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Diabetes, Coronary Artery Disease, and Clinical Outcomes

Insights from Multimodality Imaging

Matias Mäenpää

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SARJA – SER. D OSA – TOM. 1953 | MEDICA – ODONTOLOGICA | TURKU 2026

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The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-952-02-0570-6 (PRINT)
ISBN 978-952-02-0571-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2026

To Vilma,

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Clinical Medicine
Cardiology and Cardiovascular Medicine
MATIAS MÄENPÄÄ: Diabetes, Coronary Artery Disease, and Clinical Outcomes: Insights from Multimodality Imaging.
Doctoral Dissertation, 108 pp.
Doctoral Programme in Clinical Research
March 2026

ABSTRACT

Coronary computed tomography angiography (CTA) allows anatomical visualization of coronary arteries and plaques while positron emission tomography (PET) myocardial perfusion imaging (MPI) provides detailed information on functional consequences of coronary artery plaques. Anatomical and functional imaging can complement each other in the assessment of coronary artery disease (CAD). Diabetes is a risk factor for development of CAD and is associated with adverse clinical outcomes. In turn, lipid-lowering medication (LLM) has a key role in prevention of CAD development and progression and reducing the risk for adverse clinical events.

We found that coronary CTA with selective downstream use of PET MPI for functional evaluation enables long-term risk stratification both in symptomatic patients with and without diabetes with suspected CAD. However, diabetes was associated with more advanced CAD and worse long-term clinical outcomes independent of myocardial perfusion results, whereas normal myocardial perfusion was associated with favorable prognosis in patients without diabetes. Quantified coronary atherosclerotic burden was an important predictor of long-term outcomes both in patients with and without diabetes. Moreover, we found that coronary CTA and PET perfusion findings guide subsequent use of LLM, which is associated with outcome benefit in patients with obstructive or ischemic CAD. Yet adherence to LLM declines over time. Multimodality imaging enables comprehensive assessment of CAD severity, helps guide risk stratification, and supports medication adherence in high-risk patients.

KEYWORDS: coronary computed tomography angiography, coronary artery disease, diabetes, positron emission tomography, prognosis

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kardiologia ja kardiovaskulaarilääketiede
Sydänkeskus ja Turun PET-keskus, Turun yliopistollinen keskussairaala
MATIAS MÄENPÄÄ: Diabetes, sepelvaltimotauti ja kliiniset lopputulokset: havaintoja monimenetelmällisestä kuvantamisesta
Väitöskirja, 108 s.
Turun kliininen tohtoriohjelma
Maaliskuu 2026

TIIVISTELMÄ

Sepelvaltimoiden tietokonetomografiatutkimus (sepelvaltimoiden TT) mahdollistaa sepelvaltimoiden ja niiden ateroskleroottisten plakkien anatomisen kuvantamisen, kun taas positroniemissiotomografiaan (PET) perustuva sydänlihaksen perfuusiokuvantaminen tarjoaa yksityiskohtaista tietoa näiden muutosten toiminnallisista seurauksista. Anatominen ja toiminnallinen kuvantaminen täydentävät toisiaan sepelvaltimotaudin arvioinnissa. Diabetes on merkittävä sepelvaltimotaudin riskitekijä ja yhteydessä huonompaan ennusteeseen. Lipidilääkityksellä on puolestaan keskeinen rooli sepelvaltimotaudin kehittymisen ja etenemisen ehkäisyssä sekä päätetapahtumien riskin vähentämisessä.

Tutkimuksessamme havaitsimme, että sepelvaltimoiden TT-tutkimus, jota täydennetään valikoidusti PET- perfuusiokuvantamisella toiminnallisen merkityksen arvioimiseksi, mahdollistaa pitkäaikaisen tapahtumariskin arvioinnin sekä diabeettisilla että ei-diabeettisilla potilailla, joilla epäillään sepelvaltimotautia. Diabetes oli yhteydessä vaikeampiasteiseen sepelvaltimotautiin sekä huonompaan pitkän aikavälin ennusteeseen, riippumatta sydänlihaksen perfuusiokuvantamisen tuloksista. Sen sijaan normaali perfuusio oli yhteydessä suotuisaan ennusteeseen ei-diabeettisilla potilailla. Kvantitatiivisesti mitattu sepelvaltimoiden ateroskleroottinen plakkikuorma oli merkittävä pitkän aikavälin ennustetekijä sekä diabeettisilla että ei-diabeettisilla potilailla. Lisäksi havaitsimme, että TT- ja PET-löydökset ohjaavat lipidilääkityksen käyttöä, joka puolestaan on yhteydessä parempaan ennusteeseen potilailla, joilla on todettu ahtauttava tai iskeeminen sepelvaltimotauti. Lääkityksen käyttöön sitoutuminen näyttää kuitenkin heikentyvän ajan myötä. Monimodaalikuvantaminen mahdollistaa sepelvaltimotaudin vaikeusasteen kattavan arvioinnin, auttaa ohjaamaan riskiluokitusta ja tukee lääkehoidon noudattamista korkean riskin potilailla.

AVAINSANAT: sepelvaltimoiden tietokonetomografia, sepelvaltimotauti, diabetes, positroniemissiotomografia, ennuste

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Abbreviations

AI	Artificial intelligence
AI-QCT	Artificial intelligence guided quantitative computed tomography
ACS	Acute coronary syndrome
CACS	Coronary artery calcium score
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCS	Chronic coronary syndrome
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance imaging
CTA	Computed tomography angiography
CVD	Cardiovascular disease
DM	Diabetes Mellitus
ECG	Electrocardiogram
FFR	Fractional flow reserve
GLP-1	Glucagon-like peptide-1
HDL	High-density lipoprotein
ICA	Invasive coronary angiography
IDF	International Diabetes Federation
LADA	Latent autoimmune diabetes in adults
LDL	Low-density lipoprotein
LLM	Lipid-lowering medication
LVEF	Left ventricle ejection fraction
MBF	Myocardial blood flow
MFR	Myocardial flow reserve
MI	Myocardial infarction
MODY	Maturity onset diabetes of the young
MPI	Myocardial perfusion imaging
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9

PET	Positron emission tomography
PET-CT	Positron emission tomography computed tomography
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
SAPT	Single antiplatelet therapy
SPECT	Single photon emission computed tomography
T1D	Type 1 diabetes
T2D	Type 2 diabetes
UAP	Unstable angina pectoris
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I **Matias Mäenpää**, Iida Kujala, Esa Harjulahti, Iida Stenström, Wail Nammas, Juhani Knuuti, Antti Saraste, Teemu Maaniitty. The impact of diabetes on the relationship of coronary artery disease and outcome: a study using multimodality imaging. *Cardiovasc Diabetol. 2023 May 31;22(1):129*

II **Matias Mäenpää**, Ruurt Jukema, Pepijn van Diemen, Sarah Bär, Pieter G Raijmakers, Ralf Sprengers, Roel S Driessen, Jeroen J Bax, Paul Knaapen, Juhani Knuuti, Ibrahim Danad, Antti Saraste, Teemu Maaniitty. Prognostic implications of quantified coronary atherosclerosis and myocardial perfusion in diabetes. *Cardiovasc Diabetol. 2025 Dec 02;24:453*

III Teemu Maaniitty, **Matias Mäenpää**, Esa Harjulahti, Iida Kujala, Iida Stenström, Wail Nammas, Juhani Knuuti, Antti Saraste. Lipid-Lowering Medication and Outcomes After Anatomical and Functional Imaging in Suspected Coronary Artery Disease. *JACC Cardiovasc Imaging. 2025 Jan;18(1):62–73*

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1 Introduction

Coronary artery disease (CAD) and diabetes mellitus (DM) are among the most common and lethal chronic diseases worldwide (1). CAD results from atherosclerotic plaque buildup in the coronary arteries, leading to restricted blood flow and an increased risk of myocardial infarction and cardiac death (2–4). Type 2 diabetes (T2D), the most common form of DM, accelerates atherosclerosis through hyperglycemia, insulin resistance, and inflammation, making patients with diabetes especially prone to severe and diffuse CAD and its complications (5).

Coronary computed tomography angiography (CTA) provides detailed anatomical visualization of the coronary arteries and atherosclerotic plaques (6). Recent developments in analysis tools have made quantitative measurement of plaque burden from coronary CTA feasible (7). However, CTA is limited in assessing whether coronary stenosis is functionally significant, i.e., causing insufficient blood supply to the myocardium (8). Positron emission tomography (PET) myocardial perfusion imaging (MPI) complements this approach by quantifying myocardial blood flow and identifying myocardial ischemia (9).

Hybrid imaging refers to combining information from two different imaging modalities, such as coronary CTA and PET, allowing a comprehensive anatomical and functional assessment of CAD and potentially enhancing clinical decision-making and risk stratification (9). Moreover, hybrid imaging and quantitative analysis tools enable detailed phenotyping of CAD from a research perspective, including in subgroups such as patients with diabetes (10). Lipid-lowering medication (LLM) is central to managing cardiovascular risk, but there is limited knowledge about its real-world use and adherence in relation to cardiac imaging findings (11).

This thesis evaluates the clinical feasibility and prognostic value of combined coronary CTA and PET perfusion imaging in patients with suspected CAD, with a special focus on patients with diabetes. Quantitative image analysis methods are used for detailed phenotyping of CAD. In addition, the relationships between hybrid imaging findings, LLM use and adherence, and long-term clinical outcomes are studied. The goal is to improve risk assessment and support individualized treatment in patients with suspected CAD.

2 Review of the Literature

2.1 Coronary artery disease

2.1.1 Pathophysiology of coronary artery disease

Coronary artery disease (CAD) is the most common cardiovascular disease (CVD) worldwide and remains the leading cause of death worldwide, accounting for an estimated 17.9 million deaths annually (WHO, 2024). Despite advances in preventive strategies, early risk factor identification, and medical therapy, CAD continues to pose a major global health burden, although age-standardized mortality rates have declined in recent decades (12).

Chronic coronary syndromes (CCS) represent the relatively stable phase of CAD and are characterized by the progressive accumulation of atherosclerotic plaques that narrow the coronary arteries and may gradually impair myocardial perfusion. CCS encompasses a broad spectrum of disease, ranging from non-obstructive CAD, where atherosclerotic plaques are present without flow-limiting stenosis, to obstructive CAD, where significant luminal narrowing restricts myocardial blood flow (MBF) and may lead to ischemia (3,4). In addition to atherosclerotic narrowing, CCS may result from functional abnormalities of the coronary circulation. These include coronary microvascular dysfunction, where MBF regulation is impaired in the absence of significant epicardial stenosis and vasospastic angina, caused by transient spasms of the epicardial arteries leading to reversible ischemia (13).

Over time, plaque growth and vascular remodelling may further restrict MBF, and in some cases, CCS may progress to acute coronary syndrome (ACS). ACS is typically precipitated by rupture or erosion of an unstable atherosclerotic plaque, which exposes thrombogenic material to the bloodstream, leading to thrombus formation and acute coronary occlusion. The resulting interruption of MBF may cause unstable angina pectoris (UAP), acute myocardial infarction (MI), or sudden cardiac death (2). **(Figure 1)**

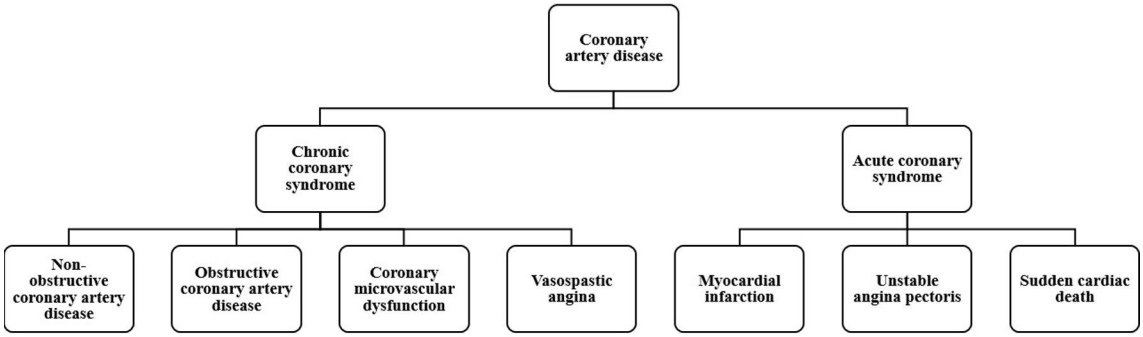

Figure 1. Manifestations of coronary artery disease. *Own drawing*

The primary risk factors for CAD include age, male sex, smoking history, hypertension, abnormal glucose metabolism, dyslipidemia, and a family history of premature CAD (14,15). In addition, other factors contribute to CAD, such as obesity, obstructive sleep apnea, an unhealthy diet, physical inactivity, and chronic stress (16). The pathophysiology of CAD is dynamic and depends on the interplay of risk factors and genetic susceptibility. The disease process begins with the accumulation of low-density lipoprotein (LDL) cholesterol particles within the inner lining of the coronary arteries. Over time, these LDL particles become oxidized and trigger an inflammatory response, leading to the formation of atherosclerotic plaques. These plaques consist of lipids, inflammatory cells, smooth muscle cells, and extracellular matrix, and they progressively narrow the coronary arteries. As plaques grow, they may obstruct MBF, leading to CCS and myocardial ischemia (4). CCS is typically characterized by stable angina, in which patients experience chest pain or chest discomfort on exertion or stress, but without acute myocardial injury (2).

2.1.2 Diagnosis and risk assessment of coronary artery disease

Current European guidelines recommend a structured four-step approach to the diagnosis, risk stratification, and management of CCS. The initial step is to exclude ACS. Once ACS is excluded, alternative explanations for the symptoms can be considered. To rule out other causes and to support a potential diagnosis of CCS, baseline investigations such as a resting electrocardiogram (ECG), routine blood tests, chest radiography, and pulmonary function testing (if indicated) are recommended. If CCS remains probable, the second step should involve transthoracic echocardiography and estimation of the clinical likelihood of obstructive CAD based on patient characteristics, including age, sex, symptom

profile, and other cardiovascular risk factors. The third step is to select an appropriate diagnostic test based on the estimated clinical likelihood and to stratify the risk of future adverse cardiac events (11).

Categories of clinical likelihood of obstructive CAD and recommended actions, adapted from the 2024 ESC guidelines on CCS:

- Very low likelihood (≤5%): Further diagnostic testing can be deferred unless symptoms persist, and non-cardiac causes have been excluded.
- Low clinical likelihood (5–15%): In patients with a low clinical likelihood, routine diagnostic testing for CAD is not recommended but may be considered if symptoms are limiting and require clarification. Coronary computed tomography angiography (CTA) can be used to exclude CAD, or other diagnostic tests can be used to adjust clinical likelihood (e.g. stress echocardiography, exercise electrocardiogram testing, cardiac magnetic resonance imaging (CMR).
- Moderate clinical likelihood (15–50%): In patients with an intermediate clinical likelihood, coronary CTA is recommended as a first-line test combined with functional imaging (e.g., preferably positron emission tomography (PET), stress echocardiography, single photon emission computed tomography (SPECT), CMR) if information on myocardial ischemia, viability or microvascular disease is desired.
- High clinical likelihood (50–85%): In patients with high clinical likelihood positron emission tomography computed tomography (PET-CT) myocardial perfusion imaging (MPI) or other feasible functional testing is recommended.
- Very high clinical likelihood (>85%): For patients with a very high clinical likelihood or patients with severe symptoms that are refractory to medical therapy or those experiencing typical angina with minimal exertion, referral to invasive coronary angiography (ICA) with fractional flow reserve (FFR) assessment is advised to confirm the diagnosis of CAD and evaluate the hemodynamic significance of coronary stenoses.

Patients with obstructive CAD or myocardial ischemia should be assessed for adverse event risk. Risk stratification is generally based on non-invasive or invasive diagnostic tests used to diagnose CAD, as well as on other patient characteristics and risk factors (17–19). Coronary stenoses and high plaque burden on coronary CTA are well-established prognostic markers with a growing body of evidence for adverse plaque characteristics being a strong predictor of adverse events (20–23). Large observational studies consistently demonstrate a robust prognostic value according to the extent of ischemia on functional imaging (24–29).

In contrast, post hoc analyses of COURAGE and ISCHEMIA randomized controlled trials (RCT) showed only anatomical CAD severity remained independent predictor of future adverse events (23,30,31). Furthermore, the PROMISE trial demonstrated coronary CTA outperforming functional testing in predicting future events. However, adding the Framingham Risk Score to the functional test result improved the prognostic value of functional testing rendering the difference between anatomical and functional testing non-significant (11,32).

In addition, patients referred to ICA-FFR showing impaired regional or global FFR (average of the sum of the FFR values in the three major coronary arteries) is strongly associated with future adverse events (33–36). Similarly, coronary CTA-derived FFR (FFR-CT) estimations demonstrate similar results (37,38). Furthermore, echocardiography is recommended for all patients suspected of CCS, as reduced LV function is a strong predictor of poor prognosis (39,40). In addition, stress electrocardiogram may refine risk assessment if performed during the diagnostic work-up (41–44).

After confirmation of the diagnosis of CCS, the fourth step includes lifestyle and risk-factor modification combined with disease-modifying medications and consideration of invasive treatment procedures when appropriate. For patients in whom revascularization is unlikely to provide benefit due to comorbidities or poor quality of life, CCS can be diagnosed clinically, and management may proceed with medical therapy alone. In cases where the diagnosis of CCS remains uncertain, non-invasive functional imaging to assess myocardial ischemia is recommended before proceeding with treatment (11).

2.1.3 Management of chronic coronary syndrome

The management of CCS aims to reduce ischemic symptoms and future cardiovascular events. This is achieved through a combination of optimal medical therapy (OMT), healthy lifestyle modifications and, if necessary, coronary revascularization. Importantly, the effectiveness of CCS management depends heavily on treatment adherence.

Healthy lifestyle modification remains the cornerstone of CCS management. Smoking cessation, adoption of a heart-healthy diet, regular physical activity, and weight management are recommended in all patients to improve prognosis and quality of life. Evidence also suggests that mental well-being significantly improves cardiovascular outcomes, even in the absence of OMT (45–49). When combined with OMT, lifestyle modifications yield additive benefits for patient prognosis. As such, lifestyle modification should be consistently encouraged and incorporated into all CCS treatment plans (50).

OMT in CCS includes medications aimed at both symptom relief and event prevention. Anti-ischemic medications are used to treat symptoms and may include beta-blockers and/or calcium channel blockers as first-line agents, with nitrates as second-line therapy. Additional options for selected patients may include nicorandil, ranolazine, ivabradine, and trimetazidine. Event-reducing medications include antithrombotic agents, lipid-lowering medications (LLM), and renin-angiotensin-aldosterone system (RAAS) inhibitors (11). Furthermore, emerging anti-inflammatory and metabolic therapies are being developed (51–53). The objective of these medications is to reduce the incidence of MI, UAP, and cardiovascular mortality by lowering thrombotic risk and slowing disease progression.

All patients with CCS should be initiated on at least low-dose aspirin (single antiplatelet therapy, SAPT), provided no contraindications exist, due to its established benefit in preventing future ACS (54,55). After ACS (with or without percutaneous coronary intervention (PCI)) or after PCI is indicated, SAPT is typically escalated to dual antiplatelet therapy (aspirin and a P2Y12 inhibitor) for a limited time, after which SAPT is continued (56,57). Extended intensified antithrombotic therapy should be considered in CCS patients at high ischemic risk without high bleeding risk (58–60). Low-dose rivaroxaban can be combined with low-dose aspirin in high-risk patients (61).

High-intensity statin therapy is indicated to lower low-density lipoprotein (LDL) cholesterol, a causal factor in atherosclerosis (62). Reducing LDL levels in patients with CAD lowers cardiovascular risk and improves outcomes and should be managed according to the most recent European guidelines (63). When statin monotherapy is insufficient or not tolerated, adjunct therapies such as ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (e.g., alirocumab, evolocumab, inclisiran), or bempedoic acid may be required to achieve target lipid levels (64–67).

Additional pharmacologic therapies should be individualized based on patient characteristics. RAAS inhibitors are particularly beneficial in patients with left ventricular dysfunction, hypertension, diabetes, chronic kidney disease, or a history of myocardial infarction and improve patient prognosis (68–74).

Beta-blockers reduce myocardial oxygen demand by lowering blood pressure and heart rate, thus alleviating symptoms. In addition, beta-blockers reduce catecholamine levels, thereby decreasing myocardial ischemia, limiting infarct size, and preventing progression to definitive infarction in acute coronary syndromes, which contributes to improved prognosis. Beta-blockers are indicated in patients with prior acute coronary syndrome and reduced left ventricular ejection fraction (LVEF), although evidence in patients without ventricular dysfunction remains inconsistent (75–80).

Calcium channel blockers may be used to reduce coronary artery spasm and improve anginal symptoms (81). Nitrates remain effective for short-term relief of angina, with long-acting agents used in combination when symptom control is inadequate (82). In patients with elevated cardiometabolic risk and obesity (BMI ≥27), glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide have shown growing evidence of improving CAD prognosis irrespective of diabetes status, due to their favourable impact on cardiovascular outcomes (53). Nicorandil, ranolazine, ivabradine and trimetazidine may be considered in selected patients as an option to alleviate symptoms (83).

While revascularization with PCI or coronary artery bypass grafting (CABG) is well established in ACS, its role in CCS is more controversial (84). The ISCHEMIA trial demonstrated that routine revascularization does not provide a survival benefit over OMT alone at five-year follow-up among patients without severe symptoms and with moderate-to-severe myocardial ischemia (85). However, extended follow-up in the ISCHEMIA-EXTEND study revealed a reduction in cardiovascular mortality among patients managed with initial invasive strategy although this was offset by a significant increase in non-cardiac mortality (86).

Subsequently, a meta-analysis further suggested revascularization in addition to OMT may decrease cardiac mortality, largely by preventing MIs (87). The revascularization strategy should be guided by anatomical complexity and patient characteristics. CABG enables complete revascularization in multivessel disease, whereas PCI with newer-generation drug-eluting stents is appropriate for less complex disease (11,88).

Despite the availability of evidence-based therapies, adherence to both pharmacological treatment and lifestyle modification remains suboptimal in patients with CCS (89,90). Poor adherence significantly undermines the effectiveness of management strategies, leading to worse outcomes, including increased rates of myocardial infarction, repeat hospitalizations, and all-cause mortality (89). In the ISCHEMIA trial, inadequate adherence to medical therapy was associated with worse clinical outcomes across both conservative and invasive treatment groups (91).

Multiple factors contribute to poor adherence. These include complex medication regimens, side effects, financial constraints, limited health literacy, and a lack of patient understanding about the chronic nature of CCS. Psychological and social barriers, such as depression, low social support, and negative beliefs about medication, are also influential. Additionally, deficits in physician–patient communication may result in misunderstandings regarding treatment goals and the importance of therapy (92,93).

Numerous interventions can be used to improve treatment adherence (47). Interventions with evidence of effectiveness include structured patient education programs, simplified pharmacotherapy using fixed-dose combination pills

(polypills), the use of digital health technologies such as mobile reminders, and coordinated multidisciplinary follow-up involving physicians, nurses, and pharmacists. Engagement strategies that enhance communication and promote shared decision-making are also essential (94,95).

2.2 Non-invasive imaging of coronary artery disease

2.2.1 Coronary computed tomography angiography

CTA is a non-invasive imaging technique that utilizes X-ray computed tomography combined with intravenously administered iodine contrast agents to provide detailed anatomical images of blood vessels. This approach allows high-resolution visualization of the coronary arteries, including the lumen and surrounding structures. The use of contrast agents in coronary CTA enables assessment of coronary artery stenosis, which is often quantified by measuring the degree of luminal narrowing. Coronary CTA can be used to assess not only the coronary artery lumen but also coronary artery plaques, providing information on their location, size, morphology, eccentricity, and composition. This makes CTA a powerful tool for the evaluation of CAD and plaque characteristics, as well as for assessing coronary artery remodelling (6). However, it is important to note that coronary CTA is prone to image artifacts, which can arise from factors such as patient motion, arrhythmias, obesity, excess calcification, or suboptimal contrast enhancement (96).

Coronary CTA has quickly evolved into a first-line tool in the diagnosis and decision-making of CAD (11). The primary role of coronary CTA in clinical practice has been to either detect or exclude the presence of obstructive CAD based on an anatomical assessment of the coronary arteries. Traditionally, a diameter stenosis of 50% or greater has been considered obstructive and used as a threshold to diagnose CAD. This criterion is commonly applied in studies comparing coronary CTA with ICA-FFR, which is used as the reference standard. However, the hemodynamic significance of stenosis, especially in the moderate stenosis range, e.g., 50–69%, is often uncertain and further functional testing may be required (97,98). One such method is coronary FFR-CT. FFR-CT has shown good agreement with ICA-FFR, but its use is limited by image quality and excess calcification (99). Advantages of FFR-CT compared with other functional testing methods are the lack of required pharmacological stress, additional contrast agent injection or additional radiation exposure. Additionally, CT-based MPI has been studied but is not yet widely standardized (100,101).

Most patients referred for coronary CTA have non-obstructive CAD, defined as a diameter stenosis of less than 50%. Although the hemodynamic impact of these

lesions is often minor, they are associated with an elevated risk of future cardiovascular events. Importantly, cardiovascular risk correlates with the extent and composition of plaques rather than with luminal narrowing alone, as non-calcified plaques are linked to plaque vulnerability and subsequent plaque rupture (102). Notably, non-obstructive lesions may progress over time and lead to ACS, especially in the presence of high-risk plaque features such as positive remodelling or low-attenuation plaque (103). Consequently, recognition of non-obstructive CAD on CTA has important therapeutic implications. Even in the absence of obstructive disease, the detection of coronary atherosclerosis may justify the initiation or intensification of preventive therapies, including lipid-lowering and lifestyle interventions, to reduce future cardiovascular risk (104).

Coronary artery calcium score (CACS) is a non-invasive imaging method that quantifies calcified atherosclerotic plaque in the coronary arteries using non-contrast CT. The most widely applied metric is the Agatston score, which integrates the area and density of coronary calcifications to provide an overall estimate of coronary plaque burden (105). CACS serves as a robust marker of atherosclerosis and provides independent prognostic value. A CACS score of zero is associated with an excellent prognosis and a very low likelihood of obstructive CAD (106), whereas increasing CACS strongly correlates with a higher risk of future cardiovascular events (107). However, unlike coronary CTA, CACS does not provide information about non-calcified plaques or luminal narrowing. This limitation is important, as non-calcified plaques are more prone to rupture than calcified plaques and are associated with worse outcomes, thereby rendering coronary CTA superior, as it enables assessment of both non-calcified and calcified plaques (108).

Quantitative coronary computed tomography angiography (qCTA) is an advanced extension of CTA that combines detailed anatomical imaging of the coronary arteries with quantitative measurements of coronary pathology derived from CTA images. Compared with conventional coronary CTA, which is primarily used to visualize coronary artery anatomy and stenosis, qCTA offers a more detailed approach by incorporating quantitative metrics that allow a deeper understanding of coronary artery disease. qCTA enables measurement of plaque burden and composition, including the identification of positive remodelling and both calcified and non-calcified plaques. qCTA is limited by the same factors as conventional coronary CTA but is most importantly constrained by the time-consuming process of manual confirmation and validation of imaging results. Recently, artificial intelligence–based algorithms have shown promise for automated qCTA, and the method is expected to see increased use in the future (109,110).

Due to the complexity of CAD detected by coronary CTA, the Coronary Artery Disease–Reporting and Data System (CAD-RADS) was developed to standardize the reporting of coronary CTA findings and help guide downstream management.

The updated 2022 version, CAD-RADS 2.0, integrates recent advances in coronary CTA technology and emerging evidence linking plaque burden and morphology to patient outcomes, reflecting a shift from purely stenosis-based reporting to a more comprehensive approach that incorporates anatomical, functional, and compositional information. CAD-RADS 2.0 supports risk stratification and guides downstream management decisions. Furthermore, it facilitates research comparability and the use of coronary CTA data in prognostic modelling and clinical decision pathways (108)

The negative predictive value (NPV) of coronary CTA is high, making it an excellent tool for ruling out significant CAD. In patients with normal coronary CTA findings, the likelihood of obstructive CAD is extremely low. In fact, these patients generally have an excellent long-term prognosis with a very low risk of major adverse cardiac events. However, the positive predictive value (PPV) of coronary CTA is lower than its NPV, which represents a key limitation of this technique (111).

Conversely, the identification of high-risk plaques (e.g., positive remodelling or low-attenuation plaque) or excess coronary artery calcification on CTA can provide additional prognostic value and guide therapeutic decisions (112). Furthermore, the SCOT-HEART trial demonstrated improved outcomes in patients in whom coronary CTA was performed in addition to routine exercise ECG testing (113). Otherwise, initial diagnostic testing with coronary CTA seems to be associated with similar outcomes to initial functional imaging tests (114). However, some studies suggest that coronary CTA provides incremental prognostic value that extends beyond functional measures (115).

RCTs comparing coronary CTA and functional testing suggest the improved outcomes may be explained with test reporting and patient management variability. In SCOT-HEART trial coronary CTA findings, even non-obstructive CAD triggered intensification of medical therapy that is thought to largely explain the improved outcomes (112,116,117). Furthermore, research suggests that coronary CTA can enhance risk prediction when combined with other clinical variables, such as age, sex, diabetes, hypertension, and smoking status (118).

2.2.2 Positron emission tomography myocardial perfusion imaging

MPI is a cornerstone in the non-invasive functional assessment of CAD. Its primary clinical utility lies in the detection of flow-limiting obstructive CAD, evaluation of myocardial ischemia, and risk stratification of patients with suspected or known CAD. Among the various MPI modalities, PET offers distinct technical and clinical advantages, allowing quantitative measurement of MBF both at rest and under stress, thereby enabling calculation of myocardial flow reserve (MFR). To assess MBF with

PET MPI, the patient is injected intravenously with a perfusion tracer at one or two time points depending on the imaging protocol: at baseline and at peak pharmacological stress-induced hyperemia.

PET enables robust absolute quantification of MBF and MFR, which enhances the sensitivity and specificity of ischemia detection, especially in complex multivessel CAD or balanced ischemia, where relative perfusion techniques such as SPECT may underestimate disease burden (119,120). In addition, PET enables measurement of LVEF reserve, which serves as a supportive tool for diagnosing and risk stratifying severe left main disease or three-vessel disease (121,122). Furthermore, PET offers superior spatial and temporal resolution, improved attenuation correction, shorter imaging protocols, and lower radiation exposure than SPECT (9,123). These advantages have led to growing consensus regarding the role of PET MPI as the preferred method in non-invasive functional CAD imaging (11)

Unlike anatomical imaging modalities such as coronary CTA, which visually assess luminal narrowing, PET provides information on the physiological consequences of coronary stenoses. This distinction is critical, as the severity of anatomical stenosis does not necessarily correlate directly with its functional significance (97,98). Furthermore, the ability of PET to detect microvascular dysfunction when combined with coronary CTA often manifesting as impaired MFR or stress MBF in the absence of obstructive CAD adds valuable diagnostic and prognostic information, particularly in populations such as women, patients with diabetes, and patients with heart failure (124).

Multiple studies have confirmed the diagnostic and prognostic superiority of PET MPI over other functional imaging methods. For example, McArdle et al. demonstrated that PET outperforms SPECT in sensitivity, specificity, and overall accuracy for diagnosing obstructive CAD (125). Parker et al. and Takx et al. further confirmed these findings through systematic reviews and meta-analyses (123,126). Importantly, Danad et al. and Rasmussen et al. have shown that PET provides incremental prognostic value beyond anatomical imaging and conventional risk factors, supporting its use in guiding patient management decisions (9,127). Additionally, Patel et al. demonstrated that a low MBF reserve measured by PET independently predicted mortality and helped identify patients with a survival benefit from early revascularization (128). PET-CT is particularly recommended by recent guidelines in obese patients, in younger patients, and in those with known or suspected diffusely impaired MBF (e.g., multivessel disease or microvascular dysfunction) (11,129).

Despite its advantages, the widespread adoption of PET MPI remains limited by cost, the availability of cyclotrons or generator-produced tracers (e.g., 15O-water, 13N-ammonia, 82Rb), scanners, and the need for technical expertise. Nevertheless, recent advances in PET tracers offer longer half-lives and improved image quality,

potentially expanding access and clinical applications (119). Moreover, integration with hybrid imaging platforms (e.g., PET-CT, PET-MRI) and artificial intelligence (AI)–driven image interpretation shows promise for the future (130).

2.2.3 Hybrid imaging

Hybrid imaging combines anatomical and functional data to improve both the diagnostic and prognostic evaluation of CAD (131). While SPECT remains widely used, the combination of coronary CTA with PET MPI is increasingly recognized as the preferred hybrid modality due to higher spatial resolution of PET, quantitative capabilities, lower radiation dose, and reduced susceptibility to artifacts. As such, routine acquisition of combined SPECT and coronary CTA imaging is currently not advised owing to the higher radiation exposure compared with MPI alone. Conversely, a more prominent role is encouraged for routine hybrid PET-CT where gains in diagnostic and prognostic value are expected. Several studies support the complementary role of the diagnostic and prognostic information provided by coronary CTA and PET MPI in the evaluation of CAD. A joint statement by EANM and EACVI encourages the use of a hybrid PET-CT approach over stand-alone modalities for three indications (132).

- Implementation of a low-dose CT for attenuation correction (routine for PET-CT) to improve diagnostic accuracy (133–135).
- Assessment of CACS by CT with complementary MPI for additional prognostic value (136–138). In fact, additional acquisition of a dedicated CT to calculate CACS is advised in patients without known CAD, given the diagnostic and prognostic value of CACS.
- Evaluation of unclear MPI findings with complementary coronary CTA to accurately localize and assign the ischemic territory (139).

Additionally, hybrid PET-CT imaging is thought to be particularly useful in several other scenarios:

- Functional assessment of intermediate coronary artery stenoses detected by coronary CTA to improve specificity for identifying obstructive CAD (108,140).
- To help differentiate multivessel CAD from microvascular dysfunction (141).
- In symptomatic patients with prior revascularization, in whom coronary CTA images may be limited by artifacts (142,143).

The hybrid PET-CT approach addresses the limitations of stand-alone PET and coronary CTA imaging. Coronary CTA provides high-resolution anatomical imaging, enabling accurate detection of coronary stenoses and atherosclerotic plaque features. PET MPI, on the other hand, offers the ability to assess the hemodynamic significance of stenoses detected by coronary CTA and to quantify MBF. This approach enhances lesion characterization, improves diagnostic accuracy, helps guide downstream treatment, and improves patient risk stratification (132).

Several studies have demonstrated the added diagnostic and prognostic value of a hybrid imaging approach. Kajander et al. reported that combining PET MPI with coronary CTA significantly improves specificity and positive predictive value for detecting obstructive CAD, compared with either modality alone (144). The EVINCI study confirmed that hybrid imaging enhances both diagnostic and prognostic performance (145). Recently, Lehtonen et al. demonstrated using a machine learning approach that downstream PET MPI after coronary CTA provided incremental prognostic value during the first four years after imaging (146). Schenker et al. (2008) found that higher CACS predicted increased event risk, even in patients without ischemia on PET (147). It should also be noted that CACS has an additive role in PET MPI for patient risk stratification (137,138).

Results with other hybrid imaging modalities are consistent with the PET-CT approach. Ghadri et al. showed that matched hybrid findings (perfusion defect in SPECT MPI with calcification in coronary CTA in the same territory) were independently predictive of worse outcomes (148). Similarly, Pazhenkottil et al. reported higher annual event rate in patients with matched SPECT-CTA findings compared to unmatched findings. Patients with normal findings had a good prognosis. Their follow-up study with longer observation and a larger cohort replicated this stratification (149,150). Furthermore, a study by van Werkhoven et al. showed that patients with both abnormal SPECT MPI and ≥50% stenosis had a substantially higher adverse event rate than those with normal imaging (151). Importantly, the CORE320 study demonstrated that short-term (2-year) prognostic value was consistent across different modalities, including SPECT-CTA and coronary CTA combined with coronary CTA-derived MPI (152). Hybrid imaging is particularly useful in high-risk anatomical scenarios such as left main or three-vessel disease. While coronary CTA alone is sensitive for detecting these lesions, it lacks specificity (153). Some evidence suggests added value for PET-derived MBF and MFR for risk stratifying these conditions (154,155).

Routine clinical utilization of hybrid imaging worldwide is not yet widely practiced and further studies are needed to better establish the impact of such imaging on the prevention and treatment of CVD (156). Limitations of hybrid PET-CT imaging are numerous and include higher radiation exposure (although still lower than SPECT-CTA), procedural complexity, costs, and limited availability. Recent

advances in low-dose CT techniques and PET tracers may help address these concerns. Emerging methods, such as AI-assisted analysis and quantitative imaging, may further enhance both accessibility and clinical utility (157).

2.3 Coronary artery disease and diabetes mellitus

2.3.1 Diabetes mellitus

Diabetes mellitus (DM) represents a major global public health challenge, currently affecting an estimated 589 million people worldwide, with type 2 diabetes (T2D) accounting for more than 90% of all cases. The prevalence of diabetes continues to rise, driven largely by aging population, urbanization, sedentary lifestyles, and increasing obesity rates. According to the International Diabetes Federation (IDF), diabetes is directly responsible for approximately 3.4 million deaths each year, with CVDs constituting the leading cause of mortality among individuals with diabetes (IDF, 2025).

In Finland, the burden of diabetes is similarly substantial, with approximately 480,000 individuals diagnosed with T2D and an additional 50,000 with type 1 diabetes (T1D) (THL, 2025). Data from the FinTerveys 2017 survey indicate that diabetes affects around 15% of Finnish men and 10% of women. Projections suggest a continued increase in prevalence over the coming decades, underscoring the growing public health and healthcare challenges posed by diabetes and its complications.

DM is defined as having a fasting plasma glucose $\geq$ 7.0 mmol/l, 2-hour plasma glucose $\geq$ 11.1 mmol/l, or hemoglobin A1c $\geq$ 6.5%/ 48 mmol/mol. Prediabetes, which represents an intermediate stage between normal glucose regulation and diabetes, is defined as impaired fasting glucose (fasting plasma glucose 6.1–6.9 mmol/l), impaired glucose tolerance (2-h plasma glucose 7.8–11.0 mmol/l in a 75 g oral glucose tolerance test), or hemoglobin A1c 6.0–6.4%/42–47 mmol/mol. Repeat testing is advisable to confirm the diagnosis. Individuals with prediabetes are at an increased risk of progressing to T2D and should undergo lifestyle modifications to prevent or delay disease progression (158). DM can be divided broadly into two groups, type 1 diabetes and type 2 diabetes. Significant overlap is recognized between these two entities, and DM is further categorized by WHO (WHO, 2019):

- Type 1 Diabetes Mellitus (T1D): An autoimmune condition leading to the destruction of pancreatic β-cells, resulting in absolute insulin deficiency. T1D accounts for approximately 5–10% of diabetes cases.
- Type 2 Diabetes Mellitus (T2D): Characterized primarily by insulin resistance and relative insulin deficiency. T2D is the most prevalent form of DM and is strongly associated with lifestyle and metabolic risk factors.

Other, less common, specific types of DM:

- Monogenic diabetes: Includes neonatal diabetes and maturity-onset diabetes of the young (MODY), resulting from single-gene mutations.
- Latent autoimmune diabetes in adults (LADA): A slowly progressive form of autoimmune diabetes that combines features of T1D and T2D.
- Gestational diabetes mellitus: Glucose intolerance first recognized during pregnancy, typically resolving postpartum but conferring an increased long-term risk of T2D.
- Secondary Diabetes: Arises from other medical conditions such as pancreatic disease, endocrinopathies, or the use of diabetogenic medications (e.g., glucocorticoids).

The risk factors for T2D comprise a combination of genetic, lifestyle, and environmental factors, many of which are shared with CAD. A family history of T2D, obesity, physical inactivity, an unhealthy diet, advancing age, certain ethnic backgrounds, hypertension, and smoking are key contributors to the development of T2D. The clinical presentation of DM can vary, with some individuals exhibiting classic symptoms such as polyuria, polydipsia, unexplained weight loss, fatigue, blurred vision, poor wound healing, and recurrent infections. However, a significant proportion of individuals with diabetes remain asymptomatic, particularly in the early stages or when the condition is undiagnosed. Given that diabetes often goes unnoticed until complications arise, routine screening is essential, especially for individuals at high risk due to predisposing factors (159).

DM is primarily characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. These defects lead to impaired glucose utilization and storage, causing elevated blood glucose levels. Over time, uncontrolled hyperglycemia and other metabolic disturbances result in progressive damage to various organs, including the heart, kidneys, eyes, and nerves, thereby contributing to the long-term complications of the disease (160). The most common complications include:

- CVD: Individuals with diabetes have an increased risk of CAD and other CVDs (161).
- Diabetic retinopathy: One of the leading causes of blindness in adults. Hyperglycemic conditions gradually damage blood vessels in the retina (162).

- Diabetic nephropathy: A leading cause of chronic kidney disease (CKD) characterized by albuminuria, hypertension and gradual loss of renal function (162).
- Diabetic neuropathy: Nerve damage, particularly in the peripheral nervous system, is common in individuals with diabetes and may lead to major complications such as diabetic foot (163).

2.3.2 The interrelation between coronary artery disease and diabetes mellitus

DM significantly increases the lifetime risk of developing CVD, with CAD representing the leading cause of morbidity and mortality among individuals with diabetes and significantly worsening outcomes in CAD (164). The primary risk factors for both conditions are largely shared, including obesity, hypertension, dyslipidemia, and tobacco use, and they synergistically worsen endothelial dysfunction, thereby promoting atherosclerosis, the underlying pathology of CAD.

Hyperglycemia in DM accelerates vascular damage and atherosclerosis through multiple interrelated mechanisms. One central process involves the formation of advanced glycation end products, which impair endothelial function, increase oxidative stress, and promote vascular inflammation and remodelling (165). Chronic hyperglycemia also contributes to the glycation and oxidation of lipoproteins, enhancing foam cell formation and worsening endothelial dysfunction. These metabolic and vascular alterations collectively accelerate the development of atherosclerotic plaques.

Oxidative stress in DM is driven by persistent hyperglycemia, resulting in the overproduction of reactive oxygen species that reduce nitric oxide bioavailability and impair endothelium-dependent vasodilation. This process increases arterial stiffness and promotes plaque instability (166). Furthermore, persistent hyperglycemia results in a pro-inflammatory state characterized by elevated levels of cytokines such as interleukin-1, interleukin-6, and tumour necrosis factor-alpha, which stimulate immune cell infiltration into the vascular wall and thereby accelerate atherosclerotic plaque progression (167).

A hallmark feature of T2D is the presence of a condition called diabetic dyslipidemia, a pro-atherogenic lipid profile consisting of elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL), and a predominance of small, dense low-density lipoprotein particles. These lipid abnormalities are often not fully captured by standard lipid panels, as LDL concentrations in T2D may remain within normal limits despite increased cardiovascular risk (168). Diabetic dyslipidemia is caused by insulin resistance, a key feature of T2D, which disrupts lipid metabolism by increasing hepatic very-low-density lipoprotein production and impairing the

clearance of triglyceride-rich lipoproteins (169). In addition, HDL particles in individuals with diabetes often lose their anti-inflammatory and vasoprotective properties, further accelerating atherosclerosis (170).

Patients with coexisting diabetes and CAD often present with more extensive coronary lesions and multivessel disease, which complicates both the diagnosis and management of CAD (171). Silent (asymptomatic) myocardial ischemia is also more prevalent in this population due to diabetic autonomic neuropathy, which blunts pain perception and may delay the recognition of CAD symptoms such as chest pain (172). Importantly, the prognosis for individuals with both diabetes and CAD is considerably worse than in patients without diabetes, with increased risks of recurrent MI, heart failure, and all-cause mortality (164). Early detection and timely intervention are particularly critical in younger individuals, in whom the coexistence of diabetes and CVD is associated with markedly worse long-term adverse outcomes (173).

The relationship between DM and CAD assessed by coronary CTA has been examined in several large observational studies. In the CONFIRM registry, 1823 patients with diabetes were propensity-matched with patients without diabetes controls and followed for five years. Patients with diabetes had approximately double the all-cause mortality of patients without diabetes in the presence of non-obstructive or obstructive CAD, while no outcome differences were observed in the absence of coronary atherosclerosis (174). Similarly, in a Danish registry, diabetes was associated with higher all-cause mortality across all CAD severity categories on coronary CTA, although MI rates did not differ significantly among those with no or non-obstructive CAD (175). Further analysis of the SCOT-HEART trial showed that patients with diabetes had higher coronary calcium scores, total coronary plaque volume, and altered plaque composition compared with patients without diabetes, despite similar rates of obstructive coronary stenosis and high-risk plaque features (176). Likewise, in the CREDENCE trial, artificial intelligence (AI)-based quantitative coronary CTA (qCTA) showed that patients with diabetes and non-obstructive CAD had greater plaque burden than patients without diabetes, and interestingly, plaque burden was similar to that observed in patients without diabetes with obstructive CAD (10).

2.3.3 Management of chronic coronary syndrome in diabetes mellitus

Management of CCS in patients with diabetes follows the same general principles as in patients without diabetes with lifestyle changes, LLMs, and antithrombotic medications remaining the cornerstone of treatment. However, in T2D, CCS management requires a comprehensive approach that targets both the metabolic and

cardiovascular aspects of the disease. The therapeutic strategy must aim not only to control blood glucose but also to manage key cardiovascular risk factors such as lipids, blood pressure, and platelet aggregation more aggressively than in patients without diabetes. As such, the European Society of Cardiology (ESC) has published dedicated guidelines for the management of CVD in patients with diabetes (177).

Glycemic control is essential in mitigating the vascular damage caused by chronic hyperglycemia. The choice of glucose-lowering agents is influenced by their potential to reduce cardiovascular risk and blood glucose levels, and by whether weight reduction is desired. Medications with proven CV benefit should be used as first-line treatment. SGLT2 inhibitors are recommended for all T2D patients with CAD regardless of HbA1c levels due to their ability to reduce the risk of cardiovascular events, body weight, hospitalization for heart failure, and progression of CKD (178). GLP-1 receptor agonists (excluding lixisenatide and exenatide) are recommended for all T2D patients with CAD regardless of BMI and HbA1c levels, as they provide significant weight loss and a lower incidence of adverse events (179).

Other medications should be considered if additional glucose control is required. Metformin is recommended for patients using SGLT2 inhibitors and GLP-1 receptor agonists when adequate blood glucose control is not achieved. The CV benefit of metformin remains inconclusive (180). Thiazolidinedione pioglitazone can be considered in T2D patients with established CAD due to its association with reduced adverse events (181). However, due to fluid retention and increased risk for heart failure associated with pioglitazone, caution is advised (182). Dipeptidyl peptidase-4 inhibitors sitagliptin and linagliptin have a proven CV safety profile and can be used (183,184). Sulphonylureas have failed to improve CV outcomes but do not have significant CV safety concerns and can be considered if additional glucose control is desired (185). Insulin therapy may be necessary in patients with more advanced T2D.

LLM remains the basis of CCS management in patients with diabetes. Statins are the primary agents of choice, and their use in individuals with diabetes is supported by robust evidence. While the principles of LLM are similar to those in patients without diabetes, patients with diabetes typically require more aggressive lipid-lowering strategies due to the frequent presence of diabetic dyslipidemia (63,186). Furthermore, the REDUCE-IT trial demonstrated a significantly lower adverse event rate in patients with diabetes who received icosapent ethyl compared with placebo, and this agent may be considered in combination with a statin in patients with hypertriglyceridemia (187).

Hypertension is another critical risk factor for both CCS and DM-related complications and is extremely common in patients with diabetes and CAD (188). Therefore, hypertension screening in patients with diabetes and CAD is strongly recommended. RAAS inhibitors are particularly beneficial in patients with diabetes

due to their renoprotective properties, but other hypertensive agents can be used as in patients without diabetes (189).

Given the heightened risk of thrombosis in patients with diabetes and CCS, antiplatelet therapy is a key component of management, and the general approach remains the same as in patients without diabetes. However, in contrast to patients without diabetes, primary prevention with low-dose aspirin for patients with diabetes without a history of CAD has been shown to be beneficial and may be considered (190,191). Additionally, low-dose rivaroxaban should be considered more readily given the high-risk profile of patients with diabetes (58,158).

In patients with diabetes and CAD, indications for myocardial revascularization are the same as those in patients without diabetes. However, in patients with diabetes and multivessel disease, CABG is superior to PCI (192–194). Furthermore, in patients with diabetes undergoing CABG, multiple arterial grafting is associated with significantly lower mortality compared with single arterial grafting, with the survival benefit being more pronounced than in patients without diabetes (88).

3 Aims

The aim of the present observational study is to evaluate the use of coronary CTA, PET MPI, and their quantitative analysis in real-world symptomatic patients with suspected obstructive CAD. The objectives of the individual studies in this article-based thesis are as follows:

1. To assess the prognostic value of a hybrid imaging strategy with selective application of PET MPI after coronary CTA in patients with suspected CAD, in the presence of diabetes or prediabetes. (Study I).

2. To study the prognostic implications of quantified coronary atherosclerotic burden and myocardial perfusion in patients with and without diabetes and suspected CAD to increase understanding of the mechanisms underlying the higher cardiovascular risk in patients with diabetes. (Study II).

3. To evaluate the use of LLM and investigate its relationship with long-term outcomes after coronary CTA and selective PET MPI in patients with suspected obstructive CAD. (Study III).

4 Materials and Methods

4.1 Study design and patient population

This thesis includes three studies (I–III) that were conducted during 2019-2025. The aim of these studies was to investigate the prognostic utility of a hybrid PET-CT approach with a focus on patients with diabetes, in whom dyslipidemia is often concurrently present.

- Study I examined long-term outcomes in patients with T2D or prediabetes and compared the prognostic value of selective hybrid PET–CT approach with patients without diabetes.
- Study II explored the prognostic implications of quantified anatomical (CTA) and functional imaging (PET MPI) findings in patients with diabetes versus patients without diabetes to clarify mechanisms underlying the increased cardiovascular risk in diabetes.
- Study III evaluated the impact of combined imaging findings on LLM adherence and its association with long-term outcomes.

Studies I–III utilized data from the Turku Cardiac CTA Registry, a retrospective database including all consecutive patients undergoing clinically indicated cardiac CTA at the Turku PET Centre since 2006. From this registry, we identified 2212 consecutive symptomatic patients (low to intermediate clinical likelihood) imaged between 2007 and 2016 due to suspected CAD. Patients with prior known obstructive CAD, prior myocardial infarction, or previous revascularization were excluded. Following the coronary CTA imaging, findings were evaluated by an attending physician, and in case of suspected obstructive stenosis on coronary CTA ($\geq$ 50% in diameter), myocardial ischemia was routinely evaluated by 15O-water PET MPI during adenosine vasodilation (stress-only protocol) if there were no contraindications. In addition, Study II further included data from a registry at Amsterdam University Medical Center.

Clinical data on diabetes status, traditional CAD risk factors, symptoms, echocardiography, exercise ECG (within six months of imaging), and medication use were retrospectively collected from electronic medical records. Medication purchases were obtained from the Finnish Social Insurance Institution (Kela) for

Studies I and III. Prediabetes was defined as impaired fasting glucose (fasting plasma glucose 6.1–6.9 mmol/l), impaired glucose tolerance (2-h plasma glucose 7.8–11.0 mmol/l in a 75 g oral glucose tolerance test), or hemoglobin A1c 6.0–6.4%/42–47 mmol/mol within six months prior to imaging. Type 2 diabetes was defined as prior diagnosis based on medical records, the use of glucose-lowering therapy (excluding off-label use), plasma fasting glucose ≥ 7.0 mmol/l, 2-hour plasma glucose ≥ 11.1 mmol/l, or hemoglobin A1c ≥ 6.5%/ 48 mmol/mol.

Follow-up data through May 2020 included all-cause mortality, myocardial infarction (MI), and unstable angina pectoris (UAP), retrieved from the Auria Clinical Informatics registry and confirmed manually. In cases of multiple events in a single patient, the first event was considered. Early invasive coronary angiography and revascularizations (PCI or CABG) within six months were also recorded.

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland, which waived individual informed consent due to observational study design. Data collection permissions were obtained from Turku University Hospital, the Finnish Institute for Health and Welfare, the Finnish Social Insurance Institution, and Statistics Finland.

In Study I, patients with type 1 diabetes (n=22), other types of diabetes (n=9), or unknown diabetes status (n=245) were excluded, as were those without PET MPI despite suspected obstructive CAD (n=62), with non-diagnostic imaging (n=128), or with missing follow-up data (n=3). The final cohort included 1743 patients. In Study III, exclusions included non-diagnostic imaging (n=142), an incomplete diagnostic protocol (n=95), and missing follow-up (n=3). The final cohort included 1973 patients.

Study II combined data from the Turku cardiac CTA registry and a registry at Amsterdam University Medical Center. In Study II, only patients who underwent both coronary CTA and PET MPI were included, resulting in a total of 1311 patients with known diabetes status, complete PET-CT data, and follow-up, imaged between 2007 and 2016 (Turku n=762; Amsterdam n=549). PET MPI was performed selectively in Turku (for suspected ≥50% stenosis) and routinely in Amsterdam. Patients with prior CAD, MI, PCI, CABG, lost to follow-up, or with non-retrievable images or unknown diabetes status were excluded. In Study II diabetes was defined as a prior diagnosis of any type of diabetes mellitus (type 1, type 2, or other) based on electronic medical records, the use of glucose-lowering therapy, plasma fasting glucose ≥ 7.0 mmol/l, 2-hour plasma glucose ≥ 11.1 mmol/l, or hemoglobin A1c ≥ 6.5%/ 48 mmol/mol.

4.2 Image acquisition and analysis

Coronary CTA and PET MPI were performed using 64- or 256-row hybrid PET–CT scanners (in Turku: GE Discovery VCT or D690, GE Healthcare, Waukesha, WI; in Amsterdam: Gemini TF 64 or Brilliance iCT, Philips Healthcare, Best, the Netherlands) and analyzed according to SCCT segmentation guidelines (195). Sublingual/oral nitrate was administered before CTA, and intravenous metoprolol (≤30 mg) was used as needed to achieve a heart rate <60 beats/min. CTA was performed with intravenous low-osmolar iodinated contrast, using prospective ECG triggering when feasible. Obstructive CAD was defined as ≥50% diameter stenosis on coronary CTA.

Dynamic [^{15}O]H_2O PET myocardial perfusion imaging was conducted during adenosine stress (140 µg/kg/min). PET data were analyzed using CardiacVUer (Amsterdam UMC, the Netherlands) or Carimas (Turku PET Centre, Finland) software to quantify absolute stress myocardial blood flow (MBF, mL/g/min) across 17 myocardial segments. Abnormal perfusion was defined as ≥2 adjacent segments with stress MBF < 2.3 mL/g/min, indicating ischemia (196). Global stress MBF was reported for the entire left ventricle, and regional stress MBF as the lowest average of two adjacent segments.

Additionally, in Study II, coronary CTA images were analyzed using an FDA-cleared AI-based quantitative CT (AI-QCT) software (Cleerly Labs, Cleerly Inc., Denver, CO), which applies convolutional neural networks for automated plaque characterization validated against expert readers and invasive coronary angiography (109,197). Obstructive CAD was defined as ≥50% diameter stenosis by AI-QCT analysis. Total plaque volume was normalized to vessel volume and expressed as percent atheroma volume (PAV), with non-calcified (NCPV) and calcified (CPV) components reported separately.

4.3 Statistical analysis

4.3.1 Study I

Continuous variables are presented as mean ± SD or median (IQR), and categorical variables as counts and percentages. Group comparisons (patients without diabetes, patients with prediabetes and patients with diabetes) were performed using one-way ANOVA (Tukey post hoc) or Kruskal–Wallis (Bonferroni post hoc) tests for continuous variables and the chi-square test for categorical variables. Survival was assessed using Kaplan–Meier curves and Mantel–Cox log-rank test. Cox proportional hazards models were used to identify predictors of the composite endpoint (mortality, MI, or UAP); significant univariable predictors ($p < 0.05$) were

entered into multivariable models. Annual event rates were calculated and compared using Poisson regression. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed with IBM SPSS Statistics version 27.

4.3.2 Study II

Continuous variables are presented as median (IQR), and categorical variables as counts and percentages. Group comparisons were performed using ANOVA or Kruskal–Wallis tests (with Bonferroni correction) for continuous variables and the chi-square test for categorical variables. Two-way ANOVA was used to assess the main and interaction effects of diabetes and perfusion status. Survival was analyzed using Kaplan–Meier estimates and log-rank tests. Cox proportional hazards models were used to identify predictors of the composite endpoint, with follow-up truncated at 7.0 years. Multivariable models were constructed parsimoniously, including one CTA-based variable (PAV) and one PET-based variable (regional stress MBF) at a time to avoid multicollinearity. The proportional hazards assumption was assessed using time-dependent covariates. A landmark analysis (0.5–7 years) was performed to exclude early events (<6 months). Annual event rates were compared using Poisson regression (with Bonferroni correction). All tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 29.

4.3.3 Study III

Continuous variables are presented as mean ± SD or median (IQR), and categorical variables as counts and percentages. Group comparisons were performed using ANOVA (Tukey post hoc), Kruskal–Wallis tests (Bonferroni-corrected post hoc), and chi-square tests. LLM purchase rates at different time points were compared within each imaging group using McNemar's test. Predictors of LLM purchase within 6 months were assessed using multivariable logistic regression, including age, sex, cardiovascular risk factors, symptoms, baseline LLM use, and CAD phenotype. Predicted probabilities (propensity scores) were log-transformed and included in Cox proportional hazards models to evaluate predictors of the composite endpoint (mortality, MI, or UAP). Significant univariable predictors ($p < 0.05$) were entered into multivariable models. Annual event rates were calculated as percentages based on event counts and person-time at risk. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 27.

5 Results

5.1 The impact of diabetes on the relationship of coronary artery disease and outcome: a study using multimodality imaging (Study I)

5.1.1 Patient characteristics in Study I

Among 1743 patients who underwent selective PET MPI after coronary CTA for suspected CAD, 1214 (69.7%) had no diabetes, 259 (14.9%) had prediabetes, and 270 (15.5%) had type 2 diabetes. Obstructive CAD was excluded by coronary CTA alone in 1161 patients (66.6%), whereas 582 patients (33.4%) underwent PET MPI; of these, 281 (48.3%) had normal perfusion and 301 (51.7%) had abnormal perfusion. Normal coronary arteries were most frequently observed in patients without diabetes (39.0%). The prevalence of abnormal perfusion increased stepwise from 14.5% in patients without diabetes to 20.5% in those with prediabetes and 26.7% in those with diabetes. CACS (available in 82.5% of patients) correlated with diabetes status: a zero-calcium score was observed in 40.8% of patients without diabetes, 28.8% of patients with prediabetes, and 19.5% of patients with diabetes, whereas CACS >400 was observed in 12.2%, 17.5%, and 32.9%, respectively.

5.1.2 Outcomes according to diabetes status and perfusion status after selective PET-CTA hybrid imaging

During a median follow-up of 6.43 years (IQR 4.63–8.62), 164 adverse events were recorded. In 1214 patients without diabetes there were 104 adverse events, in 259 patients with prediabetes there were 19 adverse events and in 270 patients with type 2 diabetes there were 41 adverse events. In 597 patients with normal coronary CTA there were 8 adverse events, in 564 patients with non-obstructive CAD there were 51 adverse events, in 281 patients with suspected obstructive CAD but normal perfusion there were 36 adverse events and in 301 patients with suspected obstructive CAD and abnormal perfusion there were 60 adverse events.

The annual composite event rate (death/MI/UAP) was 1.33% overall, 1.23% in patients without diabetes, 1.02% in patients with prediabetes, and 2.16% in patients

with diabetes. Event rates were higher in patients with diabetes than in those without diabetes (p = 0.003), whereas patients with prediabetes did not differ from those without diabetes (p = 0.450). When stratified by myocardial ischemia status and diabetes, patients without diabetes and normal coronary CTA had the lowest annual event rate (0.22%), whereas patients with diabetes and suspected obstructive CAD and abnormal perfusion had the highest rate (4.72%). This group had a significantly higher annual event rate compared with patients without diabetes (2.57%, p < 0.001) (Figure 2).

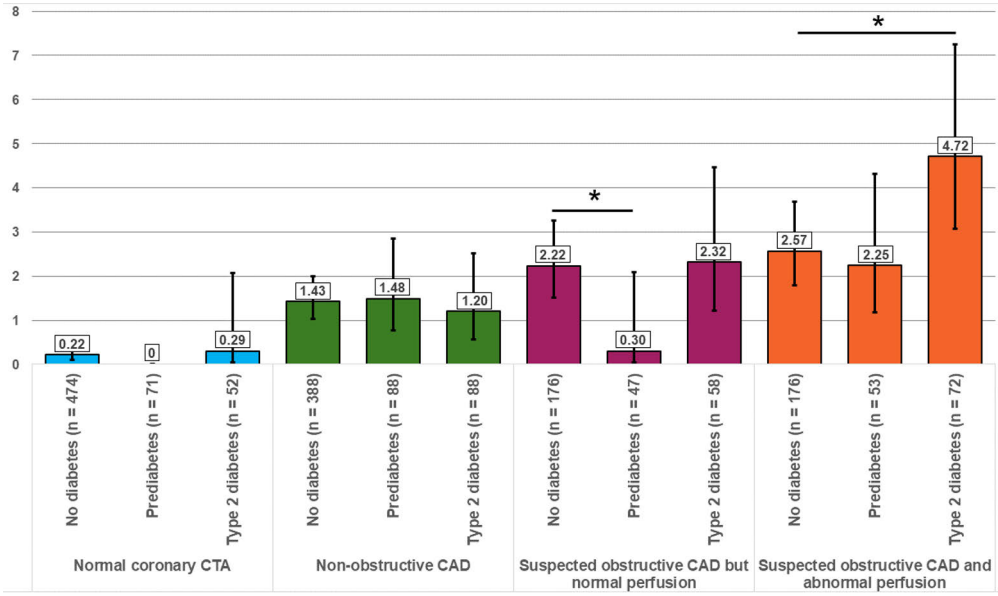

Figure 2. Annual event rates stratified by diabetes and myocardial ischemia status. CTA computed tomography angiography, CAD coronary artery disease. *Indicates statistical significance p < 0.05. (Originally published in Mäenpää et al. The impact of diabetes on the relationship of coronary artery disease and outcome: a study using multimodality imaging. Cardiovasc Diabetol. 2023 May 31;22(1):129. Reprinted by permission from Springer Nature.)

5.1.3 Predictors of adverse events after selective PET-CTA hybrid imaging

Univariable predictors included age, male sex, type 2 diabetes, hypertension, typical angina, CACS, and PET–CTA findings. In multivariable models, age, hypertension, and imaging findings remained independent predictors, whereas prediabetes and diabetes did not. Similarly, when CACS was included instead of imaging findings, only age and CACS remained significant. No significant interactions were observed between diabetes status and PET–CTA findings (p = 0.319) or calcium score (p = 0.937).

5.2 Prognostic implications of quantified coronary atherosclerosis and myocardial perfusion in diabetes (Study II)

5.2.1 Patient characteristics in Study II

Among 1311 patients who underwent both PET MPI and coronary CTA for suspected CAD, 584 (44.5%) had abnormal myocardial perfusion and 251 (19.1%) had diabetes. Specifically, 605 patients (46.1%) had normal perfusion without diabetes, 122 (9.3%) had normal perfusion with diabetes, 455 (34.7%) had abnormal perfusion without diabetes, and 129 (9.8%) had abnormal perfusion with diabetes.

Patients with diabetes had a greater atherosclerotic burden, expressed as percent atheroma volume (PAV, 11.8% vs. 7.1%, $p < 0.001$), more severe stenosis diameter (52% vs. 38%, $p < 0.001$), and a higher prevalence of obstructive CAD (55.0% vs. 42.6%, $p < 0.001$) and abnormal perfusion (51.4% vs. 42.9%, $p = 0.015$) compared with patients without diabetes. Among patients with normal perfusion, those with diabetes had approximately twice the PAV of those without diabetes (8.2% vs. 4.1%, $p < 0.001$) and more severe stenosis diameter (36% vs. 26%, $p = 0.017$), whereas regional and global stress MBF were comparable.

Patients with abnormal perfusion had a higher plaque burden (PAV 13.8% vs. 4.6%, $p < 0.001$), greater stenosis diameter (62% vs. 27%, $p < 0.001$), a higher prevalence of obstructive CAD (68.1% vs. 26.4%, $p < 0.001$), and lower global and regional stress MBF than those with normal perfusion. Within this group, plaque burden, stenosis diameter, regional stress MBF, and global stress MBF were similar between patients with and without diabetes.

Notably, patients without diabetes but with abnormal perfusion had higher PAV (13.1% vs. 8.2%, $p < 0.001$) and greater stenosis diameter (61% vs. 36%, $p < 0.001$) compared with patients with diabetes and normal perfusion, while calcified plaque volume was similar.

5.2.2 Outcomes according to quantified severity of coronary artery disease and diabetes

During a median follow-up of 7.0 years, 134 adverse events occurred. Among 605 patients without diabetes and with normal perfusion, 29 adverse events were observed, whereas 16 events occurred among 122 patients with diabetes and normal perfusion. In patients with abnormal perfusion, 66 events occurred among 455 patients without diabetes and 23 among 129 patients with diabetes.

The annual composite event rate (death/MI/UAP) was higher in patients with diabetes than in those without diabetes (2.8% vs. 1.5%, $p = 0.002$) and in patients

with abnormal versus normal perfusion (2.8% vs. 1.0%, $p < 0.001$). The most favorable outcome was observed in patients with normal perfusion and no diabetes (0.8% annual event rate), whereas patients with diabetes (2.3%), abnormal perfusion (2.6%), or both (3.2%) had significantly higher event rates (Figure 3).

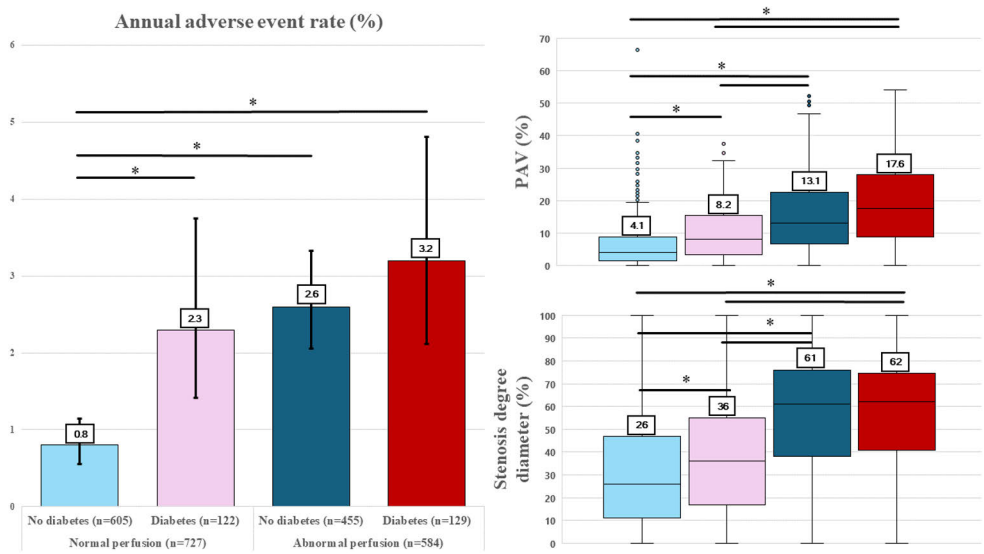

Figure 3. Bar chart (left) showing annual composite adverse event % rates (with 95% CI) stratified by myocardial perfusion and diabetes. Box plots (right) showing quantitative percent atheroma volume (PAV) and coronary diameter stenosis degree (median, IQR, and outliers similarly stratified by myocardial perfusion and diabetes. *Indicates statistical significance $p < 0.05$. (Originally published in Mäenpää et al. Prognostic implications of quantified coronary atherosclerosis and myocardial perfusion in diabetes. Reprinted by permission from Springer Nature.)

5.2.3 Predictors of adverse events stratified by diabetes status and perfusion status

In the overall cohort, univariable Cox analysis showed that increasing age, male sex, diabetes, quantitative coronary CTA and PET parameters, and early revascularization were associated with adverse outcomes. In multivariable models, higher PAV, lower regional stress MBF, and older age independently predicted adverse outcomes, whereas diabetes, sex, global stress MBF, and early revascularization did not. A significant interaction between diabetes and perfusion status was observed ($p = 0.030$).

In subgroup analyses stratified by diabetes status and perfusion status, PAV, regional stress MBF, and age independently predicted events in patients without diabetes, whereas only PAV remained significant in patients with diabetes. In patients with normal perfusion, age, diabetes, and PAV were independent predictors, while in those with abnormal perfusion, only PAV remained significant (Table 1).

Table 1. Stratified multivariable models.

Stratified multivariable models

	No diabetes		Diabetes	
Model	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (1-year increase)	1.05 (1.02–1.07)	<0.001	1.04 (1.00–1.08)	0.075
Male sex	1.13 (0.72–1.78)	0.602	1.87 (0.88–3.99)	0.104
PAV (1% increase)	1.03 (1.01–1.05)	<0.001	1.04 (1.01–1.07)	0.014
Regional sMBF (0.1 ml/g/min decrease)	1.04 (1.01–1.07)	0.016	1.01 (0.97–1.06)	0.610
Early revascularization	1.03 (0.61–1.75)	0.908	0.47 (0.20–1.11)	0.086
	Normal perfusion		**Abnormal perfusion**	
Model	HR (95% CI)	p–value	HR (95% CI)	p–value
Age (1-year increase)	1.09 (1.05–1.13)	<0.001	1.03 (1.00–1.05)	0.053
Male sex	1.61 (0.87–2.96)	0.129	1.14 (0.70–1.83)	0.604
Diabetes	2.39 (1.29–4.44)	0.006	1.09 (0.67–1.76)	0.729
PAV (1% increase)	1.06 (1.03–1.08)	<0.001	1.02 (1.00–1.04)	0.021
Early revascularization	0.57 (0.13–2.40)	0.440	0.94 (0.61–1.46)	0.784

PAV percent atheroma volume, sMBF stress myocardial blood flow

5.3 Prognostic implications of lipid-lowering therapy after anatomical and functional coronary imaging (Study III)

5.3.1 Patient characteristics in Study III

Among 1973 patients who underwent selective PET–CTA hybrid imaging for suspected CAD, dyslipidemia and diabetes were present in 62.5% and 14.8% of patients, respectively. Overall, 676 patients (34.3%) had normal coronary CTA, 640 (32.4%) had non-obstructive CAD, 325 (16.5%) had suspected obstructive CAD but normal perfusion, and 332 (16.8%) had suspected obstructive CAD with abnormal perfusion. At baseline, 27% of patients were using LLM, with prevalence increasing progressively from normal coronary CTA to suspected obstructive CAD with abnormal perfusion ($p < 0.001$). Among patients with non-obstructive CAD, 538 (84.1%) had non-extensive disease (SIS ≤4) and 102 (15.9%) had extensive disease (SIS >4). CACS (available in 1615 patients, 81.9%) correlated with CAD severity: a zero-calcium score was observed in 590 patients (36.5%), a score of 1–99 in 471 (29.2%), 100–399 in 306 (18.9%), and ≥400 in 248 (15.4%).

5.3.2 Adherence to lipid-lowering medication after coronary CTA and PET imaging

During follow-up, 9081 LLM purchases were recorded (97.2% statins and 2.8% ezetimibe). After imaging, LLM use increased across all CAD phenotypes ($p < 0.001$), ranging from 24% in patients without CAD to 91% in those with myocardial ischemia. Post-imaging LLM use was 51% in non-obstructive CAD and 72% in obstructive CAD without ischemia. Among patients with non-obstructive CAD, extensive disease (SIS >4) was associated with higher LLM use than non-extensive disease (SIS ≤4) (68% vs. 48%, $p < 0.001$).

In multivariable logistic regression, CAD severity, age, dyslipidemia, family history of CAD, and prior LLM use independently predicted post-imaging LLM purchase. During the two-year follow-up, overall LLM use declined ($p < 0.001$). At 18–24 months, 77% of patients with ischemia and 58% of those with obstructive CAD without ischemia remained on LLM (Figure 4).

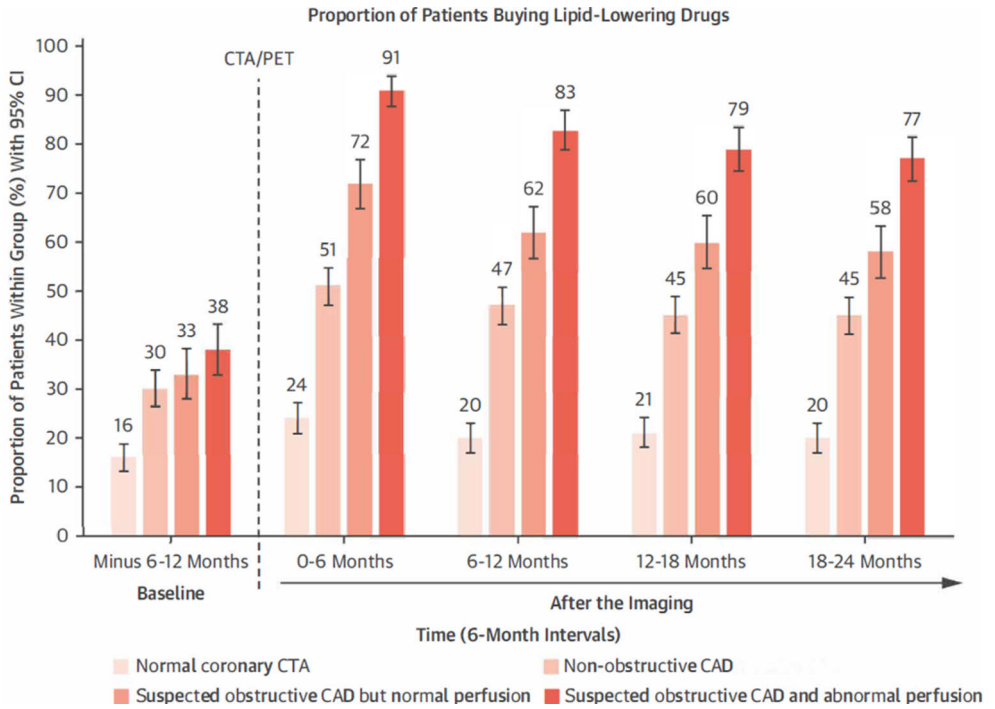

Figure 4. Proportion of patients purchasing LLM according to CAD severity by imaging. Error bars represent 95% CIs. CTA computed tomography angiography, PET positron emission tomography, CAD coronary artery disease. (Originally published in Maaniitty et al. Lipid-Lowering Medication and Outcomes After Anatomical and Functional Imaging in Suspected Coronary Artery Disease. JACC Cardiovasc Imaging. 2025 Jan;18(1):62-73s. Reprinted by permission from Elsevier.)

5.3.3 Outcomes and lipid-lowering medication after coronary CTA and PET imaging

During a median follow-up of 6.7 years (IQR 4.8–8.8), 197 adverse events occurred. Annual composite event rates (death/MI/UAP) increased with CAD severity: 0.3% in patients with normal coronary CTA, 1.4% in non-obstructive CAD, 1.8% in suspected obstructive CAD but normal perfusion, and 3.1% in suspected obstructive CAD with abnormal perfusion ($p < 0.001$). As shown in Figure 5, LLM use was associated with lower rates of death and adverse cardiac events among patients with ischemic CAD or obstructive CAD without ischemia (adjusted $p = 0.032$ and 0.004, respectively), but not among those with normal coronary CTA or non-obstructive CAD. In patients with extensive non-obstructive CAD (SIS >4), outcomes were similar regardless of LLM use.

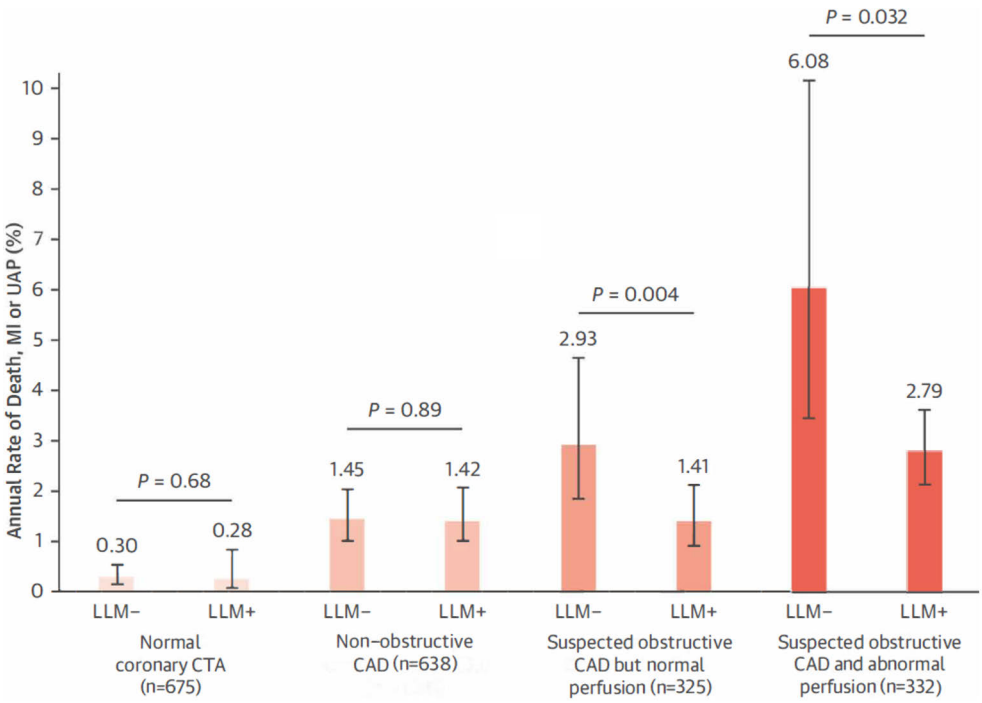

Figure 5. Annual adverse event rates in patients purchasing lipid-lowering medication (LLM+) vs not purchasing (LLM−) during the 6-month period after diagnostic imaging, categorized by CAD severity. P-values were adjusted for univariable predictors of events, including age, sex, diabetes, hypertension, and symptoms. Error bars represent 95% CIs. MI myocardial infarction, UAP unstable angina pectoris, LLM lipid-lowering medication, CTA computed tomography angiography, CAD coronary artery disease. (Originally published in Maaniitty et al. Lipid-Lowering Medication and Outcomes After Anatomical and Functional Imaging in Suspected Coronary Artery Disease. JACC Cardiovasc Imaging. 2025 Jan;18(1):62-73s. Reprinted by permission from Elsevier.)

In multivariable Cox regression, post-imaging LLM purchase independently predicted improved long-term outcomes (HR 0.64, 95% CI 0.46–0.89, p = 0.008) and remained significant after propensity score adjustment (HR 0.63, 95% CI 0.44–0.91, p = 0.014). Baseline LLM use was not associated with outcomes after adjustment.

6 Discussion

In this thesis, we investigated the diagnostic, prognostic, and therapeutic implications of combined anatomical and functional imaging in patients with suspected CAD, with particular attention to diabetes, dyslipidemia, and the use of LLM. Across three studies, we found that combined anatomical and functional coronary imaging provides robust risk stratification in patients with and without diabetes. Moreover, the presence and severity of CAD on imaging were strongly associated with the subsequent use of LLM, which in turn was associated with improved outcomes.

In Study I, a selective imaging approach with initial coronary CTA and downstream PET MPI identified patients at increased long-term risk of death, myocardial infarction, or unstable angina similarly in those with and without diabetes or prediabetes, as previously shown in the general population (198). The prevalence of obstructive CAD and myocardial ischemia was nearly two-fold higher among patients with diabetes compared with patients without diabetes, and event rates were correspondingly higher. However, CTA and PET findings allowed risk stratification in all patient groups: patients without diabetes, patients with prediabetes, and patients with diabetes. Diabetes was not an independent predictor of events in multivariable models, whereas imaging-based parameters remained significant. The combination of obstructive stenosis on coronary CTA and abnormal perfusion on PET identified the subgroup of patients with diabetes with the highest annual event rate (up to 4.7%). In contrast, approximately half of the patients with diabetes had no obstructive disease and experienced favourable outcomes. These results are in line with previous evidence showing poor outcomes in patients with diabetes with CAD (173) and favourable outcomes in patients with diabetes without CAD (199,200).

Interestingly, in Study I, patients with prediabetes had outcomes similar to those of patients without diabetes. Unexpectedly low event rates were observed in patients with prediabetes who had obstructive CAD but normal perfusion, possibly due to the small subgroup size and the low overall event rate. A higher use of statins was also observed in patients with prediabetes, which may reflect more proactive management in this subgroup and could have contributed to a better prognosis. This

pattern was also seen in Study III, where more severe CAD led to more aggressive CAD management. Overall, because patients with diabetes had the worst prognosis, these findings underscore the potential of early preventive interventions to delay diabetes progression and related cardiovascular complications.

Study I addressed selective coronary CTA and PET according to diabetes status but did not focus on the extent of atherosclerosis. With growing evidence that coronary atherosclerotic plaque burden adds complementary prognostic value to anatomical and functional imaging, this represents an important limitation of Study I (201). Moreover, the substantially higher adverse event rates in patients with diabetes and abnormal perfusion raised the question of the underlying mechanisms. For this reason, Study II expanded on the findings of Study I and aimed to integrate the prognostic value of quantified anatomical and functional measures.

In Study II, coronary plaque burden was quantified as PAV (202) and sMBF was measured from PET MPI, providing quantitative assessments of the anatomical and functional severity of CAD. Among patients with normal myocardial perfusion, those with diabetes exhibited approximately a two-fold higher plaque burden than those without diabetes and had an almost three-fold higher adverse event rate. This likely explains their higher long-term risk despite preserved perfusion. Among patients with abnormal perfusion, risk was comparably elevated irrespective of diabetes status. Plaque burden remained an independent predictor of adverse outcomes across all subgroups, whereas perfusion abnormalities had predictive value only in patients without diabetes. These findings refine those of the first study and previous evidence by suggesting that diabetes confers increased long-term risk predominantly through more extensive atherosclerosis rather than through functional ischemia alone (174,175). Quantitative CTA therefore provides valuable prognostic information even when myocardial perfusion is normal.

Previously, Murthy et al. reported a favourable prognosis in patients with diabetes and preserved MFR by 82Rb PET, in contrast to our results (209). Furthermore, Caobelli et al. reported low event rates in asymptomatic patients with diabetes and preserved MBF by SPECT (210). However, our study included only symptomatic patients and differed in that PET was performed mostly (in 66.7%) selectively after visually suspected obstructive stenosis on coronary CTA. This likely resulted in more severe atherosclerosis and higher absolute event rates. In line with our results, Assante et al. reported high event rates in the presence of diabetes or reduced MFR by 82Rb PET MPI (204). Similarly, in a recent hybrid imaging study using coronary CTA and SPECT MPI, atherosclerotic plaque burden, rather than perfusion abnormality, independently predicted outcomes in patients with diabetes (201)

The relationship between diabetes and CAD on coronary CTA has been well established in prior registry studies such as CONFIRM and SCOT-HEART, which

showed that patients with diabetes have higher plaque burden, calcium scores, and mortality compared with patients without diabetes (174,175). A later quantitative analysis from the SCOT-HEART trial showed that patients with diabetes had higher CACS, greater total plaque volume, and different plaque characteristics. However, no difference in the prevalence of obstructive CAD or visually assessed adverse plaque characteristics was observed (176). Similarly, the CREDENCE substudy, using the same AI-QCT software as ours, demonstrated higher quantitative plaque volumes in patients with diabetes than in patients without diabetes with non-obstructive CAD. Importantly, total plaque volume and plaque components were comparable between patients without diabetes with obstructive stenosis and patients with diabetes with non-obstructive stenosis (197). Study II builds on these findings by demonstrating that plaque burden predicts long-term outcomes both in patients with and without diabetes, and across normal and abnormal perfusion subgroups. This supports the biological concept that total atherosclerotic burden represents a substrate for future adverse events.

Interestingly, in Study I, patients without diabetes with suspected obstructive CAD but normal perfusion had outcomes comparable to those of patients with diabetes. In Study II, however, patients without diabetes with normal perfusion had a significantly better prognosis than patients with diabetes. This discrepancy may be explained by differences in imaging protocols. The Amsterdam registry included all patients undergoing PET MPI irrespective of coronary CTA findings, whereas Turku used a selective imaging strategy. As a result, the Amsterdam cohort included patients with less extensive atherosclerosis and more non-obstructive disease, while the selective approach in Turku introduced a selection bias toward individuals with a higher atherosclerotic burden. Furthermore, patients with diabetes and abnormal perfusion in Study I had markedly worse outcomes than patients without diabetes, whereas in Study II the prognoses were similar. These differences are also likely attributable to the contrasting imaging protocols between centres. Finally, when comparing the Turku and Amsterdam cohorts in Study II, it should be noted that patients with prediabetes were classified as patients without diabetes in the Turku cohort, whereas prediabetes status was not available in the Amsterdam data. This difference in classification may also contribute to the observed variation between study populations.

Study II demonstrated the importance of plaque burden and anatomical CAD severity as prognostic markers in patients both with and without diabetes. LLMs have a substantial impact on this aspect of CAD and can significantly reduce the progression of atherosclerotic plaque burden (205,206). Building on this, Study III focused on the implementation and outcomes of LLM after combined anatomical and functional imaging in a real-world patient cohort.

Study III investigated the implementation of LLM and its association with outcomes across different CAD phenotypes based on combined anatomical and functional imaging in real-world patients with suspected CAD. The presence and severity of CAD were independently associated with LLM use within six months after coronary CTA and PET imaging. Although compliance declined during two years of follow-up, LLM use was associated with long-term outcome benefits both in the presence of myocardial ischemia and in anatomically obstructive CAD.

In Study III, patients with abnormal perfusion had the highest rate of adverse events (3.1%), similar to Study I. In this subgroup, LLM was implemented effectively (91% using medication after imaging), with a subsequent 54% reduction in adverse event rates. Similarly, in patients with suspected obstructive CAD but normal perfusion, LLM use was associated with a 52% risk reduction, comparable to that observed in ischemic CAD. This result aligns with similar observations of LLM adherence from SCOT-HEART, where 86% of patients with obstructive CAD used statins one year after imaging (116). In contrast, the use of LLM in Study III was lower in patients with obstructive CAD without ischemia (72%) and in those with non-obstructive CAD (51%), consistent with previous studies (207–210). Outcomes did not differ significantly between LLM users and non-users in the absence of obstructive CAD, likely reflecting a low overall plaque burden and low event rates. Previous studies also suggest that the beneficial effects of LLM appear mainly in more extensive CAD (207,208,211). A concerning finding in Study III was that the use of LLM decreased during follow-up across all imaging groups, including patients with myocardial ischemia, where LLM is most critical. This is consistent with earlier studies and adds to the evidence that identification of plaques or CAD on coronary CTA significantly increases adherence to LLM (212,213).

Together with the findings from Studies I and II, this raises the question of whether the identification of ischemia, when considered alongside diabetes status and plaque burden, warrants more aggressive preventive therapies. Nonetheless, the results of Study III expand on the findings of the first two studies by linking imaging-based CAD severity directly to secondary prevention benefits. Both obstructive and ischemic CAD identify patients who derive the greatest prognostic benefit from LLM. Diabetes amplifies plaque burden and thereby increases long-term risk but does not alter the relative prognostic value of imaging findings or the benefit of secondary prevention. The consistent association between plaque burden and outcomes in patients both with and without diabetes highlights the central role of plaque burden as the substrate of risk, while the observed benefits of LLM confirm that modifying this substrate translates into improved prognosis.

These findings also have implications for clinical management. First, coronary CTA can serve as an effective first-line diagnostic test in patients both with and without diabetes, identifying those who may safely defer further testing. Second,

quantification of atherosclerotic plaque burden provides incremental prognostic value and may help identify high-risk patients even when perfusion appears normal. Third, combined anatomical and functional assessment can inform a more personalized use of preventive therapies such as LLM, thereby improving CAD management.

The present studies have several limitations inherent to their retrospective and registry-based design. While unique in their use of national registry data to capture medication purchases rather than patient-reported medication use or prescriptions, Study III did not examine the intensification of LLM among individuals already receiving LLM at baseline following imaging. Moreover, due to the time period of Study III, newer lipid-lowering agents such as PCSK9 inhibitors were unavailable. This provides an opportunity for future research to assess these agents, as well as other medications with proven cardiovascular benefits, including SGLT2 inhibitors and GLP-1 receptor agonists.

While Studies I and III utilized the national database of the Social Insurance Institution of Finland to identify medication purchases, this was not feasible in Study II due to its multicentre design. Consequently, adjustment for factors such as diabetic kidney disease, duration of diabetes, glycaemic control, lipid levels, and specific drug classes was not possible. Despite relatively large cohorts and long follow-up durations, the number of clinical events was relatively low in these cohorts with suspected chronic CAD, reducing statistical power in subgroup analyses.

The selective hybrid imaging protocol used at Turku University Hospital may have introduced selection bias due to the higher prevalence of atherosclerosis among patients referred to PET perfusion imaging. However, this would likely affect patients with and without diabetes similarly. In Study II, the inclusion of patients from Amsterdam University Medical Center probably enhances the generalizability of the findings. Most patients underwent a stress-only protocol, and therefore rest MBF, MFR, and specific microvascular indices were not available, representing a limitation across all three studies.

Finally, as the studies included only symptomatic patients, the results cannot be generalized to asymptomatic populations. Composite endpoints were used instead of individual outcomes to improve statistical power, and all-cause mortality was assessed rather than cardiovascular mortality due to limited data on causes of death. This approach helps reduce event verification bias. Importantly, event adjudication was performed manually but without formal blinding.

7 Summary/Conclusions

7.1 Study I

Coronary CTA followed by selective downstream use of PET MPI predicts outcomes in patients with suspected CAD similarly in the presence of type 2 diabetes. In approximately half of the patients with diabetes, obstructive CAD could be excluded by coronary CTA alone, which was associated with a favorable outcome. The prevalence of hemodynamically significant CAD was nearly two-fold higher in patients with type 2 diabetes than in those without diabetes. The combination of hemodynamically significant CAD and type 2 diabetes was associated with the highest adverse event rate during long-term follow-up; however, no significant interaction was observed between prediabetes or type 2 diabetes status and the prognostic value of CTA/PET imaging findings.

7.2 Study II

Diabetes is associated with anatomically and functionally more severe CAD. Myocardial perfusion stratifies risk in patients without diabetes, whereas patients with diabetes have impaired long-term outcomes irrespective of perfusion findings. Quantified coronary atherosclerotic burden, measured as percent atheroma volume (PAV), predicts long-term outcomes in both patients with and without diabetes.

7.3 Study III

Combined coronary CTA and PET MPI guide the use of LLM in patients with suspected CAD. Adherence to LLM declined during the two years of follow-up and warrants special attention. LLM use was associated with long-term outcome benefit in the presence of obstructive CAD or myocardial ischemia.

Acknowledgements

My deepest gratitude goes to my supervisors, Docent Teemu Maaniitty and Professor Antti Saraste, for their guidance and continuous support throughout my PhD journey. Their encouragement and scientific insight have been invaluable.

I am grateful to Docent Markku Eskola for serving as the opponent at the public defense of my doctoral thesis. I sincerely thank Adjunct Professor Henrik Engblom and Professor Mika Kähönen for their careful review of this thesis and their valuable comments.

I thank the information technology specialists and biostatisticians for their assistance with technical and statistical challenges. I also acknowledge the staff of the Turku PET Centre and the investigators of the cardiovascular research group for their collaboration and support. I am especially grateful to Professor Juhani Knuuti for his advice. I thank all co-authors of the publications included in this thesis for their contributions.

I gratefully acknowledge financial support from the Finnish Cardiac Society, the Finnish Foundation for Cardiovascular Research, the Turku University Foundation, the Orion Research Foundation, the Finnish Medical Foundation, and the Paulo Foundation.

Finally, my warmest thanks go to Vilma Turunen for her love and unwavering support. Your presence has been my greatest source of strength and balance.

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TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2026

ISBN 978-952-02-0570-6 (PRINT)
ISBN 978-952-02-0571-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)