Outcomes with Revascularization vs. Medical Therapy According to Plaque Burden from Coronary Computed Tomography Angiography

Short Title: Revascularization According to Plaque Burden

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Word Count: 5454

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Abstract

Aims: We aimed to investigate, whether plaque burden from coronary computed tomography angiography (CCTA) could be used to identify patients potentially benefitting from revascularization.

Methods and Results: We assessed consecutive patients undergoing CCTA and selective 15O-water perfusion positron emission tomography for evaluation of coronary artery disease (CAD) at two tertiary care centers in Finland and the Netherlands. Per-patient percent atheroma volume (PAV) and maximum per-vessel PAV in each patient was quantified by artificial intelligence-guided quantitative computed tomography (AI-QCT). We constructed a Cox regression for death, myocardial infarction (MI), or unstable angina pectoris (uAP) including continuous PAV, revascularization, and their interaction, adjusted for calcium score, ischemia, cardiovascular risk factors, symptoms, and medication in a subcohort of 2233 patients (206 events;median follow-up 6.8 years). There was significant interaction between revascularization and continuous PAV on patient-level (p-interaction=0.042) and vessel-level (p-interaction=0.026). Revascularization was associated with a significantly lower event rate at per-patient PAV 22% (HR 0.70, 95% CI 0.43-0.98) and per-vessel PAV 22% (HR 0.64, 95% CI 0.29-0.99) or higher. In subgroup analyses, after adjustment for age, sex, cardiovascular risk factors, ischemia, antiplatelet and lipid-lowering drugs, revascularization in patients with per-vessel PAV ≥22% was associated with a significantly reduced event rate (HR 0.50, 95% CI 0.27-0.91, p=0.024) (p-interaction=0.016), whereas patient-level results remained non-significant (HR 0.62, 95% CI 0.35-1.10, p=0.104) (p-interaction<0.001).

Conclusion: In this cohort study of patients referred for CCTA, revascularization on top of medical therapy was associated with a lower rate of long-term death, MI, or uAP from per-vessel PAV of 22% upwards.

Key words: plaque burden, coronary computed tomography angiography, artificial intelligence, revascularization

Introduction

Coronary computed tomography angiography (CCTA) represents the first-line imaging modality for patients with low to intermediate pre-test probability of coronary artery disease (CAD)[1,2] and plaque burden from CCTA is an established predictor for future cardiovascular events[3,4]. Recent advances with artificial intelligence (AI) have enabled rapid plaque quantification and characterization from CCTA, pathing the way for application of quantitative plaque analysis from CCTA in routine clinical practice[5,6]. AI-guided quantitative computed tomography (AI-QCT) is a novel software solution for AI-guided CCTA analysis with approval from the US Food And Drug Administration[5,6]. Previous studies have demonstrated the strong and independent prognostic value of plaque burden by AI-QCT on top of coronary artery calcium score (CACS)[7–9], Coronary Artery Disease –Reporting and Disease System (CAD-RADS)[7,8], obstructive disease[7,8], and high-risk plaque features[8]. Moreover, in a pivotal post-hoc study of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, it was shown, that coronary plaque burden by AI-QCT improves the prediction of adverse outcomes even in a cohort of patients with moderate to severe myocardial ischemia[10]. These findings are in-line with a currently shifting treatment paradigm in CAD to target the coronary plaque itself[11]. From a pathophysiological point of view, the presence of plaque represents the substrate to cause coronary events, whereas ischemia is a consequence of coronary plaque growth, luminal narrowing, and abnormal coronary vasomotion. This raises the question, whether plaque burden could potentially be used as a target to allocate patients to myocardial revascularization. To test this hypothesis, we aimed to assess the interaction between plaque burden by AI-QCT and revascularization with respect to long-term outcomes and derive a cut-off for patients to potentially benefit from revascularization. We used total plaque burden on patient-level as an extensively validated risk marker from CCTA[3,7–10] and analogous to similar studies in the field[12], as well as per-vessel plaque burden.

Methods

Patient Population

This was a pooled cohort of 3267 symptomatic patients having undergone CCTA for the evaluation of CAD and selective hybrid 15O-water positron emission tomography (PET) perfusion imaging at Turku University Hospital, Finland, and Amsterdam University Medical Center, the Netherlands from February 2007 to December 2016. Out of these, 347 patients had no CCTA image data available, 64 were lost to follow-up, and 1 patient with vasculitis was excluded resulting in 2855 patients (**Figure 1**). Out of these, 130 were non-adherent to the hybrid imaging protocol and 128 had non-diagnostic imaging data, resulting in a total of 2597 patients with available ischemic CAD status. Since for the plaque burden cut-off derivation model, CACS was used as adjusting covariate (not available in 364 patients), the final population for cut-off derivation was 2233 patients. The derived plaque burden cut-off was then tested in a binary way adjusted for ischemia in the 2597 patients with available ischemic CAD status (**Figure 1**).

Patient Consent

The study complied with the Declaration of Helsinki. The Ethics Committees of the Hospital District of Southwest Finland and Amsterdam University Medical Center approved the study protocol and waived the need for informed consent.

Clinical Event Adjudication

Comprehensive data on all-cause death, myocardial infarction (MI), and unstable angina pectoris (uAP)[13] were collected using electronic medical records, standardized telephonic follow-up, and national registry databases. The identified events were confirmed by the investigators. The median follow-up duration was 6.8 years [interquartile range (IQR) 4.8-8.6 years).

Hybrid Imaging Protocol and Treatment

Consecutive patients undergoing CCTA at two academic sites in Finland and the Netherlands were included. Patients enrolled in Amsterdam underwent a hybrid imaging protocol with routine CCTA and 15-O-water PET perfusion imaging to assess the presence of ischemic CAD. Patients enrolled in Turku underwent a selective downstream PET approach, as reported previously[14]. According to this protocol that aligns with the most recent guideline recommendations[1], patients first underwent CCTA. In case of obstructive disease according to the initial interpretation of the CCTA (≥50% diameter stenosis by visual assessment), patients were referred to downstream PET perfusion imaging. In case of no or non-obstructive disease, further imaging was not required and the presence of ischemic CAD was excluded by CCTA alone. In all other patients, ischemia was determined by the PET result. Revascularization was defined as early planned coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 6 months from CCTA and recorded on vessel-level. The decision to perform revascularization was based on the CCTA and PET results and symptoms[15] as per standard of care. In addition, patients were treated with medical therapy as clinically indicated and informed by the imaging findings[16].

CCTA Acquisition

CCTA imaging was performed as described previously[17–19]. In brief, oral and/or intravenous metoprolol was administered to target at a stable heart rate below 65 bpm. CCTA was performed with a 64-row hybrid PET-CT scanner (GE Discovery VCT or GE D690, GE Healthcare, Waukesha, WI, USA; Gemini TF 64, Philips Gemini TF 64, Philips Healthcare, Best, The Netherlands). Patients enrolled in the PACIFIC (Comparison of Coronary CT Angiography, SPECT, PET, and Hybrid Imaging for Diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve) trial[17] in Amsterdam were imaged with a 256-slice CT scanner (Philips Brilliance iCT, Philips Healthcare, Best, The Netherlands)· Sublingual/oral nitrate was administered immediately before CCTA. Intravenously administered low-osmolal iodine contrast agents were used. Prospectively triggered CCTA acquisition was applied whenever feasible.

AI-QCT Analysis

AI-QCT is a U.S. Food and Drug Administration–cleared software service for CCTA analysis. AI-QCT analysis was performed as described previously[5,6] in a blinded fashion. In brief, coronary segments with a diameter ≥1.5 mm were included in the analysis using the 18-segment Society of Cardiovascular Computed Tomography model[20]. Plaque volume (mm^3) was calculated for each coronary segment and summed on a per-patient and per-vessel level including left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) with sidebranches. Plaque volume was normalized to the vessel volume to account for individual variation in coronary artery volume, calculated as [plaque volume (mm^3)/vessel volume (mm^3)]*100%, which is referred to as percent atheroma volume (PAV)[21]. Plaque subtypes (calcified, non-calcified, low-density non-calcified) were categorized using Houndsfield unit ranges as reported previously[7]. AI-QCT diameter stenosis ≥50% was classified as obstructive CAD. Two feature positive plaque (two FPP) was defined as plaques with the presence of low-density non-calcified plaque and positive remodelling (remodelling index ≥1.1)[22].

PET Acquisition and Analysis

The PET scans were performed using a GE Discovery VCT/D690 or a Gemini TF 64 PET/CT scanner using [^{15}O]H_2O as perfusion tracer. Patients were instructed to refrain from intake of products containing caffeine or xanthine during 24 h before the scan. Hyperaemia was induced by adenosine. In-house developed software (CardiacVUer, Amsterdam UMC, Vrije Universiteit Amsterdam, The Netherlands and Carimas software, Turku PET Centre, Turku, Finland) allowed for the generation of parametric images of quantitative hyperaemic myocardial blood flow (MBF) in mL/min/g for each of the 17 left ventricle segments according to the standard American Heart Association model[18,23,24]. A hyperaemic MBF of ≤2.3 mL/min/g in at least two adjacent segments was considered abnormal[25]. LM was considered ischemic in case of ≥50% stenosis in LM on CCTA and ischemia in both LAD and LCX territory. The basal septal segments (segment number 2 and 3) were excluded from the PET analysis because of possible interference with the left ventricular outflow tract.

Statistical Analysis

Continuous variables are shown as mean ± standard deviation (SD) or median [IQR]. Categorical variables are shown as numbers with percentages. Categorical variables were compared with the Chi square test and continuous variables with the Mann-Whitney U test. The endpoint was a composite of all-cause death, MI, or uAP. First, we ran multivariable Cox regressions to assess the prognostic impact of continuous per-patient PAV per 1% increase on top of cardiovascular risk factors (age, sex, diabetes mellitus, hypertension, current smoking, dyslipidemia, family history of CAD), the presence of ischemic CAD, and with and without CACS. The models' performance with vs. without PAV was assessed and compared with Harrell's C. Vice-versa, C-indexes of models with vs. without ischemic CAD on top of PAV in- and excluding CACS were compared. Then, we constructed a multivariable Cox model to assess the interaction between revascularization and continuous per-patient or per-vessel PAV. Vessel-level analysis was performed using the maximum per-vessel PAV in each patient. Since our endpoint composite included all-cause death, which is not vessel-specific, as well as the MI and uAP endpoints were not available on vessel-level, this approach allowed to keep explanatory and dependent variables on the same analysis level. To account for selection bias for referral to revascularization, Cox models were adjusted for factors affecting the decision on revascularization, as well as imbalances in medical treatment. We chose covariate adjustment instead of propensity matching for the main analysis to preserve the sample size and in line with similar studies in the field[12]. Furthermore, previous methodological studies have shown similar results with covariate adjustment and propensity matching[26]. The derivation Cox model included continuous per-patient or per-vessel PAV per 1% increase, revascularization, the interaction between continuous PAV and revascularization, presence of ischemic CAD (patient-level) or per-vessel ischemia (vessel-level), CACS (per 10 increase), age (≥62 vs. <62 years = median age), sex, diabetes mellitus, hypertension, smoking, dyslipidemia, family history of CAD, typical angina pectoris, anti-platelet therapy, lipid-lowering therapy, angiotensin converting enzyme (ACE)-inhibitor, angiotensin-2 antagonist, and anti-anginal medication with betablocker, calcium channel blocker, or long-acting nitrate. The sample size for this model was limited by the availability of ischemic CAD status and CACS and consisted of 2233 patients. The hazard ratios of revascularization vs. medical therapy alone were estimated at each value of PAV from 0% to 40% in 1% increments and subsequently plotted graphically.

As a sensitivity analysis, we calculated a propensity score for the referral to revascularization including ischemic CAD or per-vessel ischemia, CACS (per 10 increase), age, sex, diabetes mellitus, hypertension, smoking, dyslipidemia, family history of CAD, typical angina pectoris, as well as anti-anginal medication (betablocker, calcium channel blocker, long-acting nitrate) (**Supplemental Figure 1**). A subsequent Cox model tested the interaction between PAV per 1% increase and revascularization adjusted for the propensity score. A PAV cut-off was chosen based on association with reduced event rates.

Then, we performed a subgroup analysis of revascularization vs. medical therapy among patients with PAV below vs. above the derived threshold adjusted for ischemic CAD or per-vessel ischemia in the cohort of 2597 patients with available ischemic status. Additional adjustments were donefor age, sex, diabetes mellitus, and smoking on patient-level, as well as age, sex, diabetes mellitus, smoking, hypertension, dyslipidemia, family history of CAD, antiplatelet and lipid-lowering drugs on vessel-level – adhering to the rule of thumb with 1 adjusting covariate per 10 events... Multicollinearity was excluded by the assessment of variance inflation factors. Analyses were two-tailed and a p-value of <0.05 was considered statistically significant. All analyses were performed with Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

Patient Population

Patient characteristics according to revascularization vs. medical therapy alone are shown in **Table 1**. Overall, 286 (11.0%) of patients underwent revascularization and 2311 (89.0%) received medical therapy alone. Patient characteristics and AI-QCT analysis in the Amsterdam cohort according to 64-row CT (clinical cohort) or 256-row CT (PACIFIC trial cohort) are shown in **Supplemental Table 1**.

AI-QCT Analysis

In the total cohort, median PAV was 3.2% [IQR 1.0%-9.6%] (**Table 1**). Patients undergoing revascularization vs. medical therapy alone had significantly higher diameter stenosis (74% vs. 18%, p<0.001), PAV (16.6% vs. 2.5%, p<0.001) and a higher prevalence of two FPP (71.7% vs. 20.0%, p<0.001) (**Table 1**).

Prognostic Impact of PAV on Top of Ischemic CAD

Among 2233 patients, 206 (9.2%) experienced the composite endpoint (112 death, 58 MI, 36 uAP). Per-patient PAV remained an independent predictor of all-cause death, MI, or uAP on top of cardiovascular risk factors, CACS, and ischemic CAD (adjusted HR per 1% increase: 1.03, 95% CI 1.00-1.05, p=0.021). The C-index of the model with cardiovascular risk factors and ischemic CAD was 0.742 and improved slightly to 0.749 by the addition of PAV (p=0.039) (**Supplemental Table 2**). Vice-versa, the C-index of the model including PAV on top of cardiovascular risk factors and CACS (C-index 0.733) significantly improved by the addition of ischemic CAD (C-index

0.749, p=0.023). Results were consistent in models excluding CACS with slightly more pronounced prognostic benefit by PAV added on top of ischemic CAD (**Supplemental Table 3**).

Interaction Between Continuous Per-Patient and Per-Vessel PAV and Revascularization

In the derivation Cox model adjusted for clinical factors, CACS, ischemic CAD, and medical therapy, there was significant interaction between revascularization and continuous per-patient PAV (p-interaction=0.042) and per-vessel PAV (p-interaction=0.026) (**Table 2**). The sensitivity analysis using a Cox regression adjusted for a propensity-score (**Supplemental Figure 1**) to perform revascularization showed consistent results on patient-level (p-interaction=0.012) and vessel-level (p-interaction=0.004) (**Supplemental Table 4**). In the main model on-patient-level, the point estimate of the estimated hazard ratio of revascularization vs. medical therapy alone indicated lower event rates with revascularization at a PAV of 11%, however with a wide range of uncertainty including no effect (HR 0.98, 95% CI 0.52-1.45). At a per-patient PAV of 22% there was outcome benefit from revascularization including the upper limit of the 95% confidence interval (HR 0.70, 95% CI 0.43-0.98). This effect continued to remain significant with increasing PAV (**Figure 2A**). On vessel-level, the point estimate indicated lower event rates with revascularization at a per-vessel PAV of 9% (HR 0.97, 95% CI 0.22-1.73). At a per-vessel PAV of 22%, there was outcome benefit from revascularization including the upper limit of the 95% confidence interval (HR 0.64, 95% CI 0.29-0.99). This effect continued to remain significant with increasing PAV (**Figure 2B**).

Vessel Characteristics According to Per-Patient or Per-Vessel PAV ≥22% vs. <22%

Among patients with per-patient PAV ≥22% (N=223), overall median per-vessel PAV was 29.5% [20.9-38.1] as compared to 1.7% [0.0-7.2] among patients with per-patient PAV <22% (N=2374) (p<0.001). Among patients with PAV ≥22%, hyperemic MBF in LM/LAD, LM/LCX, and RCA territories were all significantly lower as compared to patients with PAV <22% (p<0.001 for all) (**Supplemental Table 5**). Per-vessel PAV and hyperemic MBF values according to per-patient PAV ≥22% vs. <22% and revascularization vs. medical therapy are shown in **Supplemental Table 6** and **Supplemental Figure 2**.

Overall, median per-vessel PAV in the per-vessel PAV ≥22% group was 32.8% [26.8-41.6] as compared to 5.4% [1.8-11.8] in the per-vessel PAV <22% group (p<0.001). A total of 242 (42.8%) vessels and with PAV ≥22% were ischemic vs. 163 (8.0%) with PAV <22% (p<0.001) (**Supplemental Table 7**). Hyperemic MBF values per territory are shown in **Supplemental Table 7** and PAV and hyperemic MBF values according to revascularization vs. medical therapy in **Supplemental Table 8**.

Outcomes According to Per-Patient PAV 22% and Revascularization

In the cohort of 2597 patients with available ischemic CAD status, 253 patients experienced the composite endpoint (146 death, 70 MI, 37 uAP). Patients with per-patient PAV ≥22% (N=223, 8.6%) had a significantly higher adjusted event rate as compared to patients with PAV <22% (N=2374, 91.4%) (HR 1.76, 95% CI 1.25-2.46, p=0.001) (**Supplemental Table 9**). There was significant binary interaction between revascularization and per-patient PAV 22% (p-interaction <0.001) (**Table 3, Figure 3**). Among patients with PAV ≥22%, 21/104 (20.2%) who underwent revascularization vs. 39/119 (32.8%) who received medical therapy alone experienced the composite endpoint. Crude (HR 0.59, 95% CI 0.34-1.00, p=0.051) and adjusted event rates (HR

0.62, 95% CI 0.35-1.10, p=0.104) were numerically lower with revascularization but without reaching statistical significance. Among patients with PAV <22%, crude (HR 2.08, 95% CI 1.40-3.10, p<0.001) and adjusted event rates (HR 1.71, 95% CI 1.14-2.57, p=0.010) were significantly higher for patients undergoing revascularization. (**Table 3 and Figure 3**).

Outcomes According to Per-Vessel PAV 22% and Revascularization

Stratified for each vessel (LM, LAD, LCX, RCA), there was a significantly higher adjusted rate of the composite endpoint in patients with per-vessel PAV ≥22% vs. <22% (**Supplemental Table 9, Supplemental Figure 3**). There was significant binary interaction between per-vessel revascularization and per-vessel PAV 22% (p-interaction=0.016) (**Table 3, Figure 3**). Among patients with per-vessel PAV ≥22% (N=565), 14/106 (12.6%) undergoing revascularization vs. 92/459 (20.3%) receiving medical therapy alone experienced the composite endpoint, which resulted in a significantly lower event rate after adjustment for age, sex, cardiovascular risk factors, per-vessel ischemia, and anti-platelet and lipid-lowering drugs (HR 0.50, 95% CI 0.27-0.91, p=0.024), whereas crude event rates were similar (HR 0.68, 95% CI0.39-1.19, p=0.179). Among patients with per-vessel PAV <22% (N=2032), there were similar crude (HR 1.52, 95% CI 0.74-3.10, p=0.255) and adjusted (HR 0.67, 95% CI 0.31-1.46, p=0.312) rates of the composite outcome when undergoing revascularization vs. medial therapy alone (**Table 3, Figure 3**). Two case examples with per-vessel PAV ≥22% and outcomes with medical therapy or revascularization are illustrated in **Figure 4**.

Discussion

In this observational cohort study on patients undergoing CCTA for the evaluation of CAD, we aimed to assess the interaction between AI-guided coronary plaque burden and myocardial revascularization with respect to long-term outcomes and to derive a plaque burden cut-off for patients to potentially benefit from revascularization. We found that PAV by AI-QCT was an independent predictor of death, MI, or uAP throughout long-term follow-up on top of cardiovascular risk factors, CACS, and ischemic CAD. There was significant interaction between revascularization and continuous per-patient and per-vessel plaque burden. The results suggested significantly reduced events rates with revascularization from a per-patient or per-vessel PAV of 22% upwards. This effect was consistent in a binary subgroup analysis (PAV ≥22% vs. <22%) on vessel-level after correction for ischemia, cardiovascular risk factors, and antiplatelet and lipid-lowering drugs, whereas patient-level results remained non-significant.. To the best of our knowledge, this study represents the first to assess the interaction between revascularization, AI-guided plaque burden quantification from CCTA, and long-term clinical outcomes.

Prognostic Impact of Coronary Plaque Burden on CCTA

Quantitative plaque burden from CCTA is known for its strong association with future cardiovascular events[3,4]. In previous work, we have demonstrated the prognostic value of AI-guided plaque burden quantification using AI-QCT on top of CACS[7–9], CAD-RADS[7,8], obstructive disease[7,8], high-risk plaque features[8], and myocardial ischemia[10]. Furthermore, in the randomized-controlled PREVENT (Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques) trial[27], patients with normal invasive fractional flow reserve >0.80, but ≥2/4 vulnerability features on intracoronary imaging had a lower risk of the composite ischemic endpoint throughout 2 years when undergoing preventive PCI vs medial therapy alone. The majority of included lesions (97%) had high plaque burden. This trial supports the hypothesis, that plaque burden itself could be an important target for revascularization.

Plaque Burden as Potential Target for Revascularization

Previous mainly observational studies have shown that statins can induce plaque regression and favourable changes in plaque composition from (low-density) non-calcified to more calcified plaques as measured by CCTA[28,29]. However, despite high adherence to statins in the setting of large international randomized-controlled trials like ISCHEMIA[30], future ischemic events are not eliminated and residual risk remains and increases with the amount of coronary atherosclerosis[10,31]. Also, the benefit of revascularization on survival in patients with ischemic CAD could not be demonstrated by randomized-controlled trials[30,32], although revascularization reduces the rate of spontaneous MI and cardiovascular death over the long-term[33–35].

Coronary events are ultimately caused by instability at the plaque-level, i.e. plaque rupture or erosion, that occur in 75% of the cases in lesions without significant luminal narrowing at their initial evaluation[4]. This gives rise to the hypothesis, that revascularization may need to be targeted at the event substrate itself, i.e. the plaque burden and composition, rather than the late phenomenon of flow-limitation.

Consistent with previous evidence[10], in our study, we found independent prognostic impact of plaque burden on top of ischemic CAD, and vice-versa ischemic CAD on top of PAV. However, while current recommendations for revascularization are based on ischemia[1,2], plaque burden as a potential target for revascularization represents a novel concept that was tested in this study. In our study, we found significant interaction between continuous per-patient and per-vessel plaque burden and revascularization. The results from the derivation model suggested lower event rates with revascularization in patients with a per-patient or per-vessel PAV ≥22%. In the subsequent subgroup analyses, there was also significant binary interaction between per-patient or per-vessel PAV ≥22% and revascularization. The individual event rates in the subgroup of patients with per-patient PAV ≥22% were only numerically lower with revascularization without reaching statistical significance. However, the vessel-level analysis indicated a 50% (9% to 73%) event rate reduction with revascularization after correction for age, sex, cardiovascular risk factors, per-vessel ischemia, and antiplatelet and lipid-lowering drugs. The absence of a significant effect on patient-level in this subgroup analysis may be explained by lack of power given the relatively small subgroup sample size (type II error), residual confounding, or true absence of a patient-level effect. Thus, the results suggest per-vessel PAV ≥22% as a potential target to allocate patients to revascularization, whereas the results for per-patient PAV ≥22% remain not fully conclusive from this analysis. Both, per-patient and per-vessel PAV cut-offs were determined at PAV 22%, which may be surprising, since rather a higher cut-off on vessel-level as compared to patient-level may have been expected. However, the results appear plausible, since it corresponds to approximately 75% of per-vessel PAV in patients with per-patient PAV ≥22% (25. percentile = per-vessel PAV 20.9%). Furthermore, the 22% PAV cut-off represents the lower range and the median per-vessel PAV in the ≥22% group was 32.8% [IQR 26.8-41.6]. Of note, since the point estimate already indicated a benefit from revascularization at a per-vessel PAV of 9%, there might be a grey zone between PAV 9-21%, where some of the patients could already benefit from revascularization. However, confidence intervals in this PAV range were very wide and estimates imprecise. Among patients with per-patient PAV <22%, we observed significantly higher crude and adjusted event rates with revascularization, whereas no significant differences on vessel-level in patients with per-vessel PAV <22% were observed. These results may be related to the increased risk per se of patients undergoing revascularization and our analysis does not allow for further conclusion on potential negative prognostic effects of revascularization in patients with per-patient PAV <22%.

The 565 vessels withPAV ≥22% (considering the maximum per-vessel PAV in each patient) consisted most frequently of LM or LAD (81.9%), overall 323 (57.2%) were non-ischemic and 106 (18.8%) underwent revascularization, out of which 106 (86.8%) were ischemic. This demonstrates that revascularization was strongly guided by ischemia, as reported previously[15], and in line with current guideline recommendations[1,2]. Whether vessel selection for revascularization based on PAV independent of ischemia improves patient outcomes needs to be confirmed in further independent prospective studies. Specifically, the mechanistic link between per-vessel PAV and vessel-level events remains to be established. Also, the impact of PAV distribution (focal vs. diffuse) and plaque composition needs to investigated by further studies.

Limitations

The results of this study must be considered in the light of several limitations. It was an observational cohort study with all the limitations of a non-randomized design. Specifically, confounding by the indication for revascularization may not be fully eliminated despite extensive multivariable adjustment and an alternative approach using a propensity-score adjusted model to account for the referral bias for revascularization. Our endpoint was limited to all-cause mortality, since the causes of death were not available. Furthermore, this study was designed as hypothesis-testing to assess the interaction between per-patient and maximum per-vessel plaque burden in each patient and revascularization, since the endpoint composite consisted of all-cause death, which is not vessel-specific, and the MI and uAP endpoints were not recorded on vessel-level.

Therefore, the mechanistic link between plaque burden and vessel-level events remains to be established in future studies. A sequential imaging approach using PET only in patients with obstructive CAD on CCTA was applied in Turku in line with latest guideline recommendations[1], whereas in Amsterdam all patients received CCTA and PET imaging. Nevertheless, various imaging protocols mirror real-world conditions and the main analysis of this study was the interaction between PAV and revascularization, whereas ischemia acted only as adjusting covariate. Within the Amsterdam cohort, patients enrolled in the PACIFIC trial[17] represent a different subcohort with more advanced disease (higher prevalence of visually obstructive CAD and higher CACS) that was imaged with 256-slice CT than the clinical cohort imaged with 64-slice CT. However, it was shown previously, that AI-QCT provides stable results independent of CT scanner generation[36], so that the differences in AI-QCT results between these two subcohorts can be explained by patient factors. The study had a long follow-up of median 7 years, but we are only able to comprehensively report on medical therapy prescribed at the timepoint of the CCTA in this pooled cohort. However, for patients recruited at Turku University Hospital treatment adherence and outcomes according to lipid-lowering therapy have been reported previously[16]. Patients received guideline-based medical therapy valid during the study period, which predated potent novel anti-atherosclerotic therapies like proprotein convertase subtilisin/kexin type 9 inhibitors or glucagon-like peptide-1 antagonists. The effect of revascularization may differ in a population receiving these novel agents. The effect of plaque distribution (focal vs. diffuse), specific plaque subtypes as well as markers of vulnerability need to be addressed in future studies.

Conclusion

In this cohort study of patients referred for CCTA for the evaluation of CAD, revascularization on top of medical therapy alone was associated with a lower rate of long-term death, MI, or uAP from a per-vessel PAV of 22% upwards after adjustment for ischemia, whereas results for per-patient PAV remained inconclusive. Future studies are needed to validate these findings and provide the mechanistic link between plaque burden, revascularization, and vessel-level events.

Data Availability Statement

Data are made available upon reasonable request from the corresponding author.

Funding

The study was funded by the Finnish Foundation for Cardiovascular Research, Finnish State Research Funding [VTR 13403], and the Research Council of Finland. Dr. Bär was supported by the Swiss National Science Foundation [P500PM_210788] and the University of Turku, Finland. Cleerly, Inc. performed the image analysis without costs and provided an unrestricted research grant to the University of Turku.

Disclosure of interest

Dr. Bär received research grants to the institution from Medis Medical Imaging Systems, Bangerter-Rhyner Stiftung (Basel, Switzerland) and Abbott, outside the submitted work, speaker fees from Cleerly inc., and travel fees from Sanofi. Dr. Knuuti received consultancy fees from GE Healthcare and Synektik and speaker fees from Bayer, Lundbeck, Boehringer-Ingelheim, Pfizer and Siemens, outside of the submitted work. Dr. Saraste received consultancy fees from Astra Zeneca and Pfizer, and speaker fees from Abbott, Astra Zeneca, Janssen, Novartis and Pfizer. Dr. Bax received speaker fees from Abbott. Dr. Nurmohamed reports grants from the Dutch Heart Foundation (Dekker 03-007-2023-0068), European Atherosclerosis Society (2023), research funding/speaker fees from Cleerly, Daiichi Sankyo and Novartis, and is co-founder of Lipid Tools.

Dr. Danad is a member of Cleerly Scientific Advisory Board and an Associate Editor at European Heart Journal Cardiovascular Imaging. Dr. Knaapen has received research grants from Cleerly, Inc. and HeartFlow. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Table 1. Patient Baseline Characteristics

Clinical Characteristics	**All N=2597**	**Revascularization N=286**	**Medical Therapy N=2311**	**P-value**
Age, years	62 [55-68]	63 [55-69]	62 [55-68]	0.056
Sex (female), n (%)	1432 (55.1%)	72 (25.2%)	1360 (58.9%)	<0.001
Hypertension, n (%)	1395 (53.7%)	162 (56.6%)	1233 (53.4%)	0.293
Diabetes mellitus, n (%)	395 (15.2%)	69 (24.1%)	326 (14.1%)	<0.001
Dyslipidemia, n (%)	1512 (58.2%)	188 (65.7%)	1325 (57.3%)	0.006
Smoker, n (%)	445 (17.1%)	63 (22.0%)	382 (16.5%)	0.020
Family history of CAD, n (%)	1270 (48.9%)	138 (48.3%)	1132 (49.0%)	0.815
Typical angina, n (%)	636 (24.5%)	134 (46.9%)	502 (21.7%)	<0.001
Prior revascularization, n (%)	12 (0.5%)	0 (0.0%)	12 (0.5%)	0.489
Anti-platelet drug, n (%)	1308 (50.4%)	221 (77.3%)	1087 (47.0%)	<0.001
Lipid-lowering drug, n (%)	1187 (45.7%)	198 (69.2%)	989 (42.8%)	<0.001
ACE inhibitor, n (%)	451 (17.4%)	65 (22.7%)	386 (16.7%)	0.011

ATII antagonist, n (%)	518 (20.0%)	52 (18.2%)	466 (20.2%)	0.429
Betablocker, n (%)	1231 (47.4%)	183 (64.0%)	1048 (45.4%)	<0.001
Long-acting nitrates, n (%)	153 (5.9%)	24 (8.4%)	129 (5.6%)	0.057
Calcium channel blockers, n (%)	453 (17.4%)	78 (27.3%)	375 (16.2%)	<0.001
Referred for PET, n (%)	1408 (54.2%)	286 (100%)	1122 (48.6%)	<0.001
Referred for ICA, n (%)	697 (26.8%)	286 (100%)	411 (17.8%)	<0.001
Ischemic CAD, n (%)	627 (24.1%)	255 (89.2%)	372 (16.1%)	<0.001
Revascularization, n (%) - PCI - CABG	286 (11.0%) 216 (8.3%) 70 (2.7%)	286 (100%) 216 (75.5%) 70 (24.5%)	0 (0.0%) 0 (0.0%) 0 (0.0%)	-
CACS	34 [0-264]	417 [176-1198]	20 [0-173]	<0.001

AI-QCT Analysis	**All N=2597**	**Revascularization N=286**	**Medical Therapy N=2311**	**P-value**
Diameter stenosis, %	22 [9-50]	74 [63-82]	18 [8-37]	<0.001
≥50% Diameter stenosis, n (%)	673 (25.9%)	256 (89.5%)	417 (18.0%)	<0.001
Area stenosis, %	38 [15-75]	93 [87-97]	32 [13-6]	<0.001
PAV, %	3.2 [1.0-9.6]	16.6 [10.2-2.5]	2.5 [0.9-7.3]	<0.001
NCPV, %	2.5 [0.9-6.1]	9.6 [7.0-14.3]	2.1 [0.8-4.8]	<0.001
LD-NCPV, %	0 [0.0-1.0]	1.0 [0.0-1.0]	0.0 [0.0-0.0]	<0.001
CPV, %	0.5 [0.0-3.0]	5.1 [1.9-11.9]	0.3 [0.0-2.2]	<0.001
Presence of LD-NCP, n (%)	677 (26.1%)	208 (72.7%)	469 (20.3%)	<0.001
Presence of two FPP, n (%)	666 (25.6%)	205 (71.7%)	461 (20.0%)	<0.001
Remodelling index	1.3 [1.2-1.5]	1.5 [1.4-1.7]	1.3 [1.2-1.4]	<0.001
Vessel volume, mm^3	2977 [2427-3596]	2926 [2500-3458]	2981 [2417-3617]	0.698

Lumen volume, mm^3	2728 [2212-3330]	2364 [1927-2777]	2796 [2269-3386]	<0.001
Vessel length, mm	612 [542-680]	621 [554-678]	613 [545-681]	0.297

Displayed are numbers with percentage or median with interquartile range. P-values are from Chi square or Mann-Whitney U tests. Calcium score was available from 2233 patients. ACE = angiotensin converting enzyme, ATII = angiotensin II, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, CPV = calcified plaque volume, ICA = invasive coronary angiography, LD-NCPV = low-density non-calcified plaque volume, NCPV = non-calcified plaque volume, PAV = percent atheroma volume, PCI = percutaneous coronary intervention, two FPP = two feature positive plaque.

Table 2. Multivariable Cox Regression of Revascularization vs. Medical Therapy

PATIENT-LEVEL **2233 Patients** **206 Events**	**Multivariable HR (95% CI)**	**p-value**	**VESSEL-LEVEL** **2233 Patients** **206 Events**	**Multivariable HR (95% CI)**	**p-value**
Per-patient PAV, per 1%	1.04 (1.02-1.06)	0.001	Per-vessel PAV, per 1%	1.02 (1.01-1.03)	0.002
Revascularization	1.37 (0.68-2.77)	0.376	Per-vessel revascularization	1.31 (0.49-3.51)	0.589
Interaction Revascularization#PAV, per 1%	0.97 (0.94-0.99)	**0.042**	Interaction Revascularization#PAV, per 1%	0.97 (0.94-0.99)	**0.026**
Ischemic CAD	1.86 (1.28-2.69)	0.001	Per-vessel ischemia	2.32 (1.64-3.28)	<0.001
CACS, per 10	1.00 (0.99-1.00)	0.870	CACS, per 10	1.00 (0.99-1.00)	0.121
Age ≥62 years	1.55 (1.13-2.12)	0.006	Age ≥62 years	1.46 (1.07-2.00)	0.019
Sex (male vs. female)	1.32 (0.97-1.80)	0.078	Sex (male vs. female)	1.29 (0.94-1.77)	0.115
Hypertension	0.91 (0.64-1.31)	0.642	Hypertension	0.94 (0.66-1.33)	0.717
Diabetes	1.37 (0.97-1.93)	0.076	Diabetes	1.38 (0.98-1.95)	0.066
Dyslipidemia	0.96 (0.71-1.30)	0.777	Dyslipidemia	1.00 (0.73-1.35)	0.978

Smoking	1.09 (0.76-1.57)	0.645	Smoking	1.23 (0.88-1.72)	0.221
Family history of CAD	1.11 (0.83-1.48)	0.472	Family history of CAD	1.10 (0.82-1.47)	0.520
Anti-platelet drug	1.30 (0.93-1.81)	0.121	Anti-platelet drug	1.29 (0.92-1.80)	0.136
Lipid-lowering therapy	0.74 (0.52-1.04)	0.078	Lipid-lowering therapy	0.73 (0.52-1.04)	0.079
Betablocker	0.97 (0.71-1.33)	0.861	Betablocker	1.00 (0.73-1.36)	0.999
ACE-inhibitor	1.34 (0.91-1.97)	0.134	ACE inhibitor	1.24 (0.84-1.83)	0.272
AT-II-antagonist	1.20 (0.80-1.79)	0.386	ATII-antagonist	1.17 (0.79-1.75)	0.428
Calcium channel blocker	1.33 (0.94-1.86)	0.105	Calcium antagonist	1.43 (1.02-2.02)	0.037
Long-acting nitrate	1.73 (1.11-2.70)	0.015	Long acting nitrate	1.80 (1.16-2.81)	0.009
Typical angina pectoris	1.23 (0.91-1.67)	0.177	Typical angina pectoris	1.27 (0.94-1.71)	0.124

Multivariable Cox regression for on the interaction between revascularization and continuous percent atheroma volume (PAV) per-patient (left side) and maximum per-vessel PAV for each patient (right side). ACE = angiotensin converting enzyme, AT-II = angiotensin II, coronary artery calcium score (CACS), CAD = coronary artery disease, CI = confidence interval, HR = hazard ratio, MI = myocardial infarction, PAV = percent atheroma volume, uAP = unstable angina pectoris.

Table 3. Outcomes According to Per-Patient and Per-Vessel PAV 22% and Revascularization or Medical Therapy

PATIENT-LEVEL							
2597 PATIENTS 253 EVENTS	**Revascularization N=104**	**Medical Therapy N=119**	**Crude HR (95% CI)**	**p-value**	**Adjusted^a HR (95% CI)**	**p-value^a**	**p-interaction**
Per-Patient PAV ≥22% 223 PATIENTS 60 EVENTS	21 (20.2%)	39 (32.8%)	0.59 (0.34-1.00)	0.051	0.62 (0.35-1.10)	0.104	p<0.001
Per-Patient PAV <22% 2374 PATIENTS 193 EVENTS	**Revascularization N=182**	**Medical Therapy N=2192**	**Crude HR (95% CI)**	**p-value**	**Adjusted^a HR (95% CI)**	**p-value^a**	
	29 (15.9%)	164 (7.5%)	2.08 (1.40-3.10)	<0.001	1.71 (1.14-2.57)	0.010	
VESSEL-LEVEL							
2597 PATIENTS 253 EVENTS	**Per-Vessel Revascularization N=106**	**Medical Therapy N=459**	**Crude HR (95% CI)**	**p-value**	**Adjusted^b HR (95% CI)**	**p-value^b**	**p-interaction**
Per-Vessel PAV ≥22% 565 PATIENTS 111 EVENTS	14 (12.6%)	92 (20.26%)	0.68 (0.39-1.19)	0.179	0.50 (0.27-0.91)	0.024	p=0.016

Per-Vessel PAV <22% 2032 PATIENTS 142 EVENTS	Per-Vessel Revascularization N=72	Medical Therapy N=1960	Crude HR (95% CI)	p-value	Adjusted^b HR (95% CI)	p-value^b	
	8 (11.1%)	134 (6.8%)	1.52 (0.74-3.10)	0.255	0.67 (0.31-1.46)	0.312	

Shown are cumulative events N (%) and uni- and multivariable Cox regressions (HR for revascularization vs. medical therapy) in per-patient and per-vessel PAV ≥22% and PAV <22% subgroups.[a]Adjusted for age,sex, diabetes mellitus, smoking, and ischemic coronary artery disease (CAD). [b]Adjusted for age, sex, diabetes mellitus, smoking, hypertension, dyslipidemia, family history of CAD, per-vessel ischemia, antiplatelet and lipid-lowering drugs.. CI = confidence interval, HR = hazard ratio, PAV = percent atheroma.

Figure Titles and Legends

Graphical Abstract

AI = artificial intelligence, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, CI = confidence interval, FUP = follow-up, HRadj = adjusted hazard ratio, MI = myocardial infarction, PAV = percent atheroma volume, uAP = unstable angina pectoris. Illustrated with Biorender.com.

Figure 1. Flowchart

AI-QCT = artificial intelligence-guided quantitative computed tomography, PET = positron emission tomography. Other abbreviations as for Graphical Abstract.

Figure 2. Hazard Ratio of Revascularization vs. Medical Therapy According to PAV

Abbreviations as for Graphical Abstract.

Figure 3. Outcomes According to Per-Patient or Per-Vessel PAV 22% and Revascularization vs. Medical Therapy

Event rates were adjusted for a) age,sex, diabetes mellitus, smoking, ischemic CAD; b) age, sex, diabetes mellitus, smoking, hypertension, dyslipidemia, family history of CAD, per-vessel ischemia, antiplatelet and lipid-lowering drugs. Abbreviations as for Graphical Abstract.

Figure 4. Case Examples

AI-QCT = artificial intelligence-guided quantitative computed tomography, LAD = left anterior descending, LCX =left circumflex, PCI = percutaneous coronary intervention, PET = positron emission tomography, RCA = right coronary artery, STEMI = ST-segment elevation myocardial infarction. Image reproduced with permission from Cleerly, Inc.

Graphical Abstract

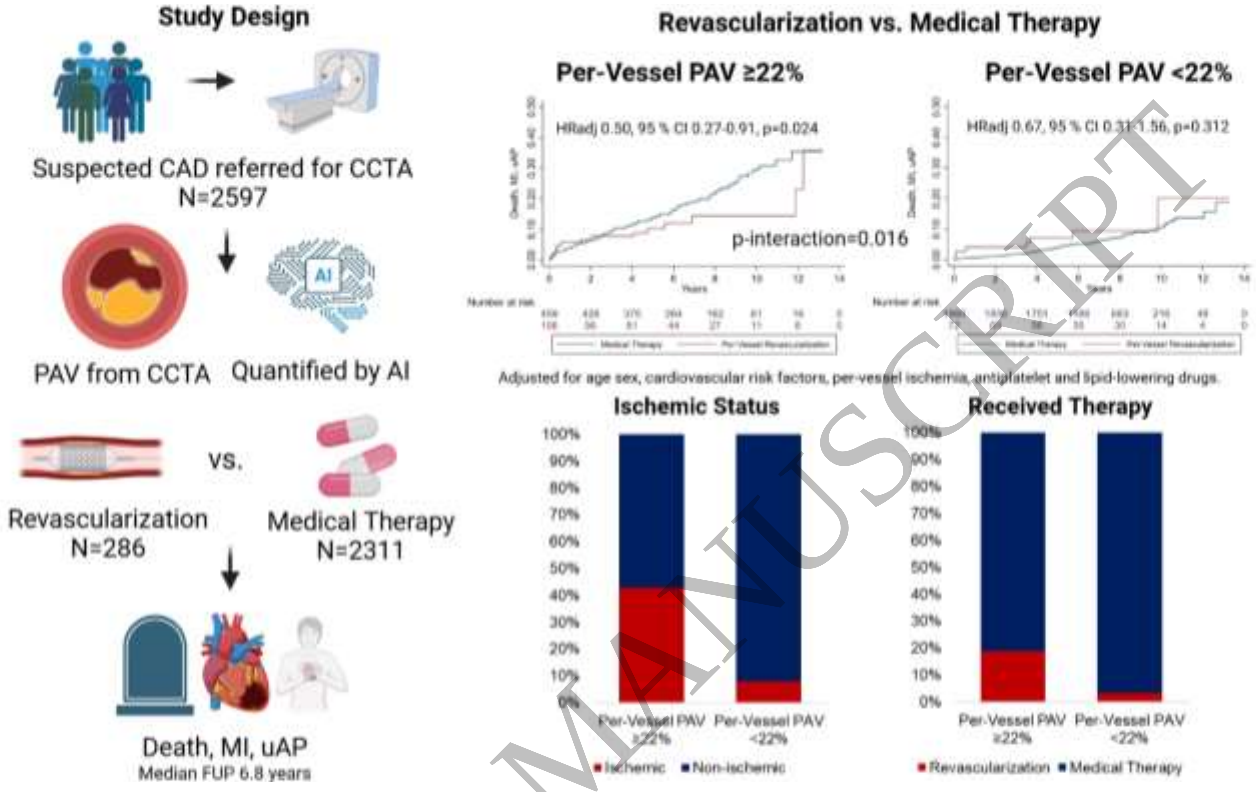

Figure 1. Flowchart

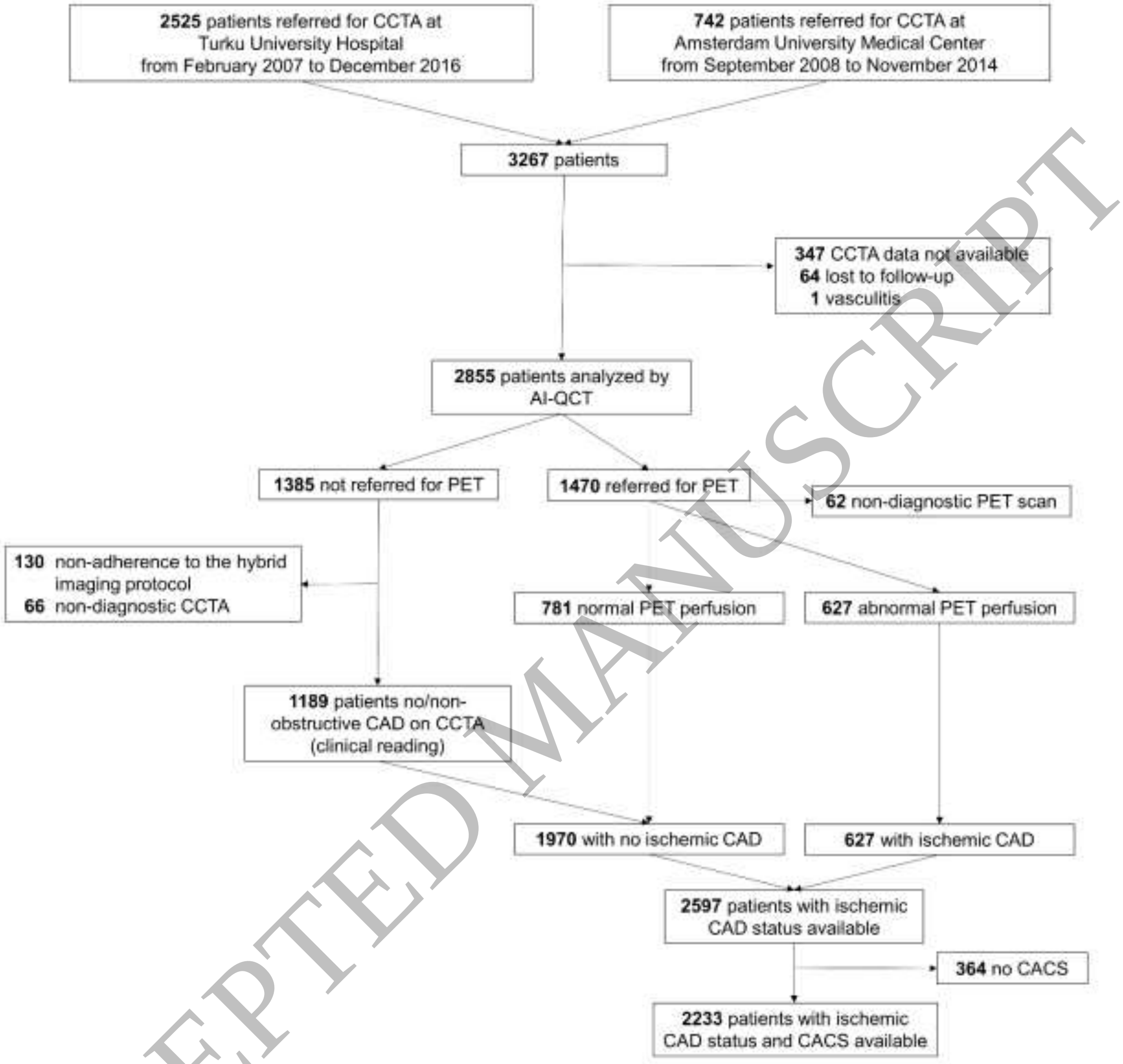

Figure 2. Hazard Ratio of Revascularization vs. Medical Therapy According to PAV for Death, MI, or uAP

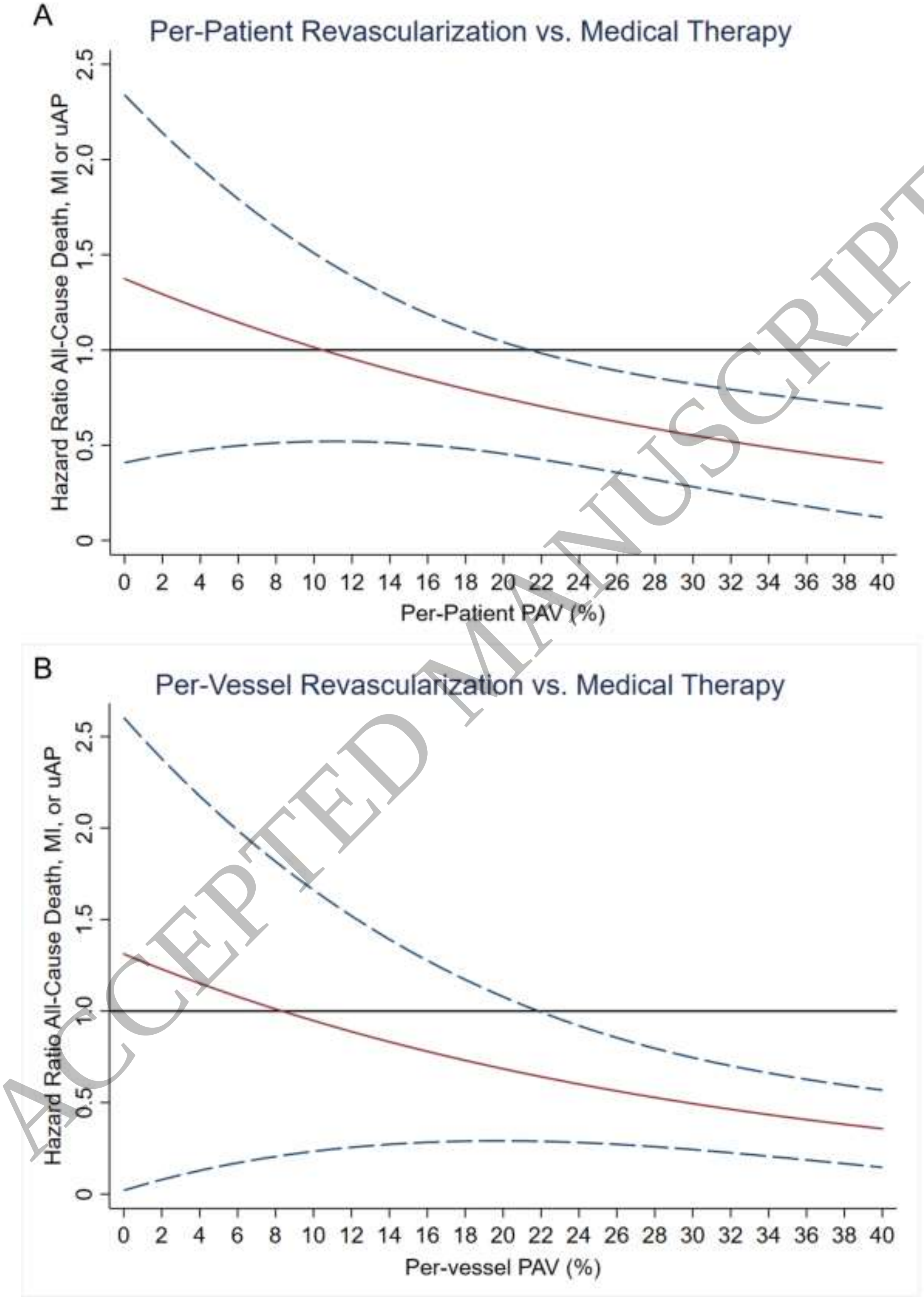
A
Per-Patient Revascularization vs. Medical Therapy
Hazard Ratio All-Cause Death, MI or uAP
0
0.5
1.0
1.5
2.0
2.5
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Per-Patient PAV (%)
B
Per-Vessel Revascularization vs. Medical Therapy
Hazard Ratio All-Cause Death, MI, or uAP
0
0.5
1.0
1.5
2.0
2.5
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Per-vessel PAV (%)

Figure 3. Outcomes According to Per-Patient and Per-Vessel PAV 22% and Revascularization vs. Medical Therapy

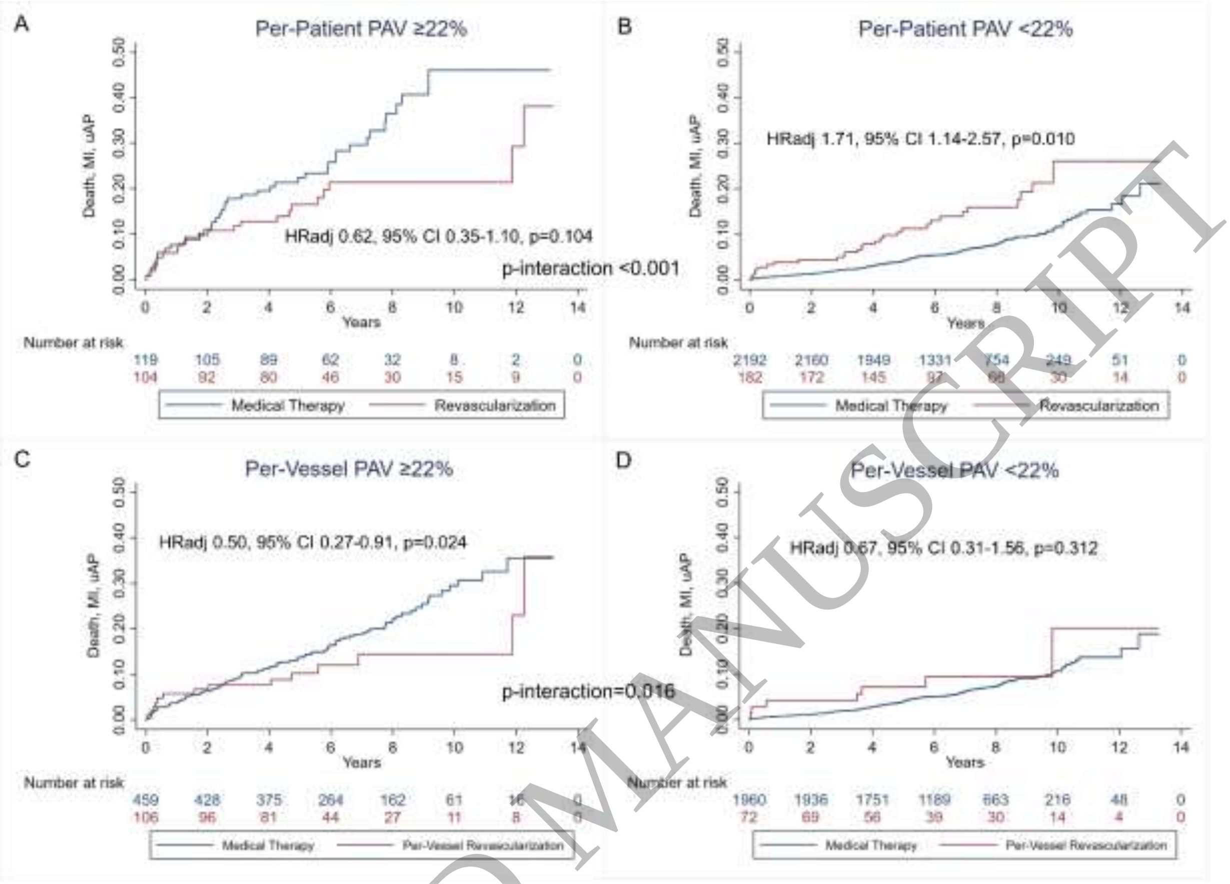

Figure 4. Case Examples