# Clinical advances in cardiovascular magnetic resonace imaging and angiography

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# Chapter 8

## Prognostic value of cardiovascular MR imaging biomarkers on outcome in peripheral arterial disease: a 6-year follow-up pilot study

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# Abstract

The objective of this pilot study was to explore the prognostic value of outcome of cardiovascular magnetic resonance (MR) imaging biomarkers in patients with symptomatic peripheral arterial disease (PAD) in comparison with traditional risk factors. Forty-two consecutive patients (mean age 64 ± 11 years, 22 men) referred for contrast-enhanced MR angiography (CE-MRA) were included. At baseline a comprehensive cardiovascular MRI examination was performed: CE-MRA of the infra-renal aorta and run-off vessels, carotid vessel wall imaging, cardiac cine imaging and aortic pulse wave velocity (PWV) assessment. Patients were categorized for outcome at 72 ± 5 months follow-up. One patient was lost to follow-up. Over 6 years, six patients had died (mortality rate 14.6%), six patients (14.6%) had experienced a cardiac event and three patients (7.3%) a cerebral event. The mean MRA stenosis class (i.e., average stenosis severity visually scored over 27 standardized segments) was a significant independent predictor for all-cause mortality (beta 3.0 ± standard error 1.3, p=0.02). Descending aorta PWV, age and diabetes mellitus were interrelated with stenosis severity but none of these were significant independent predictors. For cardiac morbidity, left ventricular ejection fraction (LVEF) and mean MRA stenosis class were associated, but only LVEF was a significant independent predictor (beta −0.14 ± 0.05, p=0.005). Diabetes mellitus was a significant independent predictor for cerebral morbidity (beta 2.8 ± 1.3, p=0.03). Significant independent predictors for outcome in PAD are mean MRA stenosis class for all-cause mortality, LVEF for cardiac morbidity and diabetes mellitus for cerebral morbidity.

# Introduction

Peripheral arterial disease (PAD) is an important clinical manifestation of vascular disease in atherosclerosis. Due to increased life expectancy the prevalence of PAD increased worldwide over the last decades by more than 20%.[1,2] The prevalence rates increase with age and are associated with increased mortality[3] and cardiac and cerebral events.[4,5] Identifying prognostic indicators for patients with PAD is important for risk factor reduction and for developing new therapies.[6,7] Assessment of traditional risk factors remains essential for risk stratification,[8] however, evidence on the utility of non-invasive imaging for risk assessment in cardiovascular disease (CVD) is growing.[9] Several previous studies observed high risk of mortality and cardiovascular events in patients with PAD, diagnosed with non-invasive testing techniques as segmental blood pressure, Doppler ultrasonography[3] and ankle-brachial index (ABI).[10,11] Moreover, progressive PAD with declining ABI values was shown to be significantly and independently associated with increased cardiovascular risk.[4] However, ABI has also been associated with high false negative rates in prediction of outcome[12] and underestimation of prevalence of PAD.[13]

In recent years contrast-enhanced magnetic resonance angiography (CE-MRA) has evolved into an important non-invasive imaging technique in patients suspected with symptomatic PAD.[14] In clinical routine, CE-MRA is now widely used for diagnosis, work-up and treatment planning. In our institute, a patient population with symptomatic PAD underwent a comprehensive MRI examination consisting of not only CE-MRA of the run-off vessels, but also carotid vessel wall imaging, cardiac cine imaging for assessing left ventricular volume, mass and function, and assessment of the aortic pulse wave velocity (PWV) from velocity-encoded MRI as a surrogate marker of aortic stiffness. This study was performed 6 years ago with the aim to evaluate the association of stenosis severity on CE-MRA with imaging biomarkers describing cardiovascular morphology and function. Our results showed a stronger association between PWV measured in the descending aorta and severity of PAD in the peripheral arteries than the PWV in the proximal aorta and the normalized wall index (NWI), measured with black-blood MRI in the common carotid artery.[15] The purpose of the current pilot study was to evaluate if these biomarkers obtained with cardiovascular MR imaging showed prognostic value of outcome after a follow-up period of 6 years in relation to traditional risk factors [i.e., age, gender, body mass index (BMI), hypertension, diabetes mellitus, levels of triglyceride (TG) and high-density lipoprotein (HDL) in blood plasma samples, ABI and Fontaine class]. Therefore, a follow-up evaluation of the patient population with symptomatic PAD was performed to examine which cardiovascular MR imaging biomarker or traditional risk factor is an independent predictor for all-cause mortality, cardiac or cerebral morbidity.

# Materials and Methods

In our study, 42 consecutive patients (23 men; mean age 64±10 years) were included from July 2008 to October 2009. All patients were clinically referred for CE-MRA evaluation in the work-up for PAD. The following baseline patient characteristics were obtained: age, gender, weight, length, BMI, hypertension, diabetes mellitus, levels of TG and HDL in blood plasma samples, ABI and Fontaine class. A cut-off value of BMI>30 was used to classify obesity and levels of TG≥150 mg/dL and HDL≤50 mg/dL in women or ≤40 mg/dL in men as associated with metabolic syndrome.[16]
In all patients, a comprehensive cardiovascular MRI examination was performed consisting of CE-MRA of the run-off vessels, carotid vessel wall imaging, cardiac cine imaging and assessment of the aortic PWV from through-plane velocity-encoded MRI. In all patients, the glomerular filtration rate (GFR) was >60 mL/min/1.73 $m^2$. No adverse reactions or complications occurred during or after MRA. Institutional Review Board approval and written informed consent was obtained from all patients.
Of note, a study of this patient population has been published describing the site-specific association between descending aorta PWV and peripheral arterial stenosis severity.[15] Furthermore, data of 20 patients of the present study has been used previously in a study comparing different MRA techniques of the run-off vessels.[17] However, none of these publications reported outcome data, which is the purpose of the current study.

## MRI protocol

MRI was performed using a 3T MRI system (Achieva X-series, release 2.1; Philips Healthcare, Best, The Netherlands). CE-MRA was performed in three consecutive stations and has been described before.[17] In short, standardized three-station single-injection CE-MRA was performed, including the abdominal aorta, iliac arteries and run-off vessels. The contrast protocol consisted of a biphasic contrast injection using an MRI-compatible injector (Spectris MR injector; Medrad, Indianola, PA). In total, 0.1 mmol/kg body weight gadoterate meglumine (Gd-DOTA, Guerbet, Paris, France) was administered. The first half of the contrast bolus was administered at 1.2 mL/s and the remaining half at 0.5 mL/s. Contrast injection was followed by 15 mL saline flush at 0.6 mL/s. Timing of the contrast arrival was determined by means of automatic bolus timing (BolusTrak; Philips Healthcare, Best, The Netherlands). For signal transmission and reception a quadrature body coil was used in all three stations. Preceding the CE-MRA procedure, the vessel wall of the left common carotid artery was imaged in all patients. A multi-slice two-dimensional (2D) black-blood imaging sequence was used.[18] Starting from the carotid flow divider, eight contiguous slices of 2 mm thick were acquired in caudal direction. To maximize contrast between the carotid vessel wall, the lumen blood pool and the surrounding tissue, a 2D dual-inversion-recovery

(black-blood) gradient-echo technique with spectral selective fat suppression was used. Vector-cardiogram (VCG)-triggering was used for gated data collection at end-diastole and data was acquired at each RR interval. A two-element Flex-M surface coil was positioned around the neck of the patient.
Furthermore, cardiac cine images were acquired in multi-slice short-axis orientation using a dedicated six-element cardiac coil for signal reception.[19] A balanced steady-state free-precession technique was used with retrospective VCG-gating. Each slice was acquired using breath-holding present one average heartbeat. Finally, the aortic PWV, defined as the flow wave propagation speed, was assessed regionally in the aorta, from two through-plane velocity-encoded MRI acquisitions: one transecting the ascending and descending thoracic aorta and one transecting the distal abdominal aorta.[20] The six-element cardiac coil was used for signal reception and both velocity-encoded MRI acquisitions were non-segmented gradient-echo sequences with a maximal velocity sensitivity of 150 cm/s at the proximal level and 100 cm/s at the distal level. Retrospective VCG-gating was used with a maximal number of phases reconstructed, resulting in a true temporal resolution of 9.8 ms.

## Image analysis

MR angiographic images were reviewed at random and in consensus by two MR radiologists (HvdB and AT; 16 and 18 years of experience with CE-MRA, respectively). CE-MRA images were analyzed on a remote workstation. The arterial tree from infrarenal aorta down to the peripheral arteries was divided into 27 segments (Figure 8.1). The severity of each stenosis was visually graded according to a five point scale: class 1 (0%–stenosis), 2 (1–50%), 3 (51–75%), 4 (76–99%) and 5 (100%). The highest stenosis class per segment was determined, and next, the highest stenosis class over all available segments (maximal 27) was determined, resulting in one value per patient (max MRA stenosis class). Also, the mean MRA stenosis class, obtained from the highest stenosis class per segment and averaged over all available segments was calculated. Stenosis classification per patient was performed blinded from carotid vessel wall and aortic PWV analysis.
Cross-sectional carotid vessel wall area (VWA) and total vessel area were obtained using VesselMass software (Leiden University Medical Center, Leiden, The Netherlands). From the eight acquired slices over the common carotid artery, the center four slices were included for analysis. The NWI[21] was calculated as NWI = VWA/total vessel area.
Acquired cardiac short-axis images were analyzed on a remote workstation (View Forum, Philips Healthcare, Best, The Netherlands). Manual segmentation of the left ventricle was performed by a MR radiologist (HvdB, 16 years of experience with cardiac MR), resulting in endo- and epicardial contours for end systolic and end

diastolic phases. From planimetry, the end systolic and end diastolic volumes were calculated, as well as the left ventricular ejection fraction (LVEF) and LV mass.
The aortic PWV was obtained after velocity mapping at the ascending, thoracic descending and abdominal aorta. From systolic flow wave-time curves, aortic arch PWV and descending aorta PWV were obtained automatically using the transit-time method.[20]
In all patients mean MRA stenosis class, max MRA stenosis class, aortic arch PWV, descending aorta PWV, and carotid NWI were determined. In all patients but one the LVEF and LV mass were obtained. One patient could not tolerate multiple breath-holding and evaluation of short-axis LV images was not possible in this patient.
After a period of 6 years, mean baseline values of the cardiovascular MR imaging biomarkers were categorized for outcome. The primary outcome end point was all-cause mortality. The secondary end points were cardiac event (i.e. myocardial infarction, heart failure, coronary artery intervention) and cerebral event (i.e., stroke).

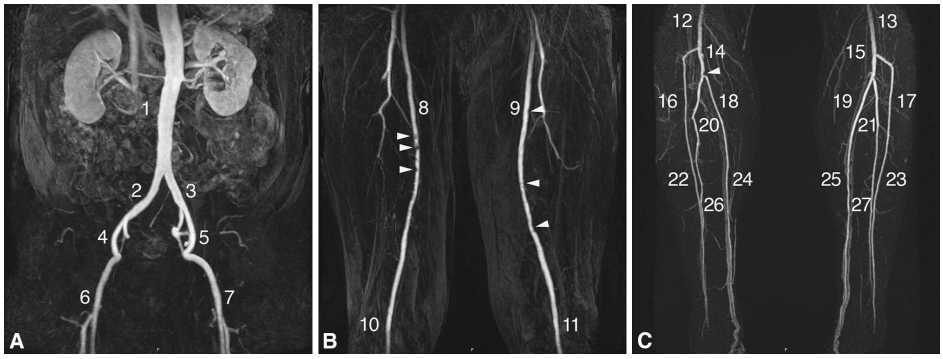


Figure 8.1 3T coronal CE-MRA maximum-intensity-projection images with 27 segments in a 68-year-old man presenting with claudication of the right leg. **A** Infra-renal aorta and iliac arteries with no stenosis. **B** Atherosclerotic changes in the right and left superficial femoral artery (*arrowheads*). **C** Stenosis in the right tibiofibular trunk (*arrowhead*). Minor venous enhancement on both sides. Segment numbering: *1* the infrarenal aorta; *2, 3* common iliac arteries; *4, 5* external iliac arteries; *6, 7* common femoral arteries; *8, 9* superficial femoral arteries; *10, 11* popliteal arteries in the thigh station; *12, 13* popliteal arteries in the calf station; *14, 15* tibiofibular trunk; *16–21* proximal and *22–27* distal halves of the anterior and posterior tibial arteries and peroneal arteries.

## Statistical analysis

Shapiro–Wilk tests were performed to test normality of data distribution. Variables are expressed as mean ± standard deviation (SD) or median (interquartile range), where appropriate. Mann–Whitney *U* tests were performed to determine significance of differences between groups of patients. Binomial logistic regression analysis with backward likelihood ratio was performed to investigate which of the predictors was

an independent significant predictor for mortality, a cardiac or cerebral event. A p value of <0.05 is considered statistically significant. Statistical analysis was performed using IBM SPSS software version 23 (Armonk, NY, USA).

## Results

For forty-one patients, 6 year follow-up data was available (one patient was lost to follow-up as no information of this patient was available since baseline examination). Baseline characteristics of these 41 patients are presented in Table 8.1. Only age of the patients, weight, length, BMI, ABI and LV mass were normally distributed. The mean follow-up period of the surviving patients was 72±5 months. Over the course of 6 years, six patients had died (mortality rate 14.6%). Six patients (14.6%) had experienced a cardiac event (i.e., three patients underwent bypass graft surgery from which one died after heart failure, one patient underwent percutaneous transluminal coronary angioplasty, one patient developed tachycardia and died, and one patient was diagnosed with heart failure and died). Three patients (7.3%) experienced a cerebral event (i.e., two cerebrovascular accident and one transient ischemic attack). One patient (2.4%) had undergone carotid endarterectomy.

Table 8.1 Baseline patient characteristics

| | |
|---|---|
| Age (years) | 64 ± 11 |
| Gender (M/F) | 22 / 19 |
| Weight (kg) | 76 ± 14 |
| Length (cm) | 170 ± 10 |
| BMI | 26.0 ± 3.7 |
| BMI > 30 (yes/no) | 8 / 33 |
| Hypertension (yes/no) | 27 / 14 |
| Diabetes Mellitus (yes/no) | 6 / 35 |
| TG (mg/dL) | 151 (115 – 213) |
| TG ≥ 150 mg/dL (yes/no) | 13 / 28 |
| HDL (mg/dL) | 52 (43 – 62) |
| HDL ≤ 50 mg/dL in men, ≤ 40 mg/dL in women (yes/no) | 13 / 28 |
| Fontaine class (stages I/IIa/IIb/III/IV) | 0 / 23 / 11 / 4 / 3 |
| ABI in rest | 0.75 ± 0.21 |
| Mean MRA stenosis class | 1.4 (1.2 – 1.8) |
| Max MRA stenosis class | 5 (4 – 5) |
| Aortic arch PWV (m/s) | 8.3 (7.0 – 10.5) |
| Descending aorta PWV (m/s) | 8.6 (6.4 – 11.2) |
| LVEF (%) | 60 (56 – 64) |
| LV mass (g) | 90 ± 25 |
| Carotid NWI | 0.47 (0.43 – 0.52) |

BMI: Body Mass Index; TG: Triglyceride; HDL: High-density lipoprotein; ABI: ankle-brachial index; MRA: magnetic resonance angiography; PWV: pulse wave velocity; LVEF: left ventricular ejection fraction; NWI: normalized wall index

Mean or median baseline values of the predictors, categorized for outcome (i.e., all-cause mortality, cardiac event, cerebral event), are presented in Table 8.2. Mann–Whitney *U* tests were performed to investigate the statistical significance between patient groups categorized for outcome. Age, diagnosis of diabetes mellitus, mean stenosis class and descending aorta PWV were significantly different among patients categorized for all-cause mortality. Mean stenosis class and LVEF were significantly different among patients categorized with or without cardiac event and diagnosis of diabetes mellitus was significantly different among patients categorized with or without cerebral event. Binomial logistic regression analysis was performed to investigate which of the predictors is an independent significant predictor for all-cause mortality, a cardiac or cerebral event. For all-cause mortality only the mean MRA stenosis class was a significant independent predictor (beta 3.0±standard error 1.3, p=0.02), for a cardiac event LVEF was a significant independent predictor (beta −0.14 ± standard error 0.05, p=0.005) and diagnosis of diabetes mellitus was a significant independent predictor for a cerebral event (beta 2.8 ± standard error 1.3, p=0.03).

## Discussion

The present pilot study prospectively evaluated the prognostic value of cardiovascular MR imaging biomarkers (i.e., mean MRA stenosis class, max MRA stenosis class, aortic arch PWV, descending aorta PWV, LVEF, LV mass, and carotid NWI) obtained in a comprehensive MR imaging study in patients with PAD over an approximately 6 year period. The prognostic value of these imaging biomarkers was compared to traditional risk factors such as age, BMI, TG and HDL levels in blood plasma, diabetes mellitus and hypertension. We evaluated which biomarker is an independent predictor for all-cause mortality, or cardiac or cerebral morbidity. The main findings of our preliminary study are: (1) For all-cause mortality, age, diabetes mellitus, mean MRA stenosis class and descending aorta PWV were significant predictors. However only mean MRA stenosis class was independently significant. (2) For cardiac morbidity, mean MRA stenosis class and LVEF were significant predictors, however, only LVEF was a significant independent predictor. (3) For cerebral morbidity, only diagnosis of diabetes mellitus but none of the described cardiovascular MR imaging biomarkers was a significant independent predictor in this explorative study.

Table 8.2 Mean baseline value of predictors categorized for outcome at 6-year follow-up.

| | All-cause mortality over 6-year follow-up | | | Cardiac event over 6-year follow-up | | | Cerebral event over 6-year follow-up | | |
|---|---|---|---|---|---|---|---|---|---|
| | Yes (N=6) | No (N=35) | p | Yes (N=6) | No (N=35) | p | Yes (N=3) | No (N=38) | p |
| Age (years) | 73 ± 9 | 63 ± 10 | 0.02* | 71 ± 10 | 63 ± 10 | 0.11 | 62 ± 12 | 64 ± 11 | 0.66 |
| Gender (M/F) | 4/2 | 18/17 | 0.52 | 3/3 | 19/16 | 0.86 | 2/1 | 20/18 | 0.64 |
| BMI | 25.2 ± 3.4 | 26.1 ± 3.8 | 0.56 | 25.5 ± 3.6 | 26.1 ± 3.8 | 0.69 | 27.1 ± 4.0 | 25.9 ± 3.7 | 0.60 |
| BMI>30 (yes/no) | 1/5 | 7/28 | 0.85 | 1/5 | 7/28 | 0.85 | 1/2 | 7/31 | 0.54 |
| Hypertension (yes/no) | 5/1 | 22/13 | 0.34 | 4/2 | 23/12 | 0.97 | 2/1 | 25/13 | 0.98 |
| Diabetes Mellitus (yes/no) | 0/6 | 6/29 | 0.01* | 1/5 | 5/30 | 0.88 | 2/1 | 4/34 | 0.007* |
| TG (mg/dL) | 148 (75 – 281) | 151 (115 – 213) | 0.99 | 104 (75 – 190) | 159 (115 – 213) | 0.29 | 177 (124 – 283) | 146 (113 – 213) | 0.80 |
| TG ≥150 mg/dL (yes/no) | 3/3 | 10/25 | 0.31 | 1/5 | 12/23 | 0.40 | 1/2 | 12/26 | 0.95 |
| HDL (mg/dL) | 62 (43 – 73) | 49 (43 – 60) | 0.52 | 52 (38 – 73) | 52 (43 – 61) | 0.93 | 49 (48 – 62) | 53 (42 – 63) | 0.87 |
| HDL ≤50 mg/dL in men, ≤40 mg/dL in women (yes/no) | 0/6 | 13/22 | 0.07 | 3/3 | 10/25 | 0.31 | 1/2 | 12/26 | 0.95 |
| ABI | 0.68 ± 0.20 | 0.75 ± 0.16 | 0.31 | 0.64 ± 0.17 | 0.76 ± 0.16 | 0.10 | 0.78 ± 0.14 | 0.74 ± 0.17 | 0.69 |
| Mean MRA stenosis class | 2.1 (1.7 – 2.6) | 1.4 (1.2 – 1.6) | <0.001* | 1.8 (1.3 – 2.6) | 1.4 (1.2 – 1.7) | 0.02* | 1.3 (1.3 – 1.3) | 1.4 (1.2 – 1.9) | 0.52 |
| Max MRA stenosis class | 5 (4 – 5) | 5 (4 – 5) | 0.52 | 5 (4 – 5) | 5 (4 – 5) | 0.52 | 4 (3 – 5) | 5 (4 – 5) | 0.60 |
| Aortic arch PWV (m/s) | 8.4 (6.7 – 14.3) | 8.3 (6.8 – 10.3) | 0.91 | 7.7 (6.7 – 11.5) | 8.8 (6.8 – 10.7) | 0.78 | 7.7 (4.6 – 7.7) | 8.8 (7.1 – 10.7) | 0.38 |
| Descending aorta PWV (m/s) | 11.3 (8.7 – 15.6) | 7.9 (6.2 – 10.0) | 0.01* | 9.1 (5.3 – 14.5) | 8.1 (6.6 – 11.2) | 0.27 | 7.7 (5.3 – 7.6) | 8.7 (6.5 – 11.3) | 0.43 |
| LV EF (%) | 49 (38 – 66) | 60 (56 – 65) (N=34) | 0.10 | 39 (37 – 52) | 61 (58 – 65) (N=34) | <0.001* | 82 (63 – 82) | 60 (54 – 64) (N=37) | 0.34 |
| LV mass (g) | 100 ± 31 | 88 ± 24 (N=34) | 0.33 | 106 ± 32 | 87 ± 23 (N=34) | 0.09 | 88 ± 28 | 90 ± 26 (N=37) | 0.86 |
| Carotid NWI | 0.45 (0.43 – 0.50) | 0.47 (0.42 – 0.52) | 0.85 | 0.49 (0.46 – 0.58) | 0.46 (0.42 – 0.51) | 0.14 | 0.47 (0.36 – 0.47) | 0.47 (0.43 – 0.52) | 0.96 |

BMI: Body Mass Index; TG: Triglyceride; HDL: High-density lipoprotein; ABI: ankle-brachial index; MRA: magnetic resonance angiography; PWV: pulse wave velocity; LVEF: left ventricular ejection fraction; NWI: normalized wall index. * statistically significant.

The Task Force of American College of Cardiology and American Heart Association emphasizes the value of traditional risk factors assessment for risk stratification in CVD,[8] but also acknowledged the added value of non-invasive imaging.[9] As atherosclerosis is a systemic process in CVD and each vascular bed shows differential patterns of plaque development, mediated by clinical, genetic and comorbid factors that are associated with the disease[22] the use of multisite imaging may improve risk discrimination for disease-specific outcomes.[15,23] To our knowledge this is the first prospective follow-up study to describe the prognostic value of cardiovascular MR imaging biomarkers obtained in a comprehensive MR imaging protocol in patients with symptomatic PAD and to compare to traditional risk factors. Large-scale studies in symptomatic PAD patients have found a three to six times higher risk for mortality from CVD and a 2.5 times higher overall mortality rate.[3,24] Moreover, long-term prognosis in patients with PAD after endovascular therapy is extremely poor for high-risk symptomatic patients.[25] Therefore, evaluation of new imaging biomarkers may be important in the work-up and risk stratification in patients with symptomatic PAD, or with CVD in general. Several studies have presented association of traditional biomarkers derived from conventional techniques with all-cause mortality, cardiac events, and cerebral events in patients with PAD. Kals et al. reported an independent relationship between arterial wall stiffness obtained with tonometry and all-cause and cardiovascular mortality. Increased small artery elasticity was directly related to mortality in patients with PAD whereas large artery stiffness was not significantly related.[26] In recent literature MRI with velocity-encoding has been reported and validated as an accurate non-invasive method to assess aortic PWV with high reproducibility.[20] In the present study aortic arch PWV and descending aorta PWV were evaluated for prognostic value in patients with symptomatic PAD. Aortic arch PWV showed no significant prognostic value when evaluated for all-cause mortality, or cardiac, or cerebral events. However, for all-cause mortality descending aorta PWV was a significant predictor, as well as age, diagnosis of diabetes mellitus and PAD stenosis severity visually scored on CE-MRA. This is in line with the reported result at baseline in these patients, where a strong site-specific association between descending aorta PWV and PAD stenosis severity was found, in contrast to the absent association with aortic arch PWV.[15] Also, it is well-known that aortic stiffness and aortic PWV are indeed age-dependent[27,28] and aortic PWV has been related to diabetes mellitus.[29] Therefore, interrelation between the biomarkers age, diabetes mellitus, descending aorta PWV and stenosis severity is expected. However, only stenosis severity remained a significant independent predictor for all-cause mortality whereas descending aorta PWV did not remain significant. Although our sample size maybe relatively small, this finding is in good agreement with the reported data in the study of Kals et al..[26]

Several studies using the ABI showed that a low ABI (low ABI defined as ABI <0.90) predicts all-cause mortality and cardiovascular events.[10,30] A strong trend for

increasing risk with decreasing ABI has been demonstrated.[31] Moreover, Resnick et al. showed a U-shaped association between low and high ABI (>1.40) and mortality risk, with significantly increased risk in patients with low ABI and high ABI.[11] In the clinical work-up of patients suspected of PAD, a low ABI is a strong indicator of the presence of arterial disease.[32] However, Doobay et al. showed that due to the false-negative rates a normal ABI does not rule out risk of PAD.[12] Furthermore, Wikström et al. reported that when compared with CE-MRA a low ABI may underestimate the prevalence of PAD.[13] These conflicting results indeed underline the need for evaluation of new imaging biomarkers as an alternative for ABI in the follow-up and risk stratification in patients with symptomatic PAD.

Nowadays, CE-MRA is an important tool in the diagnosis and clinical work-up in patients suspected for PAD. However, CE-MRA may not be possible in all patients, with respect to the association of nephrogenic systemic fibrosis and gadolinium.[33] Our results show that descending aorta PWV is interrelated with stenosis severity from CE-MRA and as such, may be useful as an alternative predictor for all-cause mortality when CE-MRA is not possible.

Assessment of LV systolic function is important in assessing prognosis of several cardiac diseases and risk evaluation for mortality[34] and is a recognized risk factor for postoperative morbidity after vascular surgery.[35] In our preliminary study LVEF was a significant independent predictor for cardiac morbidity in patients with symptomatic PAD. This finding underlines to assess LV function in patients with symptomatic PAD for work-up and risk stratification. Further evaluation of the underlying causes of reduced LVEF may add to the prognostic value for occurrence of future cardiac events. Reduced LVEF may have been associated with myocardial infarction in some of these patients, as this association has been shown in post infarction patients.[36] Specifically in such patients, delayed CE imaging may play an important role as an imaging biomarker additional to LVEF, as myocardial viability is related to ventricular pathology whereas LVEF does not contain such information.[37]

Araki et al. reported a markedly increased prevalence of cerebral infarction and carotid artery stenosis in patients with PAD.[38] In our patient population over 6 year follow-up period, however, in only one patient carotid endarterectomy was reported and the small number of cerebral events (N=3) did not show significant relation with the MR imaging biomarkers. Only diagnosis of diabetes mellitus showed to be a significant independent predictor for stroke. Although, the number of reported cerebral events did not account for asymptomatic cerebral events as no neuroimaging was performed.

We acknowledge important limitations of our study. First, this initial report is a pilot study and involves a relatively small size of prospectively included patients with symptomatic PAD. Second, in our study only 6 year follow-up data was available (mean follow-up period 72±5 months), which may be relatively short. Nevertheless, the findings described in this study are statistical significant and the MR imaging

biomarkers stenosis severity from CE-MRA and LVEF from cardiac cine MRI have shown prognostic value of outcome in PAD. In the present study, the novel MR imaging biomarkers PWV and carotid NWI did not show independent prognostic value on outcome in our patient population, however, their value in risk stratification has to be further elaborated in population-based long-term follow-up studies.

## Conclusion

Mean MRA stenosis class was a significant independent predictor for all-cause mortality in patients with symptomatic PAD. Descending aorta PWV, age and diagnosis of diabetes mellitus were interrelated with PAD stenosis severity and as such associated with all-cause mortality, but did not show to be significant independent predictors. LVEF was a significant independent predictor for cardiac morbidity and diagnosis of diabetes mellitus a significant independent predictor for cerebral morbidity in this patient population. Further studies with larger patient groups have to confirm these results from preliminary data of the present study.

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