions 1, 2, 3 and 4 hours pi, respectively.*



HF: heart failure; H/M ratio: heart-to-mediastinum ratio, pi: post-injection.

Figure 3. *Mean differences of H/M ratios at 1, 2 and 3 hours pi in comparison with H/M ratio at 4 hours pi in the ischemic HF and non-ischemic HF subgroups.*



Mean difference with 95% CI of H/M ratio of late ^{123}I-MIBG images at 1, 2 and 3 hours pi in comparison with H/M ratio of late ^{123}I-MIBG image at 4 hours pi analyzed with a linear mixed model in the ischemic HF (in blue) and non-ischemic HF (in red) subgroups. A difference in H/M ratio of more than 0.10 between the different acquisition times in comparison with the H/M ratio at 4 hours was considered clinically relevant.
CI confidence interval; hrs: hours; HF: heart failure; H/M ratio: heart-to-mediastinum ratio.

hours pi compared with the late H/M ratio at 4 hours pi in both subgroups. Compared to the late H/M ratio at 4 hours pi, the mean late H/M ratios at 1 and 2 hours pi were statistically significant different in the ischemic HF group (both P<0.001) as well as in the non-ischemic HF group (P<0.001 and P=0.005, respectively). In the ischemic HF group only the mean late H/M ratio at 1 hour pi exceeded the predefined clinical relevant 0.10 difference with the late H/M ratio 4 hours pi.

The mean washout rate between the early scan and the late scans at 1, 2, 3 and 4 hours pi increased from 11±12% to 21±16%, 29±17%, and 34±17%. The mean washout rates between the early scan and the late scans at 1, 2 and 3 hours pi differed all statistically significantly from the washout rate between the early and 4 hours pi scan (all P <0.001). There was no statistically significant difference between the washout rates in the ischemic HF and the non-ischemic HF subgroups.

Discussion

The present study evaluated the impact of variations in acquisition time of planar ^{123}I-MIBG scintigraphy on the late H/M ratio in patients with HF. There were statistically significant differences between the late H/M ratios at 1, 2 and 3 hours pi compared with the late H/M ratio at 4 hours pi. However, compared with the late H/M ratio at 4 hours pi, the late H/M ratios at 1, 2 and 3 hours pi did not exceed the predefined clinically relevant cut-off difference of 0.10.

The late H/M ratio is the most frequently used parameter to semi-quantitatively analyse the cardiac ^{123}I-MIBG uptake in patients with HF.[12] The Cardiovascular Committee of the European Association of Nuclear Medicine and the European Council of Nuclear Cardiology recommend calculating the late H/M ratio from planar images at 4 hours after receiving ^{123}I-MIBG.[8] This recommendation is based on several studies.[13-17] First, Nakajo et al., investigated the appropriate time for cardiac radioiodine labelled MIBG imaging.[14] This study demonstrated in rats that the accumulation of cardiac ^{131}I-MIBG in adrenergic nerves reached a maximum plateau at 4 hours pi, while the accumulation of the tracer in other compartments rapidly decreased in a period of 6 hours pi. Second, the mechanism of myocardial uptake of ^{123}I-MIBG in the presynaptic sympathetic nerve endings was elucidated by DeGrado et al.[15] This group demonstrated that ^{123}I-MIBG-uptake was mainly

between 1 and 7 minutes pi and depended primarily on both uptake-1 (the neuronal pathway via the norepinephrine transporter) as well as on uptake-2 (the extraneuronal pathway) activity. The clearance half-time of neuronal ^{123}I-MIBG uptake (via uptake-1) was 112 minutes, in contrast to the much lower clearance half-time of extraneuronal ^{123}I-MIBG uptake (uptake-2) of 22 minutes. Finally, Sisson et al. demonstrated that ^{123}I-MIBG patterns in the heart were consistent with the concept that ^{123}I-MIBG resides mostly in adrenergic neurons, mainly via the uptake-1 mechanism.[16, 17] This supports the hypothesis that the late H/M ratio at 4 hours pi mainly represents the uptake, storage and release of ^{123}I-MIBG in the myocardial vesicles at the nerve terminals, while accumulation in extraneuronal compartments is relatively low.

In the present study only small differences (≤ 0.10) were observed between the late H/M ratios at 1, 2 and 3 hours pi compared with the commonly used late H/M ratio at 4 hours pi. Subgroup analysis between patients with ischemic and non-ischemic HF showed similar results. At patient level, a high percentage of patients (50%) exceeded a difference of 0.10 between the late H/M ratio at 1 hour pi compared to the late H/M ratio at 4 hours pi. In contrast, between the late H/M ratio at 2 hours pi and the late H/M ratio at 4 hours pi the percentage of patients who exceeded a difference of 0.10 was much lower (19%). In comparison with the late H/M ratios at 3 and 4 hours pi only 4% of the patients had a difference of more than 0.10. These results are in line with a previous investigation by Kline et al., who demonstrated a small difference in late heart-to-lung ratio in 4 healthy subjects between 1 and 2 hours after administration of 74 MBq ^{123}I-MIBG of approximately 1.3 versus 1.44.[3] More recently, Giorgetti et al. reported the mean H/M ratios at different acquisition times in 6 pigs after administration of 54±14 MBq ^{123}I-MIBG using a cadmium zinc telluride camera. The mean H/M values ± SD, at 125 minutes, extrapolated to 176 and 240 minutes, were 4.33%±1.23%, 3.95%±1.46% and 3.63%±1.64%, respectively. In addition, Okuda et al. demonstrated in 96 patients that the mean count density in the cardiac ROI and the mediastinum ROI at 3 hours were highly correlated with the mean count density in the cardiac ROI and the mediastinum ROI at 4 hours ($r=0.98$, $P<0.0001$ and $r=0.89$, $P<0.0001$). As well as, the fact that there was only a small mean difference of 0.02 between the late H/M ratios at 3 and 4 hours pi (1.88±0.56 and 1.86±0.57, respectively).[9] Slow efflux of ^{123}I-MIBG from the neuronal compartments can probably explain the small differences between late H/M ratios in the latter and the present study. [13, 18]

The present results show that, at group as well as at an individual patient level, the change in the late H/M ratios between 2 and 4 hours pi is limited and probably not clinically relevant. Since the late H/M ratio has been proven to provide important information in predicting prognosis in HF patients,[4] our results may have clinical implications by allowing a more flexible and/or shorter interval between the injection of ^{123}I-MIBG and the acquisition time of the late scan for the determination of the late H/M ratio, especially in patients with HF.

With a shorter interval between the injection of ^{123}I-MIBG and the "late" scan the washout rate will change. Previous studies have shown that the instant myocardial uptake of ^{123}I-MIBG uptake normalized for blood pool activity is close to zero after 3 hours.[10] Evaluating the washout rate at least 3 hours after radiotracer injection is therefore recommended. However, Arimoto et al. demonstrated in 42 patients with HF a good correlation of the early washout rate between 5 and 15 minutes and the washout rate between 15 minutes and 3 hours ($r=0.606$, $P<0.0001$).[19] Moreover, the early washout rate provided prognostic information as well. In addition, Henderson et al. demonstrated that a washout rate recorded between 15 and 85 minutes showed a significant difference in 16 patients with non-ischemic cardiomyopathy compared with 14 healthy volunteers; 28±12% and 6±8% respectively ($P<0.001$).[20] Additional imaging was performed in a subset of patients (n=8) at 4 hours pi and ^{123}I-MIBG retention appeared to be lower and showed greater disparity in the washout rate. In the present study, myocardial ^{123}I-MIBG washout increased over time from 11±12% at 1 hour pi to 34±17% at 4 hours pi. The mean washout rates between the early scan and the late scans at 1, 2 and 3 hours pi differed all statistically significantly from the washout rate between the early and 4 hours pi scan (all $P<0.001$).

Limitations

It should be addressed that although myocardial washout rates were corrected for ^{123}I-decay and mediastinal background the myocardial washout rate can still be influenced by ^{123}I-MIBG washout in surrounding lung and liver tissues.[21] Moreover, more research is needed before implementing the acquisition time at 2 hours to avoid misclassification since the difference between the late H/M ratio at 2 hours pi in comparison with 4 hours pi at the patient level was not non-negligible.

Conclusion

Variation in acquisition time of ^{123}I-MIBG between 2 and 4 hours pi does not lead to a clinically significant change in the late H/M ratio. With the knowledge that the late H/M ratio is the best validated and most used prognostic parameter for cardiac sympathetic innervation in patients with HF, an earlier acquisition time seems to be justified and may warrant a more time-efficient cardiac ^{123}I-MIBG imaging protocol.

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Chapter 10

Cardiac ^{123}I-MIBG Parameters at 4 Hours Derived from Earlier Acquisitions Times

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Abstract

Background. The clinical implementation of cardiac ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy for the evaluation of prognosis in patients with heart failure (HF) is still limited. This may partially be related to the long examination time with an almost 4 hour delay between the early and late acquisition. Additionally, outcome derived at different late acquisition times cannot be compared with each other. To assess whether earlier acquisition time of the late image is justified, the aim of present study was to evaluate in a HF patient cohort whether a developed direct comparison method for cardiac ^{123}I-MIBG imaging enables comparison of washout rates and late heart mediastinum (H/M) ratios from 1 to 3 hours post injection (pi) with measurements at 4 hours pi.

Methods. Forty-eight patients with HF were clinically referred for cardiac ^{123}I-MIBG scintigraphy. The washout rate and late H/M ratio at 4 hours pi were estimated with a previous published linear model from heart and mediastinal counts at 1, 2 and 3 hour pi and compared with the actual values at 4 hour pi.

Results. The estimated washout rate and late H/M ratio at 4 hours pi from counts at 1 hour pi demonstrated large differences. However, the average estimated late H/M ratio at 4 hours pi derived from 2 and 3 hours pi did not differ with the actual late H/M ratio at 4 hours pi ($P=0.84$ and $P=0.06$). As well as, the actual and estimated washout rate at 4 hours pi derived from 3 hours pi did not differ significantly ($P=0.22$). Yet, the mean estimated washout rate at 4 hours pi derived from the acquisition at 2 hours pi showed a difference compared with the actual washout rate at 4 hours pi (25 ± 19 vs. 34 ± 17, $P<0.001$).

Conclusions. The direct comparison method for cardiac ^{123}I-MIBG imaging enables accurate estimation of the actual late H/M ratio and washout rate at 4 hours pi derived from the acquisitions at 3 hours pi. The acquisition at 2 hours pi should only be performed in exceptional cases when clinically necessary because of the existing difference between the actual and estimated washout rate at 4 hours pi derived from 2 hours pi.

Introduction

The increasing prevalence of heart failure (HF) worldwide is a major health-care problem.[1] In patients with HF the cardiac sympathetic nervous system is activated, which can be visualized with ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) imaging;[2] the procedure of ^{123}I-MIBG imaging consists of an early acquisition (15 minutes post-injection [pi]) and a late acquisition (varying between 3 and 4 hours after tracer injection). Different parameters can be extracted from these images. First, the late heart-to-mediastinum ratio (H/M ratio), which is calculated by dividing the cardiac ^{123}I-MIBG uptake by the mediastinal ^{123}I-MIBG-uptake.[3] It represents the relative distribution of cardiac sympathetic nerve terminals, offering information about neuronal function from uptake to release. The other ^{123}I-MIBG parameter is the myocardial washout rate representing the tracer washout between the early and late planar ^{123}I-MIBG acquisition and therefore the washout rate provides an index of the sympathetic drive.

Several studies have shown that patients with HF and a low late H/M ratio and/or an increased washout rate, are at increased risk for cardiac death and arrhythmic events.[4-6] However, the clinical implementation of this technique is still limited. This may partially be related to the long examination time with an almost 4 hour delay between the early and late acquisition. Additionally, outcome derived at different late acquisition times cannot be compared with each other. This is of importance since most Japanese studies in contrast to Western studies perform the late acquisition at 3 hours pi.[7,8]

Recently a more time-efficient cardiac ^{123}I-MIBG protocol demonstrated only small differences between the late H/M ratio 2 and 3 hours pi compared with the late H/M ratio at 4 hours pi, suggesting that the late imaging can be performed at an earlier stage.[9] This will shorten the acquisition time and may increase patient comfort. However, the differences between the washout rates were larger and increased over time, which makes comparison of the washout rate measured at different acquisition times difficult. Okuda et al. recently developed a linear model to ease comparison of the washout rate at 3 hours pi with 4 hours pi.[10] Yet, no external validation has taken place in a HF cohort and it is unknown whether this model can be applied to estimate the washout rate and the late H/M ratio at 4 hours pi from even earlier acquisitions times than 3 hours pi.

To assess whether earlier acquisition time of the late image is justified, the present study evaluated whether the linear model based formula enables comparison of washout rates and late H/M ratios determined from acquisi-

tion times from 1 to 3 hours pi with the actual measurements at 4 hours pi in a cohort of HF patients.

Methods

Patients

The study population consisted of patients included in a previous study focusing on the change in late H/M ratio between 1, 2 and 3 hours pi in comparison with the late H/M ratio at 4 hours pi.[9] The inclusion criteria for the study population were age between 18 and 74 years and symptoms of HF New York Heart Association class (NYHA) II-IV. Excluded for that study were patients with severe shortness of breath who were unable to lie flat for several times under a gamma camera. Previous study concentrated on the determination of the late H/M ratio at 1, 2, 3 and 4 hours pi. The current evaluation will focus on a recently developed direct comparison method for cardiac ^{123}I-MIBG imaging to evaluate whether this method provides an accurate estimation of the late H/M ratio and washout rate at 4 hours pi derived from earlier (1, 2 and 3 hours pi) acquisitions to overcome differences in late H/M ratios and washout rates between different acquisitions. The population consisted of 50 patients with HF and NYHA II-IV from two centers (Leiden, Netherlands and Pisa, Italy) clinically referred for cardiac ^{123}I-MIBG scintigraphy between 2012-2015. The study was approved by the Medical Ethical Committee from the Leiden University Medical Centre (the Netherlands) and the Medical Ethical Committee from the Fondazione Toscana/CNR Gabriele Monasterio (Italy) and complied with the Declaration of Helsinki. All patients signed the informed consent form.

^{123}I-MIBG data acquisition and analysis

The protocol of the ^{123}I-MIBG data acquisition and analysis have been described in detail.[9] In brief, after an intravenous bolus injection of 185 MBq ^{123}I-MIBG (AdreView; GE Healthcare, Princeton NJ) 5 frontal planar images of the chest were obtained 15 minutes pi (early scan) and 1, 2, 3 and 4 hours pi (late scans). All examinations were performed with a Siemens ECAM (Pisa, Italy) or a Toshiba GCA 7200/PI (Leiden, The Netherlands) scanner with dual head gamma cameras in combination with low-energy high-resolution collimators with a matrix 256 x 256. The Siemens ECAM scanner has a 1.23 zoom factor and 1.9 mm pixel size and the Toshiba scanner a 1.5 zoom factor and 1.4 mm pixel size 1.4 mm.

Post-processing enhanced a manually drawn polygonal region-of-interest (ROI) over the myocardium including the left cavity and a rectangular ROI upon the upper half of the mediastinum. The H/M ratio was calculated by dividing the mean counts per pixel within the cardiac ROI by the mean counts per pixel in the mediastinal ROI. The washout rate with correction for background and physical decay of ^{123}I was calculated with the following formula: $WR_{BKG\ and\ decay\ corrected} = [(\{H\}_e - \{M\}_e) - (\{H\}_l - \{M\}_l\ x^{123}I\ decay\ correction)] / (\{H\}_e - \{M\}_e)\ x\ 100$.

In this formula {H} represents the mean counts per pixel in the cardiac ROI and {M} represents the mean counts per pixel in the mediastinal ROI in the early ($_e$) and late ($_l$) images.[11]

Estimation of ^{123}I-MIBG parameters

To estimate the mean cardiac counts per pixel of ^{123}I-MIBG at 4 hours derived from acquisitions at 1, 2 and 3 hours pi, the following formula was extracted from the linear regression model between 3 and 4 hours pi, provided by Okuda et al.[10]: $\{H\}_{ih\text{-}estimated} = (1.039^{i-j}\ x\ \{H\}_{jh\text{-}actual}) - ((1.039^{i-j-1} + 1.039^{i-j-2} + \ldots + 1)\ x\ 0.067\ x\ \{H\}_e)$. $\{H\}_{ih\text{-}estimated}$ represents the estimated mean count density in the cardiac ROI at *i* hours pi and $\{H\}_{jh\text{-}actual}$, the actual mean count density in the cardiac ROI at *j* hours. $\{H\}_e$ represents the mean count density in the cardiac ROI of the early image at 15 minutes. Thus, the formulas for the estimated mean cardiac counts per pixel of ^{123}I-MIBG at 4 hours from acquisitions at 1, 2 and 3 hours pi were:

Cardiac counts at 1 hour pi: $\{H\}_{4h\text{-}estimated} = (1.122\ x\ \{H\}_{1h\text{-}actual}) - (0.209\ x\ \{H\}_e)$,
Cardiac counts at 2 hours pi: $\{H\}_{4h\text{-}estimated} = (1.080\ x\ \{H\}_{2h\text{-}actual}) - (0.137\ x\ \{H\}_e)$,
Cardiac counts at 3 hours pi: $\{H\}_{4h\text{-}estimated} = (1.039\ x\ \{H\}_{3h\text{-}actual}) - (0.067\ x\ \{H\}_e)$.

In addition, to estimate the mean mediastinal counts per pixel of ^{123}I-MIBG at 4 hours derived from acquisitions at 1, 2 and 3 hours pi the following formula was extracted from the linear regression model between 3 and 4 hours pi, provided by Okuda et al.[10]: $\{M\}_{ih\text{-}estimated} = 0.967^{i-j} \cdot \{M\}_{jh} - ((0.967^{i\ i-j-1} + 0.967^{i\ i-j-2} + \ldots + 1)\ x\ 0.003\ x\ \{M\}_e)$. $\{M\}_{ih\text{-}estimated}$ represents the estimated mean count density in the mediastinal ROI at *i* hours pi and $\{M\}_{ih\text{-}actual}$, the actual mean count density in the cardiac ROI at *j* hours. $\{M\}_e$ represents the mean count density in the mediastinal ROI of the early image at 15 minutes. Consequently, the formulas to calculate the estimated mean mediastinal counts per pixel of ^{123}I-MIBG at 4 hours from acquisitions at 1, 2 and 3 hours pi were:

Mediastinal counts at 1 hour pi: $\{M\}_{4h\text{-}estimated} = (0.904 \times \{M\}_{1h\text{-}actual}) - (0.009 \times \{M\}_{e})$,
Mediastinal counts at 2 hour pi: $\{M\}_{4h\text{-}estimated} = (0.935 \times \{M\}_{2h\text{-}actual}) - (0.006 \times \{M\}_{e})$,
Mediastinal counts at 3 hour pi: $\{M\}_{4h\text{-}estimated} = (0.967 \times \{M\}_{3h\text{-}actual}) - (0.003 \times \{M\}_{e})$.

Afterwards, the late H/M ratio and myocardial washout rate with background and decay correction at 4 hours pi were calculated from the estimated mean cardiac and mediastinal counts per pixel at 4 hours pi.

Statistical analysis

Normally distributed variables were expressed as mean ± standard deviation and non-normally distributed variables as median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages.

To evaluate the differences in estimated and actual measured cardiac and mediastinal counts at 4 hours pi, the following analyses were performed. First, the estimated cardiac and mediastinal counts derived from 1, 2 and 3 hours pi were compared with the actual cardiac and mediastinal counts at 4 hours pi using a paired samples t-test. In addition, the agreement of the estimated and the actual cardiac and mediastinal counts at 4 hours was evaluated with the Pearson's correlation and Bland Altman analysis. Similarly, these analyses were repeated for the comparison of the estimated and actual late H/M ratios and washout rates.

Furthermore, the sensitivity and specificity for the threshold of < 1.6 of the actual late H/M ratio were calculated for the estimated late H/M ratio at 4 hours pi derived from the 1-, 2- and 3-hour scan (4). As well as, the sensitivity and specificity for the threshold of ≥ 27% of the actual washout rate at 4 hours pi were computed for the estimated washout rate at 4 hours pi derived from the 1-, 2- and 3-hour scan (12).

Statistical analysis was performed using SPSS software (Version 22.0, SPSS IBM Corp., Armonk, New York, USA). A two-sided P-value of <0.05 was considered statistically significant.

Results

Patients

The clinical characteristics of the patients are depicted in Table 1. Of the study population 2 patients (4%) were excluded since 1 patient withdrew his informed consent after the examination and 1 patient did not have an acquisition 4 hours

pi due to logistic reasons. The final population comprised 48 patients with HF of which 77% (37/48) were male with a mean age of 64±9 years.

Planar ^{123}I-MIBG image analysis

Results of the planar ^{123}I-MIBG images of the early and late scans at 1, 2, 3 and 4 hours pi and the actual acquisition time-intervals after ^{123}I-MIBG injection are shown in Table 2. In the total study population the late H/M ratio decreased over time and was 1.60±0.18 at 1 hour, 1.56±0.19 at 2 hours pi and 1.54±0.19 at 3 hours pi and differed all significantly from the late H/M ratio of 1.52±0.20 at 4 hours pi (P <0.001, P<0.001 and P=0.02, respectively). The washout rate increased over time from 11±11 at 1 hour pi, 21±16 at 2 hours pi, 28±17 at 3 hours pi to 34±17 at 4 hours pi. The washout rate at 1, 2 and 3 hours were all significantly different from the washout rate at 4 hours pi (all P<0.001).

Estimated and actual ^{123}I-MIBG parameters

The estimated mean cardiac and mediastinal counts per pixel for 4 hours pi determined from the cardiac and mediastinal counts at 1, 2 and 3 hours pi are depicted in Table 3.

The Pearson's correlation was excellent between the estimated cardiac counts at 4 hours pi determined from the late acquisitions at 1, 2 and 3 hours pi and the actual cardiac counts at 4 hours pi (r=0.995, r=0.996 and r=0.996; all P<0.001, Figure 1). In the Bland-Altman analysis there was a bias of -11.4 (95%CI-30.4;7.6), -5.8 (95%CI-15.8;4.2) and -2.5 (95%CI -9.0;4.0) between the actual and estimated cardiac counts at 4 hours pi calculated from the late scan at 1, 2 and 3 hours pi, respectively.

Depicted in Figure 2, the estimated mediastinal counts at 4 hours pi determined from the late acquisitions at 1, 2 and 3 hours pi and the actual mediastinal counts at 4 hours pi demonstrated excellent Pearson's correlations (r=0.994, r=0.994, r=0.995, respectively, all P<0.001). In the Bland-Altman analysis there was a bias of -6.1 (95%CI-16.2;4.1), -3.7 (95%CI-10.1;2.7) and -1.9 (95%CI -6.5;2.7) between the actual and estimated mediastinal counts at 4 hours pi calculated from the late scan at 1, 2 and 3 hours pi, respectively.

Estimated and actual late H/M ratio

The mean estimated late H/M ratio at 4 hours pi derived from the counts at 1, 2 and 3 hour pi were 1.58±0.19, 1.52±0.20 and 1.50±0.20, respectively. Compared with the actual late H/M ratio at 4 hours pi (1.52±0.20) the differences with the estimated late H/M ratio at 4 hours pi from 1, 2 and 3 hours pi were 0.06, 0.002 and -0.015, respectively (P<0.001, P=0.84 and P=0.06, respectively).

Table 1. *Characteristics of the study population*

Patient characteristic	Total group (N=48)
Age (years)	64±9
Sex (male)	37 (77%)
Height (cm)	176 ± 9
Weight (kg)	85 ± 14
Cardiovascular risk factors	
Diabetes mellitus*	7 (15%)
Obesity, BMI ≥ 30 (kg/m²)	7 (15%)
Family history of CVD†	19 (40%)
Hypercholesterolemia‡	26 (54%)
Hypertension§	29 (60%)
Current smoker	8 (17%)
Ejection fraction (%)	31 (IQR 25-37)
CRT-D / ICD therapy	31 (65%)
Medication	
ACE-/AT II-inhibitor	44 (92%)
Beta blocker	39 (81%)
Calcium antagonist	3 (6%)
Lipid-lowering agent	34 (71%)
Antiplatelet/OAC therapy	41 (85%)
Diuretics	37 (77%)
Oral antidiabetics	8 (17%)
Insulin	3 (6%)
Nitrates	3 (6%)
Ischemic CMP	25 (52%)
NYHA class	
I	11 (23%)
II	26 (54%)
III	11 (23%)
NT-proBNP (pg/L)	811 (IQR 419-1265)

ACE: angiotensin converting enzyme inhibitor; AT-II: angiotensin-II; BMI: Body Mass Index, CRT-D: cardiac resynchronization therapy defibrillator; CVD: cardiovascular disease; HF: heart failure; ICD: implantable cardioverter defibrillator; IQR: interquartile range; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; OAC: oral anticoagulant.

* *Self-reported history of Diabetes Mellitus and/or treatment with antidiabetics,*

† *presence of coronary artery disease in first-degree family members at age <55 years in men and <65 years in women,*

‡ *Self-reported history of hypercholesterolemia and/or treatment with lipid-lowering drugs,*

§ *Self-reported history of hypertension and/or use of antihypertensive medication, or a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.*

Table 2. *^{123}I-MIBG scintigraphy results*

MIBG scintigraphy	Total group (N=48)
Actual acquisition time after injection (in minutes)	
Early scan	15 (IQR 13-19)
Late scan 1H	66 (IQR 62-71)
Late scan 2H	118 (IQR 115-122)
Late scan 3H	177 (IQR 176-182)
Late scan 4H	239 (IQR 236-245)
Heart/mediastinum ratio	
Early scan	1.60±0.15
Late scan 1H	1.60±0.18
Late scan 2H	1.56±0.19
Late scan 3H	1.54±0.19
Late scan 4H	1.52±0.20
Washout rate[a] (%)	
Late scan 1H	11±11
Late scan 2H	21±16
Late scan 3H	28±17
Late scan 4H	34±17

H: hour(s); HF: heart failure; IQR: interquartile range.
[a]Washout rate with ^{123}I-decay and background correction

Table 3. *Actual and estimated cardiac and mediastinal counts per pixel at 4 hours calculated from 1, 2 and 3 hours pi.*

	Estimated counts at 4 hours pi	Actual counts at 4 hours pi	Difference between estimated and actual counts at 4 hours pi	P-value
Cardiac counts per pixel				
H_1	55±39	44±30	11(95%CI 9;14)	<0.001
H_2	50±34	44±30	6 (95%CI 4;7)	<0.001
H_3	47±32	44±30	2 (95%CI 1;3)	<0.001
Mediastinum counts per pixel				
M_1	35±23	29±19	6 (95%CI 5;8)	<0.001
M_2	33±21	29±19	4 (95%CI 3;5)	<0.001
M_3	31±20	29±19	2 (95%CI 1;3)	<0.001

H_1: mean heart counts per pixel from 1 hour pi, H_2: mean heart counts per pixel from 2 hour pi, H_3: mean heart counts per pixel from 3 hour pi, M_1 mean mediastinal counts per pixel from 1 hour pi, M_2 mean mediastinal counts per pixel from 2 hour pi, M_3 mean mediastinal counts per pixel from 3 hour pi.

Figure 1. *Pearson's correlation and Bland-Altman analysis of the relationship between the actual and estimated cardiac counts at 4 hours pi from the cardiac counts at 1, 2 and 3 hours pi.*

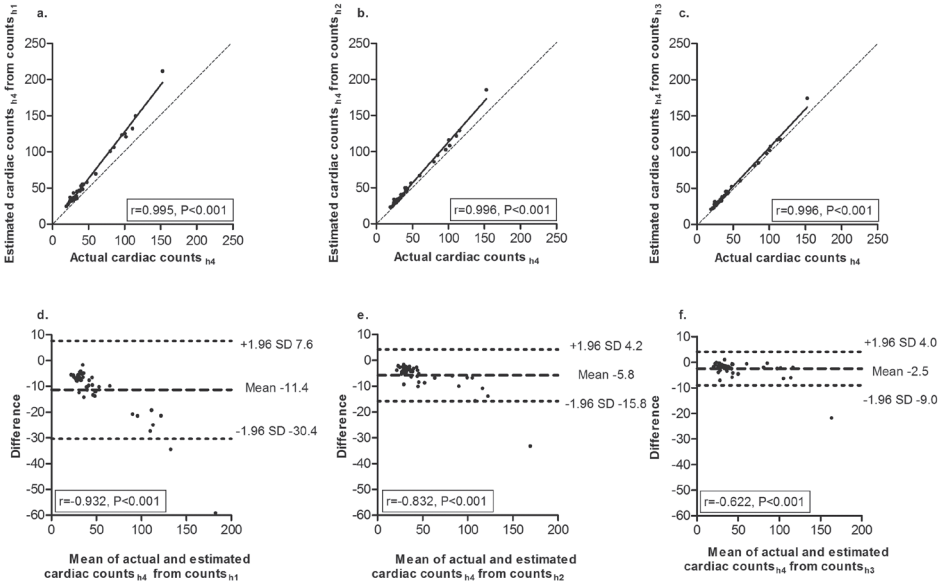


Figure 2. *Pearson's correlation and Bland-Altman analysis of the relationship between the actual and estimated mediastinal counts at 4 hours pi from the mediastinal counts at 1, 2 and 3 hours pi.*

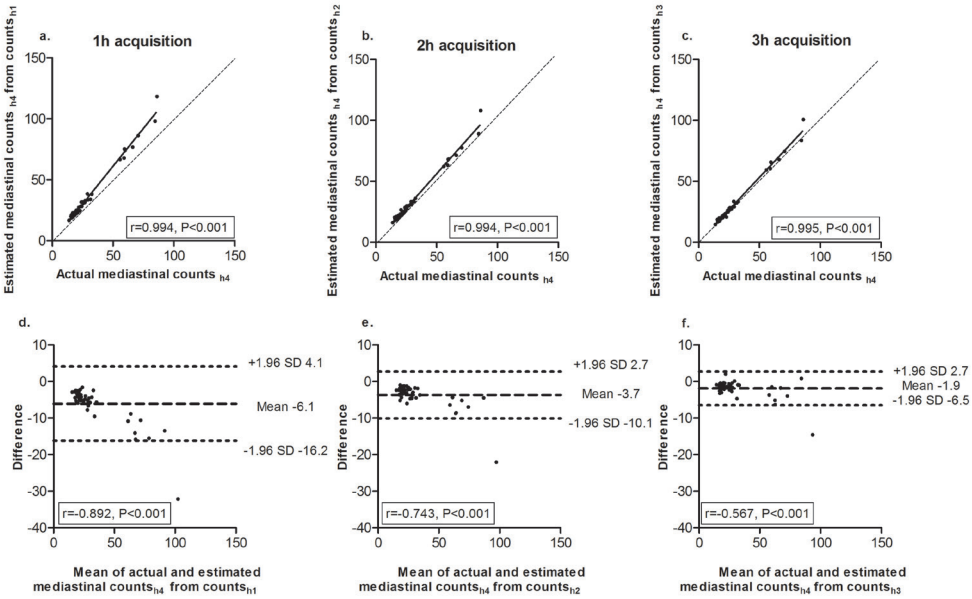


Figure 3. *Pearson's correlation and Bland-Altman analysis of the relationship between the actual and estimated heart-to-mediastinum ratio at 4 hours pi from the cardiac and mediastinal counts at 1, 2 and 3 hours pi.*

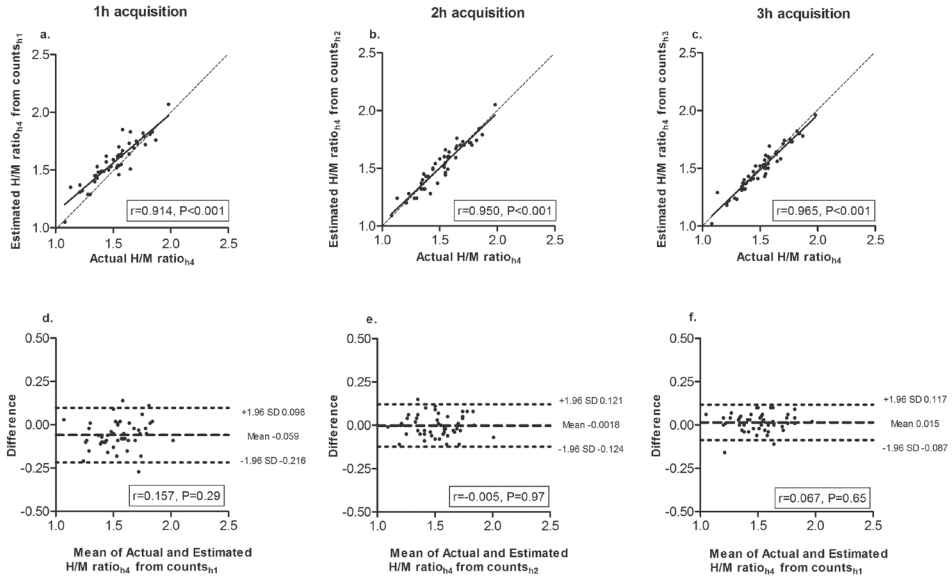
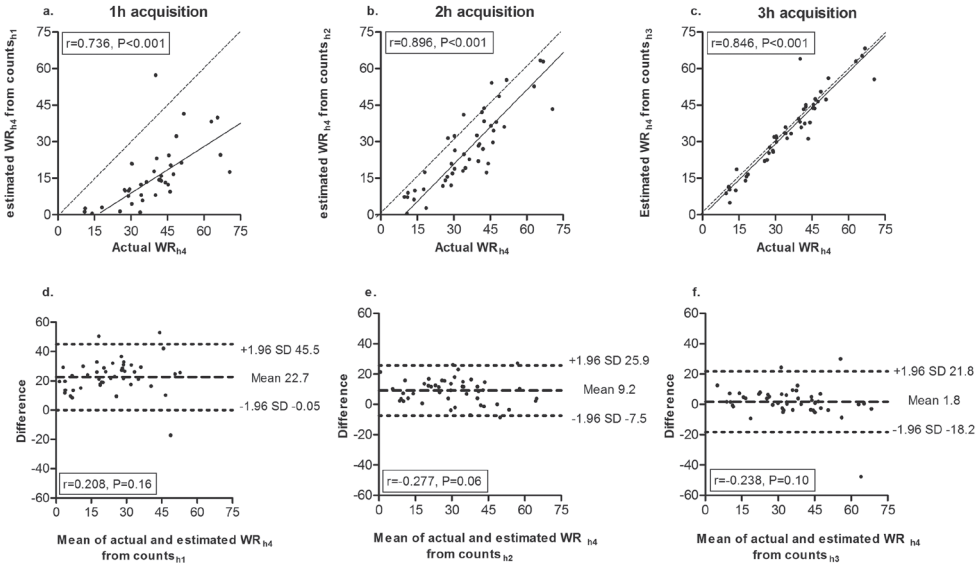


Figure 4. *Pearson's correlation and Bland-Altman analysis of the relationship between the actual washout rate at 4 hours and estimated washout rate at 4 hours from the late acquisitions at 1, 2 and 3 hours pi.*



There was a positive correlation between the actual late H/M ratio at 4 hours pi and estimated late H/M ratio at 4 hours pi derived from the scans at 1, 2 and 3 hours pi (Figure 3). The Pearson's Correlation was excellent between the estimated late H/M ratio at 4 hours pi derived from 1, 2 and 3 hours pi and the actual late H/M ratio at 4 hours pi, r= 0.914, r=0.950 and r=0.965, respectively (all P<0.001). In the Bland-Altman analysis there was a bias of -0.059 (95%CI-0.216;0.098), -0.0018 (95%CI-0.124;0.121) and 0.015 (95%CI-0.087;0.117) between the actual and estimated late H/M ratio at 4 hours pi calculated from the late scan at 1, 2 and 3 hours pi, respectively. No correlation existed between the difference and the mean of the actual and estimated late H/M ratios obtained from 1, 2 and 3 hours pi.

Of the 34 patients with an actual late H/M ratio < 1.6, 25 (74%), 29 (85%) and 31 (91%) patients had an estimated late H/M ratio at 4 hours pi < 1.6 derived from 1, 2 and 3 hours pi, respectively. The sensitivity and specificity for the actual late H/M ratio < 1.6 for the estimated late H/M ratio at 4 hours pi derived from the 1-hour scan were 74% and 93%, respectively. For the estimated late H/M ratio at 4 hours pi derived from 2 and 3 hours pi the sensitivity and specificity were 85% and 93%, 91% and 86%, respectively.

Estimated and actual washout rate

The mean estimated washout rate (with background and ^{123}I-decay correction) at 4 hours pi calculated from the acquisitions at 1 and 2 hours pi differed significantly from the actual washout rate at 4 hours pi, 12±15 and 25±19 in comparison with 34±17 (both P<0.001). The mean estimated washout rate at 4 hours pi derived from 3 hours pi did not differ significantly with the actual washout rate at 4 hours pi, 32±19 and 34±17, respectively (P=0.22). There was a positive correlation between the actual washout rate at 4 hours pi and the estimated washout rate at 4 hours pi derived from 1, 2 and 3 hours pi (Figure 4). The Pearson's Correlation of the actual washout rate at 4 hours and the estimated washout rate at 4 hours obtained from the scan at 1 hour pi was strong (r=0.736) and excellent for the estimated washout rate at 4 hours from the 2- and 3-hour pi scan (r=0.896 and r=0.846, respectively). In the Bland-Altman analysis for the actual and estimated washout rate there was a bias of 22.7 (95%CI 0;45), 9.2 (95%CI -7.5;25.9) and 1.8 (95%CI -18.2;21.8) between the actual and estimated washout rate at 4 hours pi calculated from cardiac and mediastinum counts at 1, 2 and 3 hours pi. No correlation existed between the difference and the mean of the actual washout rate at 4 hours pi and the estimated washout rate at 4 hours pi derived from 1,2 and 3 hours pi.

Of the 34 patients with an actual late H/M ratio < 1.6, 25 (74%), 29 (85%) and 31 (91%) patients had an estimated late H/M ratio at 4 hours pi < 1.6 derived from 1, 2 and 3 hours pi, respectively. The sensitivity and specificity for the actual late H/M ratio < 1.6 for the estimated late H/M ratio at 4 hours pi derived from the 1-hour scan were 74% and 93%, respectively. For the estimated late H/M ratio at 4 hours pi derived from 2 and 3 hours pi the sensitivity and specificity were 85% and 93%, 91% and 86%, respectively.

Discussion

The present study demonstrated that by using the direct comparison method for cardiac ^{123}I-MIBG imaging, it is possible to provide an accurate estimation of the actual late H/M ratio and washout rate at 4 hours pi, derived from acquisitions at 2 and 3 hours pi.

The timing to acquire late planar myocardial ^{123}I-MIBG images is still 4 hours pi.[11] However, several studies calculated the late H/M ratio and / or washout rate from acquisitions at 3 hours pi.[7] Recently, we demonstrated in patients with HF only small differences (≤ 0.05) between the late H/M ratio determined at 2 and 3 hours pi compared with the late H/M ratio at 4 hours pi.[9] In addition, in the present study the late H/M ratio at 4 hours pi could be accurately estimated from the ratio at 2- and 3-hour scan pi by means of a linear model, in contrast to the 1-hour scan pi. In addition, the sensitivity and specificity of the estimated late H/M ratio derived from 2 and 3 hours pi to determine the actual late H/M ratio at 4 hours pi <1.6 were high. These findings may allow a more time-efficient cardiac ^{123}I-MIBG-imaging protocol.

The washout rate between the early and several late acquisition times increased from 11±11 between 15 minutes and 1 hour pi to 34±17 between 15 minutes and 4 hours pi. This increase in washout rate over time was also observed by Henderson et al. This study demonstrated in patients with severe dilated cardiomyopathy that the global myocardial ^{123}I-MIBG concentration reduced from 117±41 at 15 minutes to 85±35 and 52±14 at 85 and 240 minutes, respectively.[13]

To correct for the increasing washout rate over time Okuda et al. developed a linear model using the early and 3-hour planar image which makes comparison of the washout rate determined at 3 hours pi with 4 hours pi possible.[10] In that study, total population (n=96) was randomly divided into two groups:

one group for the creation of a linear regression model between the heart and mediastinal counts at 3 and 4 hours pi and group 2 for the clinical validation. The results demonstrated that the estimated washout rate at 4 hours pi by the linear regression model determined from the early and 3-hour pi scan did not differ from the actual washout rate at 4 hours pi.

Similar results were detected in present HF cohort between the actual and estimated washout rate at 4 hours pi from the 3-hour scan pi. In addition, the sensitivity and specificity for the threshold of ≥ 27% of the actual washout rate at 4 hours pi were high for the estimated washout rate at 4 hours pi derived from 3 hours pi. Only small differences were found between the actual and estimated washout rate at 4 hours pi from the 2-hour scan pi. Although the specificity for the threshold of ≥ 27% of the actual washout rate at 4 hours pi was high (100%) for the estimated washout rate at 4 hours pi derived from 2 hours pi, the sensitivity was relatively low (63%). This means that patients with an estimated washout rate ≥27% at 4 hours derived from the 2-hour scan do not need a second scan at 4 hours pi. Within present study population, 22/48 (42%) patients could be excluded for a second scan at 4 hours pi.

A large difference was observed between the actual and estimated washout rate at 4 hours pi derived from the 1-hour pi scan. Therefore, the formula seems not useful for the estimation of the washout rate from the 1-hour pi scan.

In the created formula for the cardiac and mediastinal counts at the acquisition at 1, 2 and 3 hours pi to estimate the counts at 4 hours pi, it is assumed that the clearance of ^{123}I-MIBG is linear over time and that extra-neuronal ^{123}I-MIBG uptake plays no pivotal role. This is in line with data showing that ^{123}I-MIBG clearance has a clear distinction between an early more accelerated phase and a slower linear phase.[14] These findings are corroborated by an earlier study by Morozumi et al., which demonstrated in 15 healthy subjects that the mean counts per pixel in the cardiac and upper mediastinal ROI was linear over time.[15] In addition, Dae et al. concluded that non-neuronal uptake does not seem to be operational in humans since there was no ^{123}I-MIBG uptake on early and late planar images present in post-cardiac transplant patients.[16] However, in the present study there was an overestimation of the estimated cardiac and mediastinal counts at 4 hours from the 1-hour scan pi which resulted in a lower estimated washout rate and a significant higher mean late H/M ratio compared to the actual numbers. Possibly, the cardiac ^{123}I-MIBG uptake at 1 hour pi and in some extent at 2 hour pi is affected by attenuation of the liver, which is more present at the early hours pi since the clearance time of ^{123}I-MIBG in the liver is shorter.[15,17]

Limitations

Since there were differences between the actual and the estimated washout rate at 4 hours pi calculated from the scan 2 hours pi, implementation of the late scan at 2 hours pi to estimate the washout rate at 4 hours pi needs to be evaluated in larger cohorts.

Conclusion

By using the direct comparison method for cardiac ^{123}I-MIBG imaging it is possible to accurately estimate the actual late H/M ratio and washout rate at 4 hours pi, derived from acquisitions at 3 hours pi. This will allow a more time efficient protocol, increase the clinical implementation in patients with HF and ease comparison of ^{123}I-MIBG parameters from acquisitions from 3 with 4 hours pi. The acquisition at 2 hours pi should only be performed in exceptional cases when clinically necessary because of the existing difference between the actual and estimated washout rate at 4 hours pi derived from 2 hours pi.

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PART IV

SUMMARY AND CONCLUSIONS


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Chapter 11

Summary, conclusions and future perspectives

Summary

The aim of the studies presented in this thesis was to evaluate the clinical value of different imaging techniques and invasive strategies in the prevention, management and prognosis of ischemic heart disease. In more detail, **Part I** explored the role of coronary computed tomography angiography (CTA) in the early detection of coronary artery disease (CAD), while **Part II** explored the most effective revascularization strategy in patients with ST-elevation myocardial infarction (STEMI) and multi-vessel CAD. **Part III** evaluated the clinical relevance of 2-dimensional strain echocardiography and ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy in patients with ischemic heart disease and ways to optimize the use of these non-invasive imaging techniques.

PART I: DETECTION OF ATHEROSCLEROSIS AND VARIATIONS IN CORONARY ANATOMY

Chapter 2 of the thesis used coronary CTA in patients at high-risk with diabetes mellitus (DM) to detect or exclude CAD. The coronary CTAs of 425 clinically referred patients at high-risk with DM without chest-pain syndrome or a history of cardiac disease were evaluated, revealing that 73% had some degree of CAD defined as any stenosis ≥ 30%, of whom 48% had obstructive CAD, defined as any stenosis ≥ 50%. But, 27% had no CAD, and 52% of the patients with any CAD had non-obstructive CAD. Moreover, the present study demonstrated that the number and presence of other traditional cardiovascular (CV) risk factors (i.e. hypercholesterolemia, hypertension, obesity, family history of CV disease and current smoker) were not associated with a higher frequency of CAD, except for hypertension. Accordingly, coronary CTA may be used in patients at high-risk with DM to determine who needs aspirin as primary prevention of CAD events.

Coronary CTAs performed to determine the presence of CAD frequently show an intramural course of a coronary artery, defined as any epicardial segment that runs intramurally through the myocardium which completely surrounds the vessel. **Chapter 3** examined whether the presence of an intramural course of a coronary artery in patients without obstructive CAD was associated with worse outcomes. Evaluating the data of 947 patients with a low-to-intermediate pre-test probability and who did not have obstructive CAD on coronary CTA results demonstrated that in 22% of the patients their

coronary CTA showed an intramural course of a coronary artery. During a median follow-up of 4.9 years (IQR 3.2 to 6.9 years) there was a low event-rate of 43 events (4.5%); with 13 (1.4%) patients being hospitalized due to unstable angina, 7 (0.7%) patients suffering a non-fatal myocardial infarction, while 23 (2.4%) patients died. No differences occurred in the event rates between patients with and those without an intramural course of the coronary artery. This suggests that no therapeutic adjustments are warranted for patients with an intramural course of a coronary artery on coronary CTA.

PART II: MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

There is ongoing debate about the most effective invasive treatment for patients presenting with STEMI and multi-vessel CAD. The purpose of **chapter 4** was to assess whether there are any differences in the short- and the long-term all-cause mortality rates in patients with complete or incomplete revascularization. Evaluating the endpoint all-cause mortality in 518 patients with a first STEMI and multi-vessel CAD, 31 mortalities (6%; of which 28 during index hospitalisation) were recorded in the first 30 days and 98 mortalities (19%) during long-term follow-up (with a median of 6.7 years). The group of patients with incomplete revascularisation showed a higher mortality rate during both periods than those with complete revascularization. However, after correcting for relevant clinical variables, incomplete revascularisation was no longer independently associated with all-cause mortality during either period. This observational study supports findings of previous reports (with shorter follow-up), suggesting that complete revascularization has no benefits over incomplete revascularization in patients with first STEMI and multi-vessel CAD in terms of all-cause mortality.

To find out whether any subgroups with STEMI and multi-vessel CAD benefit (more) from complete rather than incomplete revascularization **Chapter 5** investigated gender-specific differences in all-cause mortality. The study population consisted of 375 men and 115 women with a first STEMI and multi-vessel CAD without cardiogenic shock at admission or left main (LM) stenosis. Within the first 30 days, the mortality rates for men and women having received an incomplete revascularization were higher than the rates recorded for men and women having received a complete revascularization. However, this association disappeared after correction for baseline character-

istics and angiographic features. Of the 30-day survivors, men with incomplete revascularization had a 3.1-fold higher mortality risk during the 5-year follow-up than men with complete revascularization. In contrast, women who survived the first 30 days had similar mortality risk as men with complete revascularization independently of (incomplete or complete) revascularization strategy.

PART III: PROGNOSIS IN ISCHEMIC HEART DISEASE

Since the introduction of primary percutaneous coronary intervention (PCI), survival of acute myocardial infarction has risen greatly, thereby inevitably increasing the number of patients with chronic ischemic heart disease. One of the main predictors of a poor prognosis after STEMI is the infarct size. Although the echocardiographic parameter of left ventricular global longitudinal strain (LV GLS) correlates well with infarct size, this relationship is influenced by various factors. **Chapter 6** investigated how myocardial ischemia modulates the correlation between LV GLS and infarct size as determined with single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in 1,128 patients with a first STEMI treated with primary PCI. Similar to other studies, a moderate correlation between the LV GLS and infarct size on SPECT MPI was observed in the total population ($r=0.58$, $P<0.001$). This correlation was weakened by the presence of ischaemia; the correlation between LV GLS and infarct size on SPECT MPI was $r=0.66$ ($P<0.001$) in the group of patients without ischaemia, whereas in patients with mild or moderate to severe ischemia, the correlations were reduced to $r=0.56$ and $r=0.38$, respectively (both $P<0.001$). Even after adjustment for known confounders, residual ischemia remained independently associated with more impaired LV GLS. Accordingly, this study demonstrated that the correlation between LV GLS and infarct size as assessed with SPECT MPI is not straight forward, particularly in the presence of residual ischemia.

Another main predictor of worse prognosis is denervated myocardium, which can be visualized by ^{123}I-MIBG scintigraphy. **Chapter 7** explored recent trends in ^{123}I-MIBG SPECT imaging in patients with heart failure. This review provides evidence of an increased use of ^{123}I-MIBG SPECT imaging in the clinical management of this patient population. In addition to planar imaging, one of the main advantages of ^{123}I-MIBG SPECT imaging is that it also provides information about regional myocardial sympathetic innervation, which is of particular interest in patients with ischemic heart disease.

Since cardiac denervation not only occurs in patients with heart failure, ^{123}I-MIBG imaging could also be of relevance in the evaluation of other cardiac diseases. **Chapter 8** provides an overview of the potential clinical indications for ^{123}I-MIBG imaging to evaluate the cardiac sympathetic activity beyond heart failure. The technique appears potentially relevant in the following clinical indications: 1) after heart transplantation since complete denervation of the allograft occurs after heart transplantation, 2) in case of arrhythmias, and 3) in amyloidosis. In addition, ^{123}I-MIBG SPECT imaging provides additive information for the evaluation of patients with cardiovascular risk factors such as DM, (resistant) hypertension, and obesity.

However, before above-mentioned indications should be included in cardiac guidelines, ^{123}I-MIBG imaging first needs to be included in the current heart failure guidelines. Given that in this group the success of the imaging technique has been proven, with results demonstrating in the past that heart-failure patients with a low late heart-to-mediastinum (H/M) ratio and/or an increased washout rate are at increased risk of arrhythmic events and cardiac death. One of the great disadvantages of ^{123}I-MIBG imaging is the long waiting period (up to 4 hours) between the two necessary scans. Focusing on ways to optimize the clinical usefulness of the technique, **Chapter 9** investigated whether performing the late cardiac ^{123}I-MIBG scan earlier than 4 hours post-injection has a relevant impact on the late H/M ratio. To this end, 49 patients with heart failure were scanned at 15 minutes (early scan) and at 1, 2, 3 and 4 hours (late scans) after an ^{123}I-MIBG injection. The results demonstrated that in the scans performed between 2 and 4 hours post-injection variations did not lead to clinically significant changes in the late H/M ratios. Earlier acquisition times therefore seem to be justified, clearing the way for more patient-friendly and time-efficient cardiac ^{123}I-MIBG imaging protocols.

The implementation of ^{123}I-MIBG imaging in clinical and study settings is also limited due to the lack of standardization, with large differences in the acquisition times of the late scans complicating the comparison of outcomes. To overcome this problem, **Chapter 10** evaluated a method in which the washout rates and late H/M ratios obtained 1 to 3 hours post-injection were compared with the measurements conducted 4 hours post-injection. The actual and estimated 4-hour washout rates and late H/M ratios derived from the counts made 1 hour post-injection demonstrated large differences. Whereas the estimated late 4-hour H/M ratios derived from the 2- and 3-hour post-injection counts did not differ from the actual ratios after 4 hours ($P=0.84$ and $P=0.06$). The actual and estimated 4-hour post-injection washout rates derived from the 3-hour counts also did not differ significantly

from each other (P=0.22). However, the mean estimated 4-hour washout rates derived from the 2-hour acquisitions did show a significant difference compared to the actual 4-hour washout rates (25±19 vs. 34±17, P<0.001). Therefore, the direct comparison method enables accurate estimation of the actual late H/M ratio and washout rate at 4 hours post-injection derived from the acquisitions at 3 hours post-injection. Because of the marked difference between the actual and estimated washout rates, estimations based on acquisitions made 2 hours post-injection should only be performed in exceptional cases, where the clinical relevance is high.

Conclusions and future perspectives

The diversity in medicine and the scope of both non-invasive and invasive diagnostic instruments and treatments for ischemic heart disease have grown exponentially the last few decades. The objective of this thesis was to establish the value of different imaging techniques and treatments targeting different stages of ischemic heart disease. The results reported have demonstrated that multimodality imaging is of high relevance in patients with ischemic heart disease, facilitating the decision-making process in different groups of patients and allowing medical and (non-)invasive treatments to be better tailored to individual cases from prevention to treatment while potentially improving prognoses.

Part I

If coronary CTA shows evidence of atherosclerosis in patients at high-risk with DM this may support the decision to start preventive treatment with aspirin. Whereas starting diabetic patients without atherosclerosis on aspirin seems unnecessary, especially since its use is not without hazards. However, further work is needed to evaluate whether not prescribing aspirin to this latter group is indeed justified. Additionally, more information is needed to establish at which age a first coronary CTA scan is opportune and whether or not, and if so, at which intervals scans should be repeated given that atherosclerosis is an ongoing process.

A common finding on coronary CTA is the presence of an intramural course of a coronary artery. However, since in patients with this anomaly event rates are low and similar to those found in patients without the anomaly, management and treatment do not appear to warrant adaptation. To date, the importance of this coronary anomaly appears to be overestimated, with even

chirurgical correction being performed as a therapeutic solution. Still, future research is needed. Perhaps that only patients with an intramural course of a coronary artery on coronary CTA with systolic compression on invasive coronary angiography need (additional) treatment (which is only in the minority of the patients the case).

Part II

Patients with first STEMI and multi-vessel CAD as evidenced by the initial angiogram did not benefit from complete revascularization in comparison with incomplete revascularization in terms of all-cause mortality. This is of importance, since more invasive interventions are not without hazards (e.g. procedure complications or stent thrombosis), while costs are relatively high. On the other hand, landmark trials did show that the risk of adverse cardiovascular events in patients having received immediate complete revascularisation was reduced relative to that reported for peers having undergone incomplete revascularisation. It should be noted that the largest differences in these trials between patients with and without complete revascularization occurred in PCI frequency.

Sub-analyses in this thesis demonstrated that men who survived the first 30 days on the long run benefit from complete revascularization in comparison with incomplete revascularization independent of baseline characteristics. In contrast, women did not demonstrate any difference between incomplete and complete revascularization in comparison with men with complete revascularization. It would be of interest to conduct a larger-scale investigation into the need of a gender-tailored revascularization strategy for STEMI survivors with multi-vessel CAD.

Part III

The correlation between LV GLS and myocardial infarct size assessed with SPECT MPI is not straight forward. Results demonstrated that the extent of ischemia influenced the correlation of LV GLS and infarct size on SPECT MPI: the group of patients with residual myocardial ischemia showed a weaker correlation between LV GLS and infarct size compared to patients without ischemia. This finding is of importance for a correct interpretation of LV GLS values. To increase the clinical usefulness and reliability of LV GLS it is of importance to fully elucidate which factors influence this parameter.

The results reported on in this thesis not only underline the value of evaluating the presence of denervation of the heart with ^{123}I-MIBG scintigraphy in patients with ischemic heart disease, they also underscore the technique's

relevance for other clinical indications. Therefore, it is of importance that implementation and standardization of ^{123}I-MIBG imaging in current guidelines will occur. Hopefully this process is eased with present evidence that shorter waiting periods are justified and comparison of results between different acquisition times is possible with a direct comparison method.

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Appendices

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Nederlandse samenvatting, conclusies en toekomstperspectieven

Nederlandse samenvatting

Onze kennis over ischemische hartziekten is de laatste decennia exponentieel gegroeid mede door de ontwikkeling en uitbreiding van verschillende diagnostische technieken en behandelmogelijkheden. Helaas blijft ondanks deze ontwikkelingen ischemisch hartlijden de nummer 1 doodsoorzaak, verantwoordelijk voor 1 op de 3 sterfgevallen wereldwijd.

In dit proefschrift worden diverse aspecten van een aantal beeldvormingstechnieken en invasieve-strategieën besproken ter preventie, behandeling en prognose van ischemische hartziekten. **Deel I** evalueert de rol van een computertomografie (CT) coronairangiografie voor de vroege detectie van coronairatherosclerose. **Deel II** onderzoekt wat de beste invasieve-strategie is bij patiënten met een ST-segment elevatie acuut myocardinfarct (STEMI) met meervatslijden. En **Deel III** onderzoekt de klinische waarden van 2-dimensionale strain echocardiografie en ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) scintigrafie in patiënten met ischemische hartziekten en onderzoekt manieren om het gebruik van deze non-invasieve beeldvormingstechnieken te optimaliseren.

DEEL I: DETECTIE VAN ATHEROSCLEROSE EN VARIATIES IN CORONAIR ANATOMIE

Hoofdstuk 2 van dit proefschrift onderzoekt de prevalentie van coronairlijden op een CT-scan van de coronairen in patiënten met diabetes mellitus (DM) en een sterk verhoogd cardiovasculair risicoprofiel. Hiertoe zijn 425 diabetes patiënten geïncludeerd met een sterk verhoogd cardiovasculair risicoprofiel. Deze patiënten waren verwezen voor een CT-scan van de coronairen zonder dat ze klachten hadden van pijn op de borst of een voorgeschiedenis van coronairlijden. Van de totale onderzoeksgroep had 73% enige vorm van coronairlijden dat was gedefinieerd als een stenose in een van de coronairen van ≥30%, hiervan had 48% obstructief coronairlijden (≥50% stenose). Verder bleek dat het type of aantal traditionele cardiovasculaire risicofactoren (bestaande uit hypertensie, hypercholesterolemie, roken, overgewicht en een positieve familieanamnese voor hart- en vaatziekten) niet van invloed was op de prevalentie van coronairlijden, behoudens de aanwezigheid van hypertensie. Hierbij was de prevalentie hoger bij patienten met hypertensie in vergelijking tot de andere risicofactoren. Bovenstaande resultaten laten zien dat het uitvoeren van een CT-scan van de coronairen van toegevoegde waarde kan zijn naast de aanwe-

zigheid van traditionele risicofactoren in de besluitvorming voor het wel of niet starten van acetylsalicylzuur voor de primaire preventie van hartziekten in patiënten met DM. Het starten van een bloedverdunner bij patiënten zonder coronairlijden lijkt niet zinvol.

Frequent wordt er op een CT-scan van de coronairen een intramyocardiaal beloop (van een gedeelte) van de coronair gezien. Onduidelijk is of de aanwezigheid van een intramyocardiaal beloop van de coronair therapeutische consequenties zou moeten hebben. **Hoofdstuk 3** onderzoekt of de aanwezigheid van een intramyocardiaal beloop van een van de coronairen geassocieerd is met een slechtere prognose. In de onderzoekspopulatie bestaande uit patiënten zonder obstructief coronairlijden op de CT-scan had 22% een intramyocardiaal beloop van de coronair op CT-scan. Gedurende een langdurige follow-up (mediaan 4.9 jaren) was het aantal cardiovasculaire events bestaande uit ziekenhuisopname in verband met instabiele angina pectoris, een niet fataal myocardinfarct en overlijden laag (43 events; 4.5%). Hierbij werd er geen significant verschil gezien tussen de patiënten met en zonder een intramyocardiaal beloop van de coronairen. Deze resultaten suggereren dat er geen therapeutische consequenties noodzakelijk zijn bij patiënten met een intramyocardiaal beloop van de coronair op een CT scan.

DEEL II: BEHANDELING VAN EEN ACUUT MYOCARD INFARCT

In patiënten met een STEMI is het verkrijgen van een spoed coronairangiogram en aansluitend revascularisatie van het aangedane vat de gouden standaard. Het initiële angiogram toont in meer dan de helft van deze patiënten meervats coronairlijden. Momenteel zijn er veel discussies over de beste invasieve-strategie (incomplete dan wel complete revascularisatie) met betrekking tot de vernauwing in het vat dat niet gerelateerd is aan het acute myocardinfarct. In **hoofdstuk 4** wordt een betere overleving gezien in de patiëntengroep met complete revascularisatie in vergelijking met de patiënten met een incomplete revascularisatie op zowel korte en lange termijn. Echter, na correctie voor klinische relevantie variabelen, werd er geen verschil meer gezien in overleving op zowel korte- als lange termijn. Deze resultaten komen overheen met eerdere observationele studies. Dit suggereert dat er geen voordeel in overleving wordt bereikt door complete revascularisatie in patiënten met een STEMI en meervatslijden.

Vrouwen met een STEMI hebben in vergelijking tot mannen een hogere kans op overlijden. Dit wordt onder andere veroorzaakt doordat zij vaak ouder zijn bij presentatie en meer co-morbiditeit hebben. Onbekend is echter of er man-vrouw verschillen zijn in overleving tussen verschillende invasieve-strategieën. **Hoofdstuk 5** kijkt of er mogelijk man-vrouw verschillen zijn in overleving tussen patiënten met complete revascularisatie en incomplete revascularisatie op korte en lange termijn. In de onderzoeksgroep van 490 patiënten, van wie 115 vrouwen, werd er na correctie voor patiëntkarakteristieken en angiografische kenmerken binnen 30 dagen geen verschil gevonden tussen mannen en vrouwen in overleving tussen incomplete en complete revasculairsatie. Gedurende een follow-up van 5 jaar hadden mannen, die de eerste 30 dagen hadden overleefd, met incomplete revascularisatie een 3 maal hoger risico op overlijden dan mannen met complete revascularisatie. Daarentegen hadden vrouwen, die de eerste 30 dagen hadden overleefd, een zelfde kans op overleving onafhankelijk van de revascularisatie-strategie.

DEEL III: PROGNOSE VAN ISCHEMISCHE HARTZIEKTEN

Sinds de introductie van percutane coronaire interventies is de prognose van patiënten met een hartinfarct aanzienlijk verbeterd. Dit heeft geleid tot een toename van het aantal patiënten met chronisch ischemisch hartlijden. Een van de belangrijkste voorspellers voor een slechte prognose is de grootte van het hartinfarct. De globale longitudinale strain van de linker ventrikel (LV GLS) is een goede echocardiografische parameter voor de infarct grootte. Deze waarde wordt echter door verschillende factoren beïnvloed. **Hoofdstuk 6** onderzoekt of en hoe de aanwezigheid van ischemie de correlatie beïnvloed van LV GLS en infarctgrootte vastgesteld met een myocard perfusie scintigrafie in patiënten met een eerste STEMI behandeld met primaire percutane coronaire interventie (PCI). Evenals in eerdere studies werd er in de totale studiepopulatie bestaande uit 1.128 patiënten een redelijke correlatie tussen LV GLS en infarctgrootte gezien. Deze correlatie werd verzwakt door de aanwezigheid van ischemie: in de groep van patiënten met een groot gebied van ischemie was de correlatie een stuk zwakker ($r=0.38$, $P<0.001$) dan in de groep van patiënten zonder ischemie ($r= 0.66$; $P<0.001$). Dit verschil bleef bestaan na correctie voor reeds bekende factoren die de LV GLS meting beïnvloeden. Hieruit kan worden geconcludeerd dat de correlatie van LV GLS

en infarctgrootte niet eenvoudig is en mede wordt beïnvloed door de aan- dan wel afwezigheid van ischemie.

Een andere belangrijke voorspeller voor een slechte prognose in patiënten met een hartinfarct is de verminderde sympathisch neuronale opname in het myocard. Dit kan worden gevisualiseerd met een ^{123}Iodine gelabeld norepinephrine analoog ^{123}I-MIBG. Gebruikelijk is om de verminderde neuronale opname zichtbaar te maken met planaire opnames en weer te geven als hart-mediastinale ratio (H/M ratio). Ook kan de cardiale uitwas tussen de vroege en late planaire opname worden berekend, de zogenaamde 'washout ratio'.

Hoofdstuk 7 demonstreert in een review de trends in het gebruik van beeldvorming met ^{123}I-MIBG in patiënten met hartfalen. De review toont aan dat er een toename is in het gebruik van ^{123}I-MIBG SPECT hierbij wordt in tegenstelling tot planaire opnames ook informatie verkregen over regionale verschillen in innervatie. Cardiale denervatie wordt niet alleen gezien in patiënten met hartfalen. Hierdoor wordt deze beeldvormingstechniek ook steeds meer ingezet bij andere hartziekten. **Hoofstuk 8** geeft een overzicht van mogelijk toekomstige indicaties voor het gebruik van beeldvorming met ^{123}I-MIBG. Met name in patiënten na harttransplantatie, hartritmestoornissen en amyloïdosis kan beeldvorming met ^{123}I-MIBG van meerwaarde zijn. Het geeft tevens extra informatie in patiënten met DM, (resistente) hypertensie en obesitas.

Echter, voordat beeldvorming met ^{123}I-MIBG bij bovenstaande patiëntengroepen moet worden toegevoegd aan de richtlijn, is het van belang dat de meerwaarde van deze beeldvormingstechniek bij patiënten met hartfalen wordt erkend. Het bewijs in deze patiëntengroep is namelijk reeds ruimschoots aanwezig: studies hebben in het verleden laten zien dat patiënten met hartfalen met een lage H/M ratio dan wel een hoge washout ratio een verhoogd risico hebben op het krijgen van ritmestoornissen en overlijden. Een van de grote nadelen van deze beeldvormingstechniek in de prakijk is echter de lange wachttijd van 4 uur tussen de eerste en tweede scan. Om het gebruik te doen stijgen onderzoekt **hoofdstuk 9** of het mogelijk is om de late opname na 4 uur te vervroegen. Voor dit onderzoek is er behalve na 15 minuten en 4 uur ook een opname gemaakt na 1 uur, 2 uur en 3 uur. Hierbij zijn van alle scans de H/M ratios berekend. Onderzoek laat zien dat er kleine verschillen in H/M ratio zijn tussen de scans van 2, 3 en 4 uur. Hierdoor lijkt het verkrijgen van de late opnames eerder dan na 4 uur na injectie van ^{123}I-MIBG gerechtvaardigd, waardoor een patiëntvriendelijker en tijdefficiënter protocol kan worden opgesteld.

De implementatie wordt ook bemoeilijkt door de afwezigheid van standaardisatie van beeldvorming met ^{123}I-MIBG. Hierdoor bestaan er grote verschillen in tijdstip na injectie voor de late opname. **Hoofdstuk 10** onderzoekt een methode om het vergelijken van H/M ratio maar ook de washout ratio van verschillende afnametijdstippen met de late opname na 4 uur te kunnen vergelijken. Hierbij wordt een formule gebruikt die de daadwerkelijke opname exploreert naar 4 uur.

Conclusie en toekomstperspectieven

Over de afgelopen jaren zijn zowel het aantal non-invasieve als invasieve diagnostische technieken en behandelingen in patiënten met ischemisch hartlijden exponentieel gegroeid. Het doel van dit proefschrift is om tijdens verschillende stadia van ischemische hartziekten de waarden van verschillende beeldvormingstechnieken en invasieve strategieën in kaart te brengen. De genoemde resultaten tonen aan dat non-invasieve beeldvorming van meerwaarde kan zijn bij de totstandkoming van keuzes in medicamenteuze therapieën en invasieve strategieën in de individuele patiënt in het kader van preventie tot behandeling met als doel de prognose te verbeteren.

Deel I

In het kader van primaire preventie wordt op dit moment bij diabeten met een verhoogd cardiovasculair risicoprofiel geadviseerd te overwegen acetylsalicylzuur te starten. De aanwezigheid of afwezigheid van atherosclerose op een CT coronairangiografie kan deze keuze wellicht vergemakkelijken, aangezien het starten van acetylsalicylzuur in patiënten met DM zonder atherosclerose op de CT coronairangiografie niet zinvol lijkt, rekening houdend met de bijwerkingen die niet gering zijn. Hierdoor kan bij minimaal een kwart van de patiënten bloedverdunning worden onthouden. De vraag is echter op welke leeftijd men diabeten op de aanwezigheid van atherosclerose op CT coronairangiografie zou moeten screenen en of men de CT zou moeten herhalen in de wetenschap dat atherosclerose een dynamisch en progressief proces is.

Een intramuraal beloop van de coronairarterie is een frequent voorkomende toevalsbevinding. Aangezien er geen verschil in uitkomst is tussen patiënten met en zonder een intramuraal beloop van de coronairarterie lijkt verdere diagnostiek of behandeling niet noodzakelijk. Dit is een belangrijke bevinding aangezien tot op heden chirurgische interventies ter correctie van de aanwezigheid van een intramuraal beloop van belang werd geacht. Meer

onderzoek is echter noodzakelijk. Wellicht dat bij de kleine groep van patiënten met een intramuraal beloop van de coronairarterie met systolische compressie op een invasieve coronairangiogram een behandeling wel van aanvullende waarde kan zijn.

Deel II

Patiënten met een STEMI en meervatslijden hadden geen voordeel in het kader van overleving met complete revascularisatie in vergelijking met patiënten bij wie alleen het aangedane vat dat verantwoordelijk was voor het hartinfarct werd gerevasculariseerd. Aan de andere kant laten grote gerandomiseerde studies wel voordelen zien van direct complete revascularisatie in vergelijking tot incomplete revascularisatie. Echter, de grootste verschillen werden in deze studies gezien in de frequentie van revascularisatie en niet in mortaliteit.

Resultaten in dit proefschrift laten zien dat mannen mogelijk meer baat hebben bij complete revascularisatie in vergelijking tot incomplete revascularisatie dan vrouwen. Toekomstig grootschaliger onderzoek is noodzakelijk om nader te onderzoeken waar dit verschil in zit en of er een geslacht toegesneden revascularisatie-strategie noodzakelijk is bij patiënten met een STEMI met meervatslijden.

Deel III

De correlatie tussen LV GLS en infarctgrootte is niet eenvoudig. Resultaten laten zien dat de aanwezigheid van ischemie deze correlatie verzwakt: patiënten met ischemie hebben een zwakkere correlatie tussen LV GLS en infarctgrootte dan de groep van patiënten zonder ischemie. Deze bevinding is van belang bij het interpreteren van LV GLS metingen. Om de klinische bruikbaarheid en betrouwbaarheid van deze echocardiografische parameter te vergroten is het van belang dat door middel van toekomstig onderzoek gekeken wordt of er nog meer parameters zijn die deze correlatie beïnvloeden.

Huidige resultaten benadrukken dat de prognostische waarde van verminderd sympathische neuronale opname van het myocard bij patiënten met ischemisch hartlijden groot is en dat er in de toekomst ook andere belangrijke potentiële indicaties zijn voor het gebruik van ^{123}I-MIBG scintigrafie.

Door de wachttijd tussen de vroege en late scan te vervroegen en het vergelijken van resultaten van verschillende opname tijdstippen door de directe vergelijkingsmethode te vergemakkelijken zal ^{123}I-MIBG scintigrafie hopelijk eindelijk kunnen worden geïmplementeerd in de huidige richtlijnen voor patiënten met ischemisch hartfalen.

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List of publications

List of publications

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Dankwoord

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Curriculum Vitae

Curriculum Vitae

Aukeline Carlijn Dimitriu-Leen werd geboren op 28 november 1984 in Wageningen. Tijdens haar jeugd speelde zij viool, waarbij ze als lid van het Arnhems Interscholair Orkest concertreizen heeft gemaakt naar onder andere St. Maarten, Canada en Noorwegen. Na het behalen van haar VWO diploma aan het Dorenweerd College in 2003, startte zij met de studie Geneeskunde aan het Radboud Universitair Medisch Centrum te Nijmegen.

Tijdens haar opleiding was zij actief werkzaam in het klinisch laboratorium en werkzaam in het verpleegtehuis. In 2009 behaalde zij haar artsexamen, waarbij het klinisch deel cum laude werd afgerond. Tijdens de opleiding groeide haar interesse voor de cardiologie. Na een korte periode als arts-assistent niet in opleiding in het Rijnstate ziekenhuis te Arnhem kwam zij in opleiding bij de cardiologie van het Radboud UMC te Nijmegen. Tijdens de eerste jaren van de interne en cardiologie opleiding was zij lid van diverse commissies waaronder de necrologie commissie en de antistolling commissie. Hierbij groeide haar interesse voor wetenschappelijk onderzoek. In 2014 besloot zij haar opleiding tot cardioloog te onderbreken om zich volledig op het wetenschappelijk onderzoek toe te kunnen leggen in het Leids Universitair Medisch Centrum te Leiden. De resultaten hiervan staan beschreven in dit proefschrift.

Momenteel vervolgt zij haar opleiding Cardiologie in het Radboud UMC te Nijmegen (opleider: Dr. A. van Dijk) die zij in 2020 hoopt af te ronden. Aukelien is getrouwd met George en samen hebben zij twee kinderen, Philine en Bjorn. Medio juni verwachten zij hun derde kind.