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ASSESSMENT OF ARTERIAL STIFFNESS IN POPULATIONS AT INCREASED CARDIOVASCULAR RISK

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Stockholm 2025

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2025

ISBN 978-91-8017-900-3
DOI https://doi.org/10.69622/30196714
Cover illustration: Oskar Hellqvist

Assessment of arterial stiffness in populations at increased cardiovascular risk

Thesis for Doctoral Degree (Ph.D.)

By

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The thesis will be defended in public in the main auditorium at Danderyd University Hospital, Stockholm, December 12, 2025, 9:00 AM.

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To my dear family – Maria, Greta, Albert, and Julia

“A man is as old as his arteries”

Thomas Sydenham (1624–1689)

Popular science summary of the thesis

With ageing and exposure to cardiovascular risk factors, the aorta and other large arteries become stiffer. Arterial stiffening has several negative consequences and is linked to the development of cardiovascular disease. Arterial stiffness is usually measured by the speed at which the pulse wave travels in the arteries: the pulse wave velocity. In stiff arteries, the pulse wave travels faster and the pulse wave velocity increases. The measurement of arterial stiffness has historically been performed with cumbersome, specialised equipment, which has prevented implementation of its assessment in the day-to-day clinical work, and studies of its potential as a clinical tool.

Photoplethysmography (PPG), a technology that measures light changes in the skin, enables analysis of the pulse wave form. This may be used for simplified arterial stiffness assessment. What makes PPG especially interesting is that the PPG signal is already available in many medical devices for measuring heart rate or oxygen saturation, as well as in wearable consumer devices such as smart rings and smart watches. Modern machine learning methods may be applied to study patterns in the PPG signals and other clinical characteristics, which may assist in identifying individuals having an increased cardiovascular risk, diagnosis or condition.

This thesis aimed at investigating novel and simplified arterial stiffness assessment methods and adopt machine learning for improved identification of individuals with specific cardiovascular high-risk conditions.

In Study I, we investigated 79 individuals with suspected or confirmed hypertension who underwent ambulatory blood pressure monitoring (ABPM) with simultaneous overnight PPG from the index finger. We found that a new characteristic obtained from the PPG signal, the overnight stiffness index (OSI), was correlated with established cardiovascular risk scores, markers of arterial stiffness, and blood pressure levels. OSI performed generally better compared to another previously studied overnight arterial stiffness characteristic from the PPG signal.

In Study II, in 33 generally healthy persons, we evaluated the possibility to use short daytime recordings of finger PPG to measure arterial stiffness in an improved way. We found that we could estimate arterial stiffness with good

precision by using new PPG waveform characteristics and by applying machine learning methods.

In Study III, we evaluated arterial stiffness and finger PPG measurements in 141 patients investigated with coronary computed tomography angiography for suspected symptomatic coronary artery disease. The study showed that arterial stiffness, assessed either with an arm blood pressure cuff or with the finger PPG signal, could not identify patients with moderate stenosis (narrowing) in any of the coronary arteries. However, by applying machine learning to the finger PPG signal alone, we found that these patients could be identified as effectively as with the currently recommended clinical scoring system, which requires collecting cardiovascular risk factors and evaluation of symptoms.

In Study IV, we investigated poorly controlled hypertension by ABPM in 99 patients who recently had been treated for a myocardial infarction (MI). Specifically, we studied a type of high blood pressure called masked uncontrolled hypertension (MUCH). People with MUCH take blood pressure-lowering medication, but while their blood pressure values are normal in the clinic, their blood pressure is elevated when measured at home. As a result, this condition goes undetected without home blood pressure measurements, making it difficult to identify and manage. We found that one in five patients had MUCH after myocardial infarction. A machine learning-based evaluation of 62 clinical registry variables, revealed that the diagnoses diabetes and hypertension, and impaired kidney function were the main characteristics for identifying patients with MUCH. When included in prediction models, these characteristics were good at identifying MUCH.

In conclusion, we found new and improved ways to assess arterial stiffness using the easy-to-use finger PPG method. Furthermore, we could identify high risk-individuals with coronary artery stenosis or MUCH after MI by using machine learning of PPG signals and clinical characteristics. The simplified and quick assessment of arterial stiffness and cardiovascular risk using PPG holds great potential for risk stratification in both healthcare and the general population.

Abstract

Introduction

Arterial stiffness is an established marker of cardiovascular risk. However, its full potential for clinical applications remains unconfirmed due to the lack of accessible assessment methods. Photoplethysmography (PPG), which measures instantaneous blood volume changes in the skin, may be used for evaluation of arterial stiffness. PPG is common in medical pulse-oximeters to measure oxygen saturation levels and pulse rate, and has also recently been incorporated into consumer wearable devices such as smart watches and smart rings. Furthermore, machine learning may be applied on PPG signals and clinical data, to improve assessment of arterial stiffness and to facilitate identification of individuals having an increased cardiovascular risk, diagnose or condition.

This thesis aimed to investigate assessment of arterial stiffness in populations at increased cardiovascular risk, using novel and simplified methods to enhance cardiovascular risk stratification. Specifically, we aimed at (1) evaluating an improved overnight PPG-based measure for assessing cardiovascular risk, (2) improving simple PPG- and ECG-based methods for assessing arterial stiffness, (3) evaluating whether arterial stiffness or machine learning-based PPG analysis could improve risk stratification in patients with suspected obstructive coronary artery disease (CAD), (4) predicting the clinically challenging blood pressure phenotype masked uncontrolled hypertension (MUCH) post-myocardial infarction (MI) by applying machine learning methods.

Methods and results

In Study I, associations between the novel overnight finger PPG-based stiffness index (OSI) and markers of cardiovascular risk and ambulatory blood pressure (ABP) were investigated in a population with confirmed or suspected hypertension (n=79). OSI was positively correlated with cardiovascular risk scores (SCORE2/SCORE2-OP: $\rho = 0.40$, $P = 0.002$ and Framingham: $\rho = 0.41$, $P < 0.001$), and with office ($r = 0.34$, $P = 0.002$), awake ($r = 0.40$, $P < 0.001$), and asleep pulse pressure ($r = 0.47$, $P < 0.001$), and ambulatory arterial stiffness index ($r = 0.37$, $P < 0.001$). OSI correlated with systolic ABP (asleep $r = 0.55$, awake $r = 0.42$; both $P < 0.001$) and diastolic ABP (asleep $r = 0.36$, $P = 0.001$). Generally, OSI showed stronger correlations compared to a previously studied overnight PPG-based marker of arterial stiffness.

In Study II, finger PPG and finger blood pressure were collected in generally healthy participants (n=33). Carotid–femoral pulse wave velocity (cfPWV; SphygmoCor) and brachial single cuff-based aortic pulse wave velocity (aoPWV; Arteriograph) were reference methods. PPG waveform features were extracted and engineered, and machine learning was applied for prediction model development. PPG-based models predicted cfPWV (root mean square error [RMSE] 0.70, R^2 0.74) and aoPWV (RMSE 0.52, R^2 0.92) well, which was comparable to repeatability and agreement of the reference methods. The novel PPG amplitude ratio, "Am b/Am p1", emerged as a key feature in modelling, showing strong correlations with cfPWV and aoPWV (r = -0.81 and -0.75, respectively; both $P < 0.001$).

In Study III, patients investigated with coronary computed tomography angiography (CCTA) for suspected symptomatic new-onset chronic coronary syndrome (CCS) were assessed with aoPWV by Arteriograph and index finger PPG (n=141). Arterial stiffness measures were compared with clinical risk models in their discriminatory ability for obstructive CAD (CAD-RADS [CAD-reporting and data system] ≥3, indicating at least one moderate stenosis). aoPWV and PPG-derived cfPWV were not predictive of CAD-RADS ≥3. Machine learning identified three PPG features (waveform area "Ar OS", waveform area ratio "IPA" and time span "Tm N") that provided discriminatory ability for CAD-RADS ≥3 comparable to the risk factor-weighted clinical likelihood model (receiver operating characteristic area under the curve [AUC] 0.73 [95% confidence interval 0.61-0.85] vs 0.72 [0.62-0.82]), when implemented in a random forest model.

In Study IV, patients underwent ambulatory blood pressure monitoring (ABPM) following a recent hospitalisation for a MI (n=99). The blood pressure phenotype MUCH (office blood pressure <140/90 mm Hg at ABPM start but mean 24-h blood pressure ≥130/80 mm Hg, and on antihypertensive medication) was evaluated in machine learning applied to 62 clinical registry variables. Seventeen patients (18%) were found to have MUCH post-MI. The discharge diagnoses diabetes and hypertension, and kidney dysfunction were identified as key predictors of MUCH. The best machine learning model achieved a mean cross-validation AUC of 0.82 for predicting MUCH.

Conclusions

We developed and evaluated improved arterial stiffness assessment using the easy-to-use finger PPG method. Machine learning was successfully applied to PPG signals and clinical variables to enhance arterial stiffness estimation, and to identify obstructive CAD in patients with suspected new-onset CCS, and MUCH after MI. These findings confirm the potential value of using the widely accessible PPG method and machine learning for improved cardiovascular risk stratification.

List of scientific papers

This thesis is based on the following papers, which will be referenced by their corresponding Roman numerals:

I. Hellqvist H, Rietz H, Grote L, Hedner J, Sommermeyer D, Kahan T, Spaak J. Overnight stiffness index from finger photoplethysmography in relation to markers of cardiovascular risk and vascular ageing. Heart Vessels. 2025;40(10):895-904.

II. Hellqvist H, Karlsson M, Hoffman J, Kahan T, Spaak J. Estimation of aortic stiffness by finger photoplethysmography using enhanced pulse wave analysis and machine learning. Front Cardiovasc Med. 2024;11:1350726.

III. Hellqvist H, Karlsson M, Löfmark H, Kahan T, Spaak J. Assessment of arterial stiffness and machine learning analysis of finger photoplethysmography for prediction of obstructive coronary artery disease in patients with suspected chronic coronary syndrome. *Manuscript*.

IV. Hellqvist H, Erlinge D, Lindahl B, Jernberg T, Oldgren J, James S, Al-Khalili F, Kahan T, Spaak J. Prevalence and prediction of masked uncontrolled hypertension in patients recently hospitalized for myocardial infarction. Eur Heart J Open. 2025;5(6).

Contents

List of abbreviations

AASI	Ambulatory arterial stiffness index
ABP	Ambulatory blood pressure
ABPM	Ambulatory blood pressure monitoring
AGE	Advanced glycation end-product
AHI	Apnoea–hypopnea index
aoPWV	Aortic pulse wave velocity
CACS-CL	Coronary artery calcium score-weighted clinical likelihood
CAD	Coronary artery disease
CAD-RADS	Coronary artery disease reporting and data system
CCS	Chronic coronary syndrome
CCTA	Coronary computed tomography angiography
cfPWV	Carotid–femoral pulse wave velocity
CI	Confidence interval
DC	Distensibility coefficient
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
EVA	Early vascular ageing
HMOD	Hypertension-mediated organ damage
IQR	Interquartile range
LASSO	Least absolute shrinkage and selection operator
MI	Myocardial infarction
MUCH	Masked uncontrolled hypertension
NPAT	Normalised pulse arrival time
NSTEMI	Non-ST-elevation myocardial infarction

OPPT	Overnight pulse propagation time
OSI	Overnight stiffness index
OSA	Obstructive sleep apnoea
PPG	Photoplethysmography
PPT	Pulse propagation time
PTP	Pretest probability
PTT	Pulse transit time
PWV	Pulse wave velocity
RF-CL	Risk factor-weighted clinical likelihood
RMSE	Root mean square error
ROC AUC	Receiver operating characteristic area under the curve
SI	Stiffness index
STEMI	ST-elevation myocardial infarction
SUPERNOVA	Supernormal vascular ageing
SWEDEHEART	Swedish web system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies
VSMC	Vascular smooth muscle cell

1 Introduction

Cardiovascular disease (CVD) remains the primary cause of morbidity and mortality worldwide (1). Ageing and risk factors, including hypertension, diabetes, hypercholesterolemia, smoking, metabolic syndrome, and hereditary as well as environmental factors, affect the vascular system through atherosclerotic and arteriosclerotic processes. These processes lead to deterioration of arterial structure and function and may collectively be referred to as vascular ageing (2).

Risk evaluation is crucial for providing correct preventive measures. Currently, population-based risk prediction models guide clinical decision-making in the apparently healthy and hypertensive populations (3, 4). Such risk models are predominantly based on traditional risk factors and may show limited precision due to reduced generalisability outside development cohorts and to individual variation and sensitivity to risk factors over time (5).

Arterial stiffening is a cardinal feature of vascular ageing, with several unfavourable implications for cardiovascular health (6, 7). Arterial stiffness is a well-established predictor of cardiovascular events (8) and has been proposed to provide an integrated and personalised measure of an individual's accumulated cardiovascular risk (7). Assessment of arterial stiffness may aid in risk stratification (9) and has been included in hypertension guidelines for this purpose (10, 11). At present, however, the clinical use of arterial stiffness assessment is limited due to the need for cumbersome and specialised equipment. More accessible and user-friendly methods are required for a broad implementation in clinical settings. Photoplethysmography (PPG), which measures instantaneous blood volume changes in the skin, may be used for evaluation of arterial stiffness. PPG is common in medical pulse-oximeters to measure oxygen saturation levels and pulse rate, and has also recently been incorporated into consumer wearable devices such as smart watches and smart rings. Furthermore, machine learning may be applied on PPG signals and clinical data, to improve assessment of arterial stiffness and to facilitate identification of individuals having an increased cardiovascular risk, diagnose or condition.

This thesis aimed at investigating novel and simplified arterial stiffness assessment methods and adopt machine learning for improved risk stratification.

2 Background

2.1 Structure and function of central large arteries

Central large arteries have an important conduit function and deliver blood supply from the heart to the periphery. This is effectively done due to their relatively large diameters and low flow resistance (12). These arteries, primarily the aorta, but also the carotid and cervical arteries, are elastic, which contributes to their unique function.

These central arteries have a thin intima with endothelial cells, an elastin-rich media, and a thin collagenous adventitia. The media is composed of elastic lamellae containing elastin-rich fibres, with layers of vascular smooth muscle cells (VSMCs) and collagen fibres between them (9). As the distance from the heart increases, arteries shift from elastin-rich, large and elastic, to VSMC-rich, like the medium-sized muscular arteries and smaller arterioles, which are involved in blood pressure regulation (13). Transitional arteries, primarily the abdominal aorta, have a mixed structure, with a substantial amount of both elastin and VSMCs (7).

The elastin-rich media gives central arteries a vital cushioning function and the capacity to store elastic energy generated during systole. Through elastic recoil, this energy helps to maintain blood flow during diastole, ensuring a nearly steady flow in the vasculature, referred to as the Windkessel effect (12). The elastic central arteries also facilitate a slow propagation of pulse waves. The combination of arterial stiffness, which increases progressively from the heart to more distal arteries, and changes in diameter and arterial branch points, induces wave reflections, where pulse waves are partially reflected back towards the heart (14) and merge into a net reflected wave (15). When the aortic PWV (aoPWV) is normal (*i.e.*, low), the backward reflected waves arrive to the ascending aorta in diastole. This is advantageous, as the increased aortic diastolic blood pressure enables an adequate coronary perfusion and a normal (low) aortic systolic blood pressure, which prevents excessive left ventricular afterload (12).

2.2 Pathophysiology of arterial stiffening

Several processes contribute to structural and functional changes in the arteries caused by ageing and various risk factors, ultimately resulting in vascular ageing

and arterial stiffening. Stiffening of central large arteries, particularly the aorta, has demonstrated the greatest clinical significance. Throughout this text, "arterial stiffness" or "arterial stiffening" will refer to the stiffness of large arteries.

One of the main causes of arterial stiffening is degradation of elastic fibres. The intrinsic, genetically determined ageing process, driven by enzyme-mediated degradation, occurs naturally and is largely non-modifiable (16). Other intrinsic, but non-enzymatic, age-related degradation processes also occur, involving mechanisms such as glycation, lipid binding, calcification, oxidative damage, and mechanical fatigue (17). External factors leading to extrinsic ageing of elastic fibres include air pollution, smoking, and oxidative stress (17). Unfortunately, the creation of arterial elastin is limited primarily to the foetal development period and early childhood, which means that the loss of elastin fibres is essentially irreplaceable (18).

Specific mechanisms leading to arterial stiffening include collagen deposition and advanced glycation end-product (AGE)-induced cross-linking of collagen and elastin, which result in reduced collagen proteolysis and increased elastin degradation (7). VSMCs also contribute to arterial stiffening through changes in the VSMC cytoskeleton, interactions with the extracellular matrix, and medial calcification, primarily through differentiation. They likely also act as mediators of endothelial dysfunction, resulting in changed VSMC tone. Cellular senescence in vascular cells may also contribute to arterial stiffening (19). Furthermore, inflammation affect arterial stiffness through several mechanisms (20).

Arterial stiffness also increases in the presence of hypertension (9, 14, 21). Increased blood pressure results in greater arterial wall thickness and increased loading of the stiffer collagen fibres in large arteries, which leads to higher distension pressure (14, 22). Conversely, several studies indicate that arterial stiffening precedes and predicts hypertension (23-25). Currently, it is generally accepted that arterial stiffening serves as both a cause and an effect of hypertension (26, 27), forming a vicious feedback loop that exacerbates both arterial stiffness and increased blood pressure. Additionally, the development of hypertension is further promoted by impaired interactions between large and small arteries (28).

Arterial stiffness is affected by traditional and modifiable cardiovascular risk factors other than hypertension. Chronic kidney disease leads to arterial stiffening through several processes, with arterial calcification being one of the

main causes (29, 30). In diabetes, among several contributing mechanisms, a high burden of AGEs alters the extracellular matrix function and integrity of arteries through the above-mentioned AGE-crosslinking of collagen and elastin (31). Additionally, dyslipidaemia has been linked to arterial stiffening trough the accumulation of lipids in the arterial wall (32).

Atherosclerosis (mainly a disease of the intima, leading to plaque formation) and arteriosclerosis (from Greek, literally meaning "hardening of the arteries", mainly due to pathologies in the media), occur in parallel, share risk factors, and enhance each other. This interaction has been summarised as the cardiovascular ageing continuum (33). The pathophysiological links between arterial stiffening and atherosclerosis may include endothelial dysfunction, plaque calcification, and the response to inflammation through various mechanisms (2). Thus, arterial stiffness, which is predominantly determined by arteriosclerosis, is also associated with atherosclerosis (34, 35).

2.3 Hypertension-mediated and target organ damage

The negative effects of increased arterial stiffness on different organs can be referred to as target organ damage (6, 18). A closely related concept is hypertension-mediated organ damage (HMOD), which specifically denotes structural and functional changes in arteries or organs such as the brain, heart, kidneys, and eyes caused by hypertension (11).

The heart is affected by arterial stiffening through several mechanisms. A stiff aorta increases the load on the left ventricle (36), and due to the increased aortic PWV, the reflected waves return earlier, during mid-to-late systole, which has several adverse consequences on the vascular system and the heart. These include increased systolic aortic blood pressure, while diastolic blood pressure decreases, resulting in an elevated left ventricular afterload and hypertrophy, increased oxygen demand, and reduced diastolic coronary perfusion pressure. This leads to ischaemia and a higher vulnerability to ischaemic events (7). Ultimately, arterial stiffening contributes to heart failure development (36).

Other organs, including the brain, placenta, and kidneys, also suffer adverse effects from arterial stiffening. These effects are associated with the development of dementia, pregnancy complications, and chronic kidney disease, respectively. These high-flow, low-resistance, organs are particularly sensitive to

highly pulsatile arterial pressure and flow waveforms, which can penetrate deeper into the circulation and cause microvascular damage (7, 18).

Furthermore, the arterial wall itself may be considered a target organ, and a measure of HMOD (11), since itself is negatively affected in the vicious cycle of hemodynamic dysfunction and increased pulsatility (37).

2.4 Biomechanics of arterial stiffening

The biomechanics involved in arterial stiffening can be understood with the help of several equations.

First, to determine local arterial stiffness, Laplace's law ($\sigma = Pr / h$) provides insight, where σ is mean circumferential wall stress, P the pressure, r the luminal radius, and h the wall thickness (9). This equation demonstrates, for example, how an increase in pressure results in increased wall stress.

Local arterial stiffness can also be quantified by examining the relationship between pressure and cross-sectional area through the distensibility coefficient (DC), calculated as $DC = (\Delta A / \Delta P) / A$, where $\Delta A / \Delta P$ represents area compliance and A is the minimum area (7).

Second, to assess arterial stiffness in longer (global) arterial segments, the Moens-Korteweg equation as $PWV = \sqrt{(Eh / 2\rho r)}$ can be applied (9), where PWV is the pulse wave velocity (the speed of pulse wave propagation), E is the material stiffness, h the wall thickness, r is the luminal radius, and ρ is the density of the blood. The equation shows that, with Eh representing the structural stiffness, increases in either material stiffness or wall thickness will increase PWV.

An alternative equation was later derived by Bramwell and Hill as $PWV = \sqrt{(A\Delta P / \rho \Delta A)}$ (38), where A is the mean cross-sectional area, P the pressure, and ρ the blood density. This can also be expressed as $PWV = \sqrt{1 / \rho DC}$, providing a direct link between arterial distensibility and PWV (7).

Some vascular properties affect both local and global biomechanics. The radius (r) typically increases in central arteries with age and in hypertension (28). This enlargement may have a beneficial effect by lowering PWV but can, on the other hand, lead to increased local wall stress (σ) (39).

2.5 Arterial stiffness assessment methods

The scientific interest in the association between pulse wave characteristics and diseases has a long history. One of the earliest known books on the subject, The Pulse Classic (Mai Jing), was written by Wang Shu-he circa 220 CE (40), in which peripheral pulse wave types were linked to different diseases. In recent centuries, work by, among others, William Harvey (1578–1657), Stephan Hales (1677–1746), and Thomas Young (1773–1829) developed a more modern understanding of the cardiovascular system (40). In 1863, a portable pulse wave analysis device, a sphygmograph, was invented by Étienne-Jules Marey (41). Four decades later, in 1905, a new method for auscultatory blood pressure measurement, determining both systolic and diastolic pressure, was presented by Nikolai Sergeevich Korotkoff, building on work by Scipione Riva-Rocci (42). This method laid the groundwork for clinical blood pressure measurement and treatment in the 20th century. While blood pressure management has dominated risk factor control, applications based on pulse wave assessment have been less commonly used in clinical practice (43, 44).

The aorta has a central hemodynamic role, is most prone to abnormal stiffening with ageing and exposure to risk factors, and has shown the strongest prognostic associations with cardiovascular events (13, 45). Although pulse pressure from central blood pressure and augmentation index, an index of aortic wave reflections, both reflect impaired aortic pressure pulsatility (46, 47), the most clinically used assessment methods calculate PWV in the aorta, which provide the overall best measure of aortic stiffness (13, 45).

In addition to representing either local or global assessments of arterial stiffness, measurements can also be classified as direct or indirect. Direct methods include, for instance, PWV and DC, whereas indirect methods refer to measures of arterial stiffness that rely on equations, transfer functions (13), or blood pressure measurements.

Examples of different methods for assessing arterial stiffness are listed in Table 1.

Table 1. Examples of methods for arterial stiffness assessment

Method	Equipment	Pro	Con	Comment
Invasive aoPWV *PTT from invasive pressure sensors*	Catheteri-sation lab	High temporal resolution	Invasive; expensive; limited accessibility	Gold standard (13)
MRI aoPWV *PTT from flow or arterial diameter changes*	MRI equipment	Accurate path length	Non-accessible; limited temporal resolution	Correlates with invasive aoPWV (48); best non-invasive method
cfPWV *PTT from tonometry, Doppler ultrasound, or BP cuffs*	SphygmoCor, Complior, Vicorder, ultrasound equipment	Good proxy for aoPWV	Requires trained operators; omits proximal aorta; some uncertainty in pulse travel path; path length approximations	Non-invasive gold standard; validated invasively (49)
Brachial–ankle PWV *PTT from BP cuffs*	MESI, Vascular Profiler, VaSera	Automated; easy; fast; relatively inexpensive	Ambiguity in wave travel path; reduced correlation with aoPWV	Reference values from mostly Asian populations (50)
Brachial single cuff aoPWV *PTT from PWA*	Arteriograph	Automated; easy, fast; relatively inexpensive; seemingly good proxy for aoPWV	Indirect; based on PWA; path length approximations; assumptions on wave reflections	Validated invasively (51)
PPG PWV *Waveform features from finger, wrist, etc.*	PulseTrace, Meridian, Pulse oximeters, Wearables	Automated; easy; fast; inexpensive; expandable to consumer devices	Indirect; based on PWA	Correlates with aoPWV and cfPWV (52)
Brachial PP *Systolic – diastolic BP*	Office BP or ABPM	Accessible; automated if using oscillo-metric device	Indirect	
Central PP *Based on PWA at radial, brachial, or carotid arteries*	SphygmoCor, PulsePen, Complior, Vicorder, Arteriograph	Assesses central haemodynamics	Indirect; tonometer systems require trained operators; dependent on transfer functions	
Augmentation index *Based on PWA at radial, brachial, or carotid arteries*	SphygmoCor, PulsePen, Complior, Vicorder, Arteriograph	A measure of wave reflections	Indirect; tonometer systems require trained operators; dependent on transfer functions	
Ambulatory arterial stiffness index	ABPM	Easily calculated from 24-h ABPM; integrated measure of risk	Indirect; uncertain mechanism in relation to aortic stiffness	

aoPWV, aortic pulse wave velocity (PWV); PTT, pulse transit time; cfPWV, carotid–femoral PWV; MRI, magnetic resonance imaging; BP, blood pressure; PP, pulse pressure; PPG, photoplethysmography; PWA, pulse wave analysis; PWV, pulse wave velocity; ABPM, ambulatory blood pressure monitoring.

Measures of arterial stiffness are influenced by confounding factors such as vascular tone, heart rate, and blood pressure levels, as well as by factors related to the measurement environment, including room temperature and time of day (7, 53). Several factors are shared between measurement methods, whereas others are more pronounced in specific methods.

2.5.1 Brachial blood pressure-derived indices

Brachial pulse pressure, which is easily obtained as the difference between systolic and diastolic pressure, is an indirect measure of arterial stiffness. With arterial stiffening, the pulse pressure widens, resulting in several adverse effects. Although brachial pulse pressure differs from central (aortic) pulse pressure due to the pulse pressure amplification between central and peripheral arteries (53), it has been shown to be associated with adverse outcomes and is a useful, accessible marker of cardiovascular risk (54).

Another indirect measure of arterial stiffness is the ambulatory arterial stiffness index (AASI), which is derived from ambulatory blood pressure monitoring (ABPM) recordings (55). AASI is calculated by analysing the linear relationships between systolic and diastolic blood pressure measurements, defined as 1 minus the regression slope of diastolic on systolic blood pressure values over 24 hours. Although AASI has shown only weak correlations with cfPWV, it is predictive of cardiovascular morbidity and mortality (55), likely being a more integrated marker of cardiovascular risk.

2.5.2 Pulse wave velocity

PWV is calculated as the ratio of the distance between two arterial sites to the pulse transit time (PTT) between them, providing a direct measure of arterial stiffness expressed in m/s.

The gold standard invasive measurement of aortic PWV uses catheters with pressure sensors to track the PTT from the ascending aorta to the aortic bifurcation. Magnetic resonance imaging is considered the best non-invasive method, but its use is limited due to low availability (13).

cfPWV is considered the gold standard non-invasive measurement method for arterial stiffness, featuring recordings of pulse waves at the common carotid and femoral artery sites. The traditional SphygmoCor device (AtCor Medical Pty. Ltd., West Ride, Australia) uses sequential recordings of the pulse waves and the R wave from the ECG as a reference point in time, while an updated version

(SphygmoCor XCEL) uses a femoral cuff, allowing for simultaneous and faster measurements (44). Although cfPWV has been extensively used and studied, drawbacks of the method include ambiguity of the pulse travel path (in the measurement the pulse travels both towards the carotid and the femoral arteries at the same time), the requirement of trained operators, and the usual exposure of the groin (7).

Brachial single cuff-based oscillometric methods, such as the Arteriograph (TensioMed, Budapest, Hungary), are easier to use (45). The Arteriograph assesses aoPWV through a method where the cuff is inflated 35 mm Hg above the systolic blood pressure, which leads to a better identification of the incident and the reflected pulse waves. The wave reflection is thought to predominantly take place in the aortic bifurcation. The device calculates the aoPWV by dividing the distance between the jugulum and symphysis (serving as a proxy for aortic length) by half of the time difference between the incident and reflected pulse waves (56). Although this is an indirect method that relies on pulse wave analysis and assumptions on wave reflections, it has been validated invasively (51), and is predictive of cardiovascular morbidity, events and mortality (35, 57, 58).

Brachial and ankle pressure waveforms obtained from cuffs can be used to calculate the brachial–ankle PWV (baPWV), which is defined as the distance between the brachial and the tibial arteries divided by the PTT. Although this method is simple, the pulse travel path is ambiguous as it propagates simultaneously through the arm and the thoracic aorta and includes long segments of muscular arteries in the extremities. Nevertheless, baPWV has demonstrated independent associations with cardiovascular events (50).

2.5.3 Photoplethysmography

PPG is an optical technique that measures fluctuations in light intensity in the skin, reflecting blood volume changes that enable pulse wave analysis (59, 60). PPG is frequently used in medical pulse-oximeters to measure oxygen saturation levels and pulse rate as vital signs, or during sleep studies (61). Recently, PPG has also been incorporated into consumer wearable devices such as smart watches and smart rings, and may be used for the evaluation of vascular ageing (52).

The peripheral PPG signal contains rich information on the cardiovascular system, including numerous features (*i.e.*, fiducial points and combinations of these; Figure 1), which have been shown to be associated with measures of arterial stiffness (62). These features include the pulse propagation time (PPT).

PPT is the time between the first and the second peaks in the PPG waveform, which is considered to reflect the time it takes for the pressure wave to propagate from the heart to the peripheral reflection sites and back (63, 64).

A height-normalised arterial stiffness index (SI) can be calculated as the subject's height divided by PPT (64-66). SI is related to arterial stiffness (65-67), cardiovascular risk (68), and is an independent predictor of cardiovascular outcomes and mortality (69). Other PPG features have subsequently shown stronger correlations with measures of arterial stiffness than SI, including the "spring constant" (70) and the "ageing index" ([b-c-d-e]/a) (71). However, it is also likely that the use of the PPG signal for arterial stiffness assessment can be further improved.

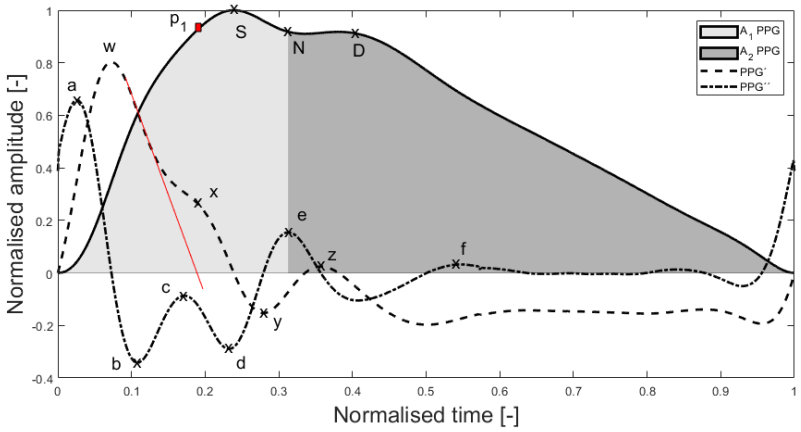

Figure 1. Normalised finger photoplethysmography (PPG) waveform (solid black line) with its first derivative (PPG', dashed line) and second derivative (PPG'', dash-dotted line). Fiducial points are indicated for: PPG (S, N, D), PPG' (w, x, y, z), PPG'' (a, b, c, d, e, f). A_1 (light grey) and A_2 (dark grey) indicate two PPG waveform areas. The red line is the tangent used for estimating the timestamp of the first systolic peak, "p1", according to (II). From (III).

PPG enables the collection of continuous data, also during sleep, which is currently not possible with other methods for assessing arterial stiffness. Studies have shown that overnight PPT (OPPT) helps stratify cardiovascular risk in models based on overnight PPG (72, 73), highlighting the potential value of overnight PPG assessment (74).

2.5.4 Other assessment methods

Other methods for arterial stiffness assessment include multi-site PPG, which, for instance, can be used for finger-toe PWV assessment (75),

ballistocardiography for assessment of aorta–leg pulse transit time (76), the cardio–ankle vascular index, reflecting arterial stiffness from the ascending aorta to the ankle (77), and new promising methods such as laser Doppler vibrometry (78).

2.6 Arterial stiffness as a marker of cardiovascular risk

2.6.1 Risk in the apparently healthy

Risk prediction models are used to guide clinical decision-making in apparently healthy individuals and include the European SCORE2 and the recent American Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) equation (3, 4). Such models are predominantly based on conventional risk factors, including age, sex, blood pressure, cholesterol levels, and smoking. These algorithms may have limited precision due to reduced generalisability outside development cohorts, as well as individual variability in, and sensitivity to, risk factors over time (5).

Characteristics such as impaired renal function, presence of coronary artery calcium, or carotid or femoral plaques, and arterial stiffening are considered target organ damage/HMOD and can improve risk evaluation (11, 79). Arterial stiffness has been proposed to provide an integrated and personalised measure of the accumulated cardiovascular risk for individuals (7) and may offer valuable information in individuals at intermediate risk, aiding in risk reclassification (9). For young individuals, where risk scores are typically not available, arterial stiffness assessment may be particularly useful (2, 80). Additionally, the evaluation of vascular health through arterial stiffness assessment in early life may facilitate early health-promoting measures (23, 80) that could reduce the risk of later CVD development (2).

The concept early vascular ageing (EVA), has been defined as faster-than-chronologically anticipated degeneration of arterial structure and function, with arterial stiffening being a central characteristic (5). Conversely, individuals with lower-than-expected vascular age for their chronological age are considered to have supernormal vascular ageing (SUPERNOVA), which is associated with a reduced risk for cardiovascular events (81). Risk estimation by arterial stiffness, especially using the easily understandable concept of EVA, may improve the communication concerning cardiovascular risk with patients and the general population (82).

2.6.2 Risk in hypertension

The demonstration of the predictive value of assessing arterial stiffness for cardiovascular events and mortality (83-85), as well as its contribution to improved risk classification compared to conventional risk algorithms (8, 86), has led to its inclusion in hypertension guidelines — most recently in the 2023 European Society of Hypertension Guidelines for the management of arterial hypertension (10), and the 2024 European Society of Cardiology (ESC) Guidelines for the management of elevated blood pressure and hypertension (11). Both these guidelines recommend considering assessment of arterial stiffness (as a measure of HMOD) using cfPWV or baPWV, or pulse pressure, as risk modifiers at the time of hypertension diagnosis (10, 11).

Furthermore, cfPWV is associated with masked hypertension, which is defined as normal office blood pressure, but elevated out-of-office blood pressure. Assessment of arterial stiffness might help identify this clinically challenging condition, which often remains unnoticed without blood pressure measurements outside the clinic (10).

Additionally, increased arterial stiffness is associated with incident hypertension (23-25). This suggests that assessing arterial stiffness may serve as a valuable marker in screening applications aimed at identifying individuals at risk of developing hypertension.

2.6.3 Risk in coronary artery disease

The associations between atherosclerosis and arterial stiffening, through shared risk factors and pathophysiological mechanisms, make arterial stiffness useful as a risk marker for CAD (33, 87).

In the primary prevention setting, studies have shown that arterial stiffness is a predictor of CAD (88, 89), and cardiovascular mortality (89, 90) in apparently healthy subjects. In the currently largest meta-analysis, based on both population-based studies and subjects with known diseases, arterial stiffness remained predictive of coronary heart disease also after adjusting for traditional risk factors (8). Another meta-analysis, involving subjects with various levels of baseline risk, found that arterial stiffness was a predictor of future cardiovascular events and all-cause mortality (85).

Measures of arterial stiffness may also play a role in the diagnosis of suspected CAD. In this setting, a meta-analysis including eight studies indicated that arterial

stiffness was diagnostic of CAD on coronary angiography (91). Of these, the only study employing cfPWV (the others used baPWV) showed that cfPWV was associated with both the presence and severity of CAD (92). Furthermore, CAD could be accurately predicted when including an index of arterial stiffness in machine learning algorithms (93).

Arterial stiffness may also be used for risk stratification in the secondary prevention of CAD. Supporting this, a study with patients who underwent coronary angiography due to chest pain showed that invasive aoPWV was an independent risk marker for future cardiovascular events (94). Furthermore, arterial stiffness has been shown to be predictive of cardiovascular events after ST-elevation myocardial infarction (STEMI) (95), and following successful percutaneous coronary intervention in patients with stable CAD (96). Arterial stiffness was also predictive of cardiovascular events and mortality in patients undergoing coronary angiography due to suspected CAD (97).

2.6.4 Risk in specific high-risk populations

Besides individuals with established hypertension or CAD, other persons with elevated cardiovascular risk may be considered for risk stratification using arterial stiffness assessment (98).

A meta-analysis in patients with chronic kidney disease showed that PWV is a major predictor of CVD and all-cause mortality, particularly in those undergoing haemodialysis (99). In one study of end-stage kidney disease, aoPWV measured by Doppler ultrasound showed that patients in the highest tertile had a 5.4-fold adjusted risk of all-cause mortality (95% confidence interval [CI] 2.4–11.9) compared with those in the lowest tertile after 72 months of follow-up (100).

Arterial stiffness has also demonstrated predictive value in populations with diabetes mellitus. In a study of subjects with type-2-diabetes and a median follow-up of 8.2 years, increases in cfPWV were associated with cardiovascular events and mortality (101). Similarly, in a study of individuals with type 1 diabetes and median follow-up of 6.2 years, higher cfPWV was associated with increased albuminuria, cardiovascular events and mortality (102).

In the elderly, in a study with a mean age 87 years, arterial stiffness was the only significant predictor of cardiovascular mortality (103).

2.7 Arterial stiffness as a treatment target

Arterial stiffening has been proposed to be used as a treatment target. A proportion of arterial stiffening is largely unmodifiable, and there are currently no approved drugs directly targeting the "de-stiffening" of arteries. However, arterial stiffening can be improved by controlling cardiovascular risk factors through both pharmacological treatments and other measures (9). For example, arterial stiffening is reduced through improved blood pressure control in patients with hypertension (104, 105), following kidney transplantation (106), with aerobic exercise training (107), and through smoking cessation (108). In the future, potential pharmacological treatment targets may involve cellular senescence, calcification, extracellular remodelling (affecting the elastin/collagen ratio), and oxidative stress (19).

In the first attempt to use arterial stiffness itself as a treatment target, the randomised controlled SPARTE (Strategy for Preventing cardiovascular and renal events based on ARTErial stiffness) trial compared a cfPWV-based treatment strategy with a classical blood pressure-targeted strategy in hypertensive patients (109). In the cfPWV treatment group, the objective was to lower cfPWV below 10 m/s using primarily an intensive blood pressure lowering strategy, but also active implementation of life style measures (including physical exercise, diet advice, and smoking cessation) to control risk factors (109). Unfortunately, the study was underpowered to draw conclusions about differences in cardiovascular outcomes between the groups. Nevertheless, it was shown that the group using the PWV-based treatment strategy had less increase in cfPWV over time, received more intense treatment, and showed lower blood pressure values compared to the control group (109).

2.8 Machine learning in cardiovascular applications

Most of the currently used cardiovascular risk scores are based on rather simple algorithms, which is preferable as long as they are sufficient for the task (110). However, today, the increasing availability of clinical data from both electronic health records, sensor signals from medical and consumer devices, along with increasing computer processing powers lay the groundwork for a new generation prediction models. These models may offer more integrated and individualised predictions to inform clinical decisions (111).

For this purpose, modern machine learning methods and artificial intelligence (AI) provide new possibilities to evaluate and learn from these large biomedical

datasets, which has also been highlighted as a potential approach for the assessment of vascular ageing (112).

Machine learning algorithms learn from data in different ways. Supervised learning, which is most common, uses labelled data, were the algorithms predict a predefined outcome based on specific variables (predictors). In contrast, unsupervised learning does not set a target outcome, allowing algorithms to freely analyse and cluster data in potentially novel ways. This approach may lead to the discovery and insights of new subgroups and characteristics (111).

A benefit of several machine learning algorithms is their ability to present variable importance and provide unbiased variable selection in the prediction of an outcome, which is important when working with high-dimensional data. This facilitates new understanding of clinical information and reduces model complexity (111), thereby enhancing potential real-world implementation.

3 Research aims

The overall aim of this thesis was to investigate assessment of arterial stiffness in populations at increased cardiovascular risk using novel and simplified methods, with the goal of improving cardiovascular risk stratification.

Specific aims:

1. To evaluate whether overnight stiffness index (OSI) provides an improved PPG-based measure for assessing cardiovascular risk and vascular ageing in a population of hypertensive subjects.
2. To develop and evaluate an improved PPG- and ECG-based method for assessing artieral stiffness using machine learning and novel PPG features.
3. To evaluate whether PPG-derived PWV, single brachial cuff-based PWV, or machine learning-based PPG analysis can improve risk stratification for obstructive CAD in patients with suspected new-onset symptomatic chronic coronary syndrome (CCS).
4. To determine the prevalence of masked hypertension and masked uncontrolled hypertension (MUCH) in patients after a recent MI, and to develop machine learning models to predict this blood pressure phenotype using clinical registry data.

4 Materials and methods

4.1 Overview of studies

An overview of the studies is found in Table 2.

Table 2. Overview of study designs, materials, and methods

	Study I	Study II	Study III	Study IV
Design	Observational, cross-sectional	Methodological, cross-sectional	Observational, cross-sectional	Observational, cross-sectional
Inclusion period	2009–2016	2020–2021	2023–2025	2016–2018
Population	Confirmed / suspected HTN n=79	General population n=33	Suspected new-onset CCS n=141	Post-myocardial infarction n=99
Exposure(s)	Overnight stiffness index (PPG)	PPG features, NPAT using ECG	aoPWV, PPG-cfPWV, PPG, risk scores	Clinical registry variables
Endpoints	CV risk, ABPM, arterial stiffness indices	cfPWV, aoPWV	Obstructive CAD	MUCH and uncontrolled hypertension

HTN, hypertension; CCS, chronic coronary syndrome; PPG, photoplethysmography; NPAT, normalised pulse arrival time; cfPWV, carotid-femoral pulse wave velocity (PWV); aoPWV, aortic PWV; CV, cardiovascular; ABPM, ambulatory blood pressure monitoring; CAD, coronary artery disease; MUCH, masked uncontrolled hypertension.

4.2 Study I

In this study, individuals who underwent ABPM (Spacelabs ABP 90217A monitors; Spacelabs Healthcare, Snoqualmie, Washington, USA) due to suspected or confirmed hypertension, with complete overnight recordings of finger PPG, were analysed.

Pulse pressure values were calculated as the mean of systolic minus diastolic blood pressure for each period (24 h, awake, and asleep), and blood pressure dipping as (mean daytime blood pressure minus mean night-time blood pressure) / mean daytime blood pressure × 100 for systolic and diastolic blood pressure. AASI was calculated as 1 minus the linear regression slope of diastolic on systolic blood pressure values during the full 24-h recording (55).

A sleep diagnostics device (SOMNOcheck micro CARDIO, Löwenstein Medical Technology GmbH, Hamburg, Germany) with built-in finger PPG at 100 Hz and continuous pulse wave analysis (ChipOx, Corscience GmbH & Co. KG, Erlangen, Germany) was performed simultaneously with the ABPM (on the contralateral arm). OPPT was calculated by the device, as the time (in ms) from the first peak to the second peak in the pulse waveform, beat by beat, and averaged for the whole sleep recording. OSI was defined as body height divided by OPPT (Figure 2).

SCORE2 / SCORE2-OP using the moderate risk region, and the Framingham risk score were calculated (3, 113, 114).

Mild, moderate and severe OSA were defined as an apnoea–hypopnea index (AHI) of ≥5 to <15, ≥15 to <30, and ≥30 events/h, respectively.

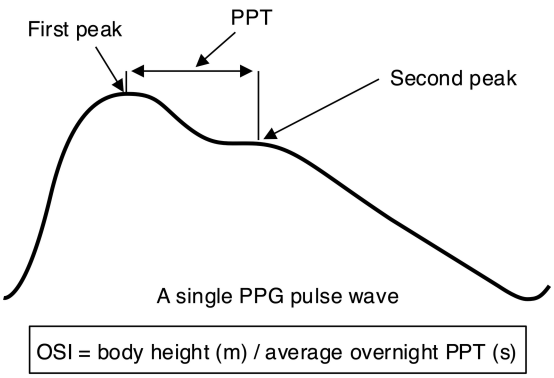

Figure 2. Overnight stiffness index (OSI) is a height-normalised measure of arterial stiffness based on the pulse propagation time (PPT), which is the time delay between the first and the second peaks of the photoplethysmography (PPG) pulse wave. From (I).

4.3 Study II

Colleagues and students at Danderyd University Hospital, Stockholm, Sweden, were invited to participate.

At the study visit, after at least 10 minutes of rest in the supine position 1) blood pressure measurements and assessments of PWV respectively 2) PPG, ECG, and finger blood pressure recordings were performed in random order as groups, as described below. The measurements were performed at a room temperature of 21–24°C in a quiet, dimly lit room and repeated within 2 weeks under similar conditions.

The original SphygmoCor device (AtCor Medical Pty. Ltd., West Ride, Australia) was used for sequential collection of the right carotid and right femoral pulse waves (49, 53). The pulse travel distance was calculated as the distance from the jugulum to the right femoral artery minus the distance from the jugulum to the right carotid artery, and the cfPWV was calculated by the device as this distance divided by the average pulse travel time (115).

The brachial single cuff-based Arteriograph (Tensiomed, Budapest, Hungary) was used for blood pressure measurements and to obtain aoPWV (51, 56, 116).

An infrared (950 nm) reflectance PPG sensor clip (ADInstruments, Dunedin, New Zealand) was placed on the right index finger pulp, and three ECG electrodes on the upper body to obtain a single-lead ECG (lead I). Continuous blood pressure from the right middle finger was recorded using the volume-clamp method (Ohmeda 2300, Finapres, Englewood, CO, USA).

A 20-s PPG sequence was used for the identification of PPG fiducial points (Figure 1) and extraction of 136 established features (Figure 3; Paper II, Supplementary Table S1). Studies of the concurrent finger blood pressure waveform provided a new way to estimate the timestamp of the first systolic peak, "p1" (Figure 1). Seventeen new features were developed, out of which 13 included the new "p1" (Figure 3; Paper II, Supplementary Table S1). One of these was the new "Am b/Am p1" ratio. Height-normalised pulse arrival time (NPAT) was derived using ECG.

PPG features were normalised for heart rate, filtered on zero variance and repeatability (within-subject coefficient of variation <20%), and used in machine learning to predict cfPWV and aoPWV according to Figure 3. The least absolute shrinkage and selection operator (LASSO) and random forest algorithms were used, and linear regression was applied using the most important PPG feature for each outcome.

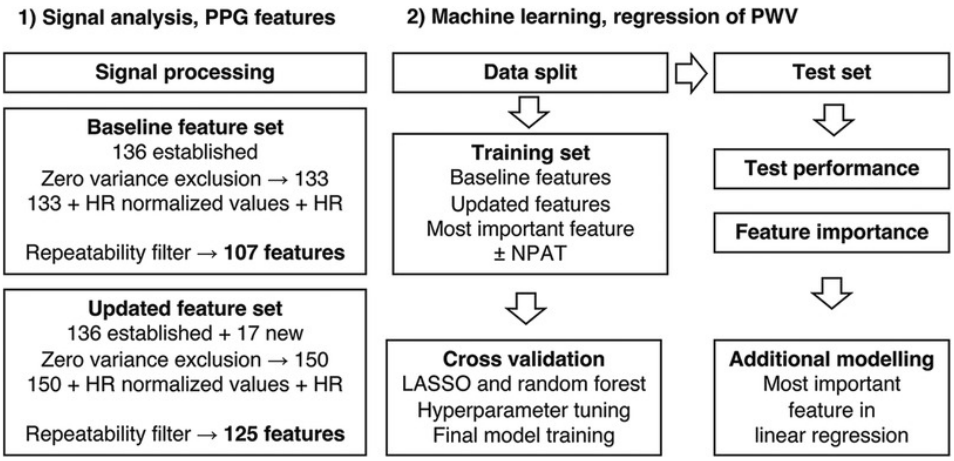

Figure 3. Study II signal analysis, feature sets, and machine learning. HR, heart rate; NPAT, height-normalised pulse arrival time; LASSO, least absolute shrinkage and selection operator. From (II).

4.4 Study III

This study included patients undergoing CCTA due to suspected new-onset symptomatic CCS.

The outcome obstructive CAD was defined as CAD reporting and data system (CAD-RADS) ≥3 (at least one moderate stenosis, ≥50%) (117).

On the study visit, after ≥5 min supine rest, PPG recordings were acquired using the same equipment as in (II) followed by aoPWV using Arteriograph.

PPG signals were processed and features extracted using the same method as in (II). The PPG-based PWV was based on the extraction of a specific amplitude ratio from the first part of the PPG waveform, which was applied in a linear regression equation to estimate cfPWV (PPG-cfPWV = 13.8 - 9.2 × "Am b/Am p1"), as presented in (II).

PTP was determined using the table system as outlined in the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes (118). The RF-CL and coronary artery calcium score-weighted clinical likelihood (CACS-CL) models were applied according to Winther et al (119). CCTA-calibrated RF-CL and CACS-CL models, denoted "(CCTA)", were also used (120).

The predictive value of aoPWV and PPG-cfPWV were assessed individually and in combination with PTP, RF-CL, and CACS-CL models.

For machine learning-based PPG analysis, the Boruta algorithm was applied for feature selection (121), and the selected features were subsequently used for modelling with logistic regression and random forest.

Established models were evaluated by receiver operating characteristic area under the curve (ROC AUC) and study-developed models were evaluated using AUC from repeated cross-validation.

4.5 Study IV

Patients hospitalised for an acute MI were included during outpatient follow-up as part of a study screening for comorbidities, including uncontrolled hypertension.

ABPM was performed at median 11 weeks (interquartile range [IQR] 9–15) after hospital discharge using Novacor Diasys Integra 2 (Novacor, Rueil-Malmaison, France). ABPM recordings were considered valid if they included at least 20 valid daytime and 7 valid night-time blood pressure measurements. A study flow chart is presented in Figure 4.

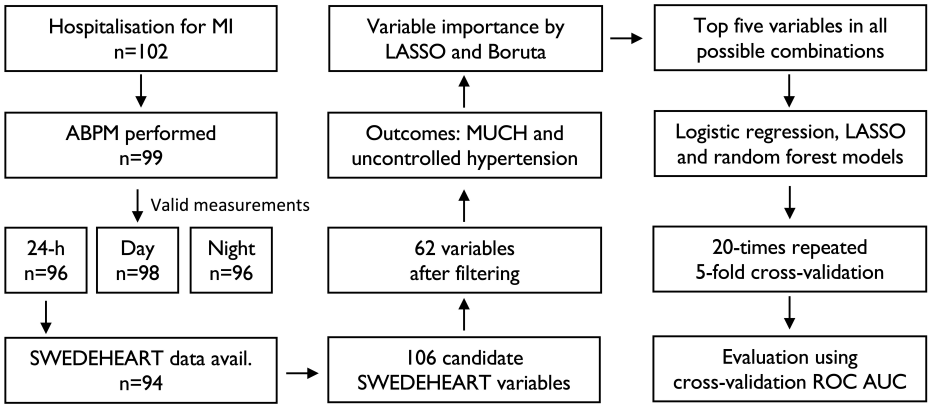

Figure 4. Study IV flow chart. MI, myocardial infarction; ABPM, ambulatory blood pressure monitoring; SWEDEHEART, Swedish web system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies; LASSO, least absolute shrinkage and selection operator; MUCH, masked uncontrolled hypertension; ROC AUC, receiver operating characteristic area under the curve. Adapted from (IV).

Twenty-four-hour, daytime, and night-time hypertension by ABPM was defined as mean (systolic and/or diastolic) blood pressure values of ≥130/80 mm Hg, ≥135/85 mm Hg, and ≥120/70 mm Hg, respectively. Office hypertension was defined as ≥140/90 mm Hg (11, 122).

Blood pressure phenotypes were defined using the office blood pressure at the time of the initiation of the ABPM, giving the following phenotypes: normotension (neither office blood pressure nor ambulatory blood pressure [ABP] was elevated), white-coat hypertension (elevated office blood pressure but not ABP), sustained hypertension (both office blood pressure and ABP elevated), and masked hypertension (normal office blood pressure but elevated ABP). Sustained and masked hypertension were defined as uncontrolled if the patient was on antihypertensive medication (122). Uncontrolled hypertension was defined as the combination of sustained uncontrolled hypertension and MUCH. The 24-h blood pressure levels were used for definition of blood pressure phenotypes, unless stated otherwise (123).

Clinical characteristics were obtained from the SWEDEHEART (Swedish web system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies) registry.

Prevalence of MUCH and uncontrolled hypertension were studied, and these conditions were predicted through machine learning based on 62 eligible variables from the registry (124). Variable selection was obtained using LASSO and Boruta algorithms. Logistic regression, LASSO, and random forest models using the top-ranked predictors were trained, and discriminatory ability was evaluated by ROC AUC using repeated cross-validation.

4.6 Statistics

4.6.1 General

Throughout the studies, descriptive data were presented as mean ± standard deviation, median (IQR), and proportions, as appropriate. Comparisons of continuous variables between groups were assessed by one-way analysis of variance, Welch's t-test, Wilcoxon's rank sum test or Kruskal-Wallis test, as appropriate, and for categorical variables by the Chi-squared test or, when frequencies were below five, by Fisher's exact test. Testing between-group differences were corrected for multiple comparisons using the Bonferroni method. Bivariate correlations were assessed using Pearson's (r) or Spearman's rank (ρ) correlation coefficients, as appropriate. A two-sided *P* value < 0.05 was considered statistically significant.

In Study I, correlations were checked to remain after removal of outliers, and differences between the Pearson's r values that were statistically significant

were tested using Williams' test. For multiple linear regression models used to adjust for confounding, model assumptions were checked through inspection of diagnostic plots and calculation of variance inflation factors. The models were evaluated after adjustment for multiple testing by the Hommel method, and in sensitivity analyses after removal of potential outliers and influential observations.

In Study II, measures of dispersion were determined by calculating the coefficient of variation and within-subject coefficient of variation. Agreement between reference equipment and performance of prediction models were assessed using root mean square error (RMSE), coefficient of determination (R^2), and Bland-Altman analysis.

In Study III and IV, prediction models were evaluated for discriminatory performance using ROC AUC. In Study III, AUCs were statistically compared using the DeLong test, and 95% CIs were obtained using the bootstrap method.

In Study IV, the mean predicted probability for each observation from resampling was used to construct ROC curves, and the threshold at maximum Youden's index was used to calculate sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

All statistical analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria).

4.6.2 Power calculations

Study I was an exploratory analysis using a novel overnight PPG parameter. Therefore, no power calculation was conducted.

Study II was investigating the correlation between PPG-ECG- and PWV measured with a reference method. We expected to find a strong correlation ($r^2 > 0.5$). When adjusting for two covariates (sex, age) in a multiple regression model with $\alpha = 0.05$ and $\beta = 0.9$, a sample size of 22 participants was required. To allow assessment of the day-to-day variability of the methods, the target sample size was increased to 32 participants.

Study III was based on a power calculation with $\alpha = 0.05$ and $\beta = 0.9$, assuming that 20% of the patients would have a stenosis on CCTA. For the PPG-ECG model (later changed to include only PPG) to achieve a predictive performance of ROC AUC = 0.75, a total of 96 patients would be required, whereas for ROC

AUC = 0.8, only 45 patients would be needed. Originally, the plan was to develop models in the first 100 patients, and to validate them in the subsequent 100 patients. However, as the study was terminated early after the recruitment of 156 patients, all patients were instead included in model development and internal validation.

Study IV was a post-MI screening study for comorbidities, which included ABPM to study uncontrolled hypertension. No power calculation was specifically applied for prediction of uncontrolled or masked uncontrolled hypertension. However, previous data indicated that approximately one in three patients post-MI were expected to have poorly controlled hypertension. Originally, 100 patients were planned for model development and the following 100 for validation. However, the study concluded with 102 enrolled patients, due to lack of continued funding, which did not allow for a dedicated validation dataset.

4.7 Machine learning

Machine learning was used in Study II-IV to facilitate improved evaluation of high-dimensional data and to develop prediction models.

Pre-processing of data included filtering (removal) of variables with zero (Study II, III, and IV) and near-zero (Study III and IV) variance, and imputation using the k-nearest neighbour algorithm (Study III and IV) (125). Variables also underwent mean-centering and scaling to unit variance (Study II, III, and IV) and transformation (Yeo-Johnsson in Study III; Box-Cox in Study IV), to improve normality, as appropriate for linear models.

For variable selection three methods were used.

First, in Study II and IV, variable importance and variable selection was performed using the LASSO algorithm (126). LASSO uses penalised regression which allows predictor coefficients to become zero, keeping only the most relevant predictors. LASSO only finds predictors that are linearly associated with the outcome, which, together with coefficient penalisation, prevent overfitting to training data.

Second, in Study II, random forest was used, which is a tree-based algorithm that need no specific pre-processing, is robust to outliers, and automatically captures non-linear relationships and interactions between variables (127).

Random forest provides built-in variable importance scoring but does not remove unimportant predictors.

Third, Boruta was used in Study III and IV, which is based on random forest variable importance scores and provides the same baseline modelling properties (121). However, in addition, Boruta uses randomised "shadow" copies of variables to provide a built-in statistical analysis for variable selection.

Development of prediction models requires strategies for effective model evaluation. Repeated cross-validation, stratified by the outcome, was used as the resampling technique for internal model validation. Repeated cross-validation involves splitting the data into multiple folds, with each fold used as a validation set once, and the remaining folds used as a training set. This process is repeated multiple times, with different random splits each time, and the results are averaged to give a more robust estimate of model performance (128).

In Study III and IV, two approaches were used to calculate ROC AUC during cross-validation: (1) the mean AUC obtained from ROC curves within each cross-validation fold, and (2) the AUC derived from a ROC curve constructed using the mean predicted probability for each observation across all resamples.

In Study II, data were also split into a training and a test set. Linear regression, LASSO, and random forest models were developed and evaluated using repeated cross-validation in the training set and subsequently evaluated in the test set.

In Study III, logistic regression and random forest models were evaluated using repeated cross-validation, and in Study IV, LASSO was also included.

In Study III, partial dependence plots and SHAP (SHapley Additive exPlanations) plots were used to facilitate model interpretation.

Machine learning was performed using the R software (R Foundation for Statistical Computing, Vienna, Austria) using a range of machine learning-specific R packages.

4.8 Ethical considerations

Study I and IV were approved by the Stockholm Regional Ethical Committee and Study II and III were approved by the Swedish Ethical Review Authority, which

was initiated in 2019. All studies were conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from each subject prior to study participation.

Study I involved patients with confirmed or suspected hypertension that underwent ABPM and overnight sleep polygraphy for screening of OSA. The two equipment being used could potentially involve disturbances for the participant. Furthermore, the participants answered questionnaires on smoking habits, stress levels, and alcohol intake which might feel personal for some. All patients with a new diagnose of sleep apnoea was referred for follow-up and treatment, which overall could be seen as positive for the patient.

Study II was a methodological study in which colleagues and students were participants. Although the medical background provided by the participants was rather sparse, it still constitutes information which might be uncomfortable to share with a colleague or a clinical instructor. The two study visits took time and required planning, and participants may have found some of the examinations uncomfortable. For this study, participants received a modest compensation (300 SEK), considered small enough not to constitute an excessive incentive for participation.

In Study III, patients from the clinical workflow undergoing investigation of potential new-onset CCS were included. The study visit involved being bare-chested and the patients were also examined with cardiac and vascular ultrasound which could be uncomfortable. Medical findings of the different investigations were communicated to the patient, if they wished, and appropriate actions (advice, treatment or referral) were taken, which could be valuable for the patient.

Study IV also involved patients from the clinical workflow, post-MI. Since they were screened for comorbidities (for example ABPM and thumb-ECG), the findings could be valuable for the patients, and involved appropriate actions by the investigators. ABPM could, however, potentially involve disturbances for the participant.

Studies II and III involved external collaboration and commercial interests. Nevertheless, these studies were investigator-initiated, and the collaborating partners had no influence on study design, data collection, analysis, or interpretation of results of the methods assessed in this thesis.

All studies involved collection, storage and handling of sensitive personal data. Good clinical practice, GDPR (general data protection regulation), and applicable regulations have been followed.

Overall, any possible risks have been considered small, and the potential benefits have been judged to outweigh them.

5 Results

5.1 Study populations characteristics

Characteristics of the study populations are summarised in Table 3.

Table 3. Characteristics of the study populations

	Study I	Study II	Study III	Study IV
n	79	33	141	99
Age, years	58.1 ± 10.8	44 (range 21–66)	58.4 [52.9; 64.9]	62.1 ± 8.2
Male sex	56 (71%)	19 (58%)	71 (50%)	73 (74%)
BMI, kg/m²	28.1 ± 4.0	25.0 ± 3.6	27.9 ± 5.1	27.8 ± 4.3
Hypertension	40 (51%)	6 (18%)	62 (44%)	58 (60%)
Diabetes	7 (9%)	-	10 (7.1%)	19 (20%)
Smoking	28 (36%)	5 (15%)	56 (40%)	46 (48%)
SBP, mm Hg	147 ± 19	119 ± 12	125 ± 13	127 ± 15
DBP, mm Hg	90 ± 11	71 ± 8	75 ± 9	75 ± 9
PP, mm Hg	57 ± 17	48 ± 7	50 ± 8	52 ± 11
cfPWV, m/s	-	6.8 ± 1.1	-	-
aoPWV, m/s	-	7.6 ± 1.6	9.9 ± 2.4	-

Values are presented as mean values ± standard deviation, median (range), median [interquartile range], or n (%). Diabetes refers to both type 1 and 2 diabetes mellitus. Smoking refers to previous smoking in Study II, and to current or previous smoking in Study I, III and IV. Being on antihypertensive medication was used as a proxy for having hypertension in Study I. The mean values of the two study visits are shown for blood pressure and pulse wave velocity (PWV) values for Study II. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; cfPWV, carotid–femoral PWV by SphygmoCor; aoPWV, aortic PWV by Arteriograph.

5.2 Study I

Study subject characteristics are found in Table 3. Median (IQR) SCORE2/SCORE2-OP 10-year CVD risk was 6.5% (4.5–10.8), and median Framingham risk score was 17% (10–27). Of 71 subjects with available AHI data, 20 (28%) showed no OSA, 27 (38%) mild OSA, 21 (30%) moderate OSA, and 3 (4%) were classified as having severe OSA.

Higher OSI was associated with increased cardiovascular risk, as shown by the discrimination of tertiles of SCORE2/SCORE2-OP (P = 0.015) and Framingham

risk score (P = 0.034), and by their positive correlations with OSI (ρ = 0.40, P = 0.002 and ρ = 0.41, P < 0.001, respectively). OSI also correlated with age alone (r = 0.45, P < 0.001).

OSI was associated with several blood pressure-derived indices of arterial stiffness (Figure 5), and after controlling for potential confounders (age, sex, body mass index [BMI], diabetes, smoking history), OSI remained independently associated with 24-h pulse pressure (B = 1.68, β = 0.31, P = 0.007, R^2 = 0.24) and asleep pulse pressure (B = 1.96, β = 0.35, P = 0.002, R^2 = 0.29), and these associations persisted also in a sensitivity analysis removing outliers and influential observations.

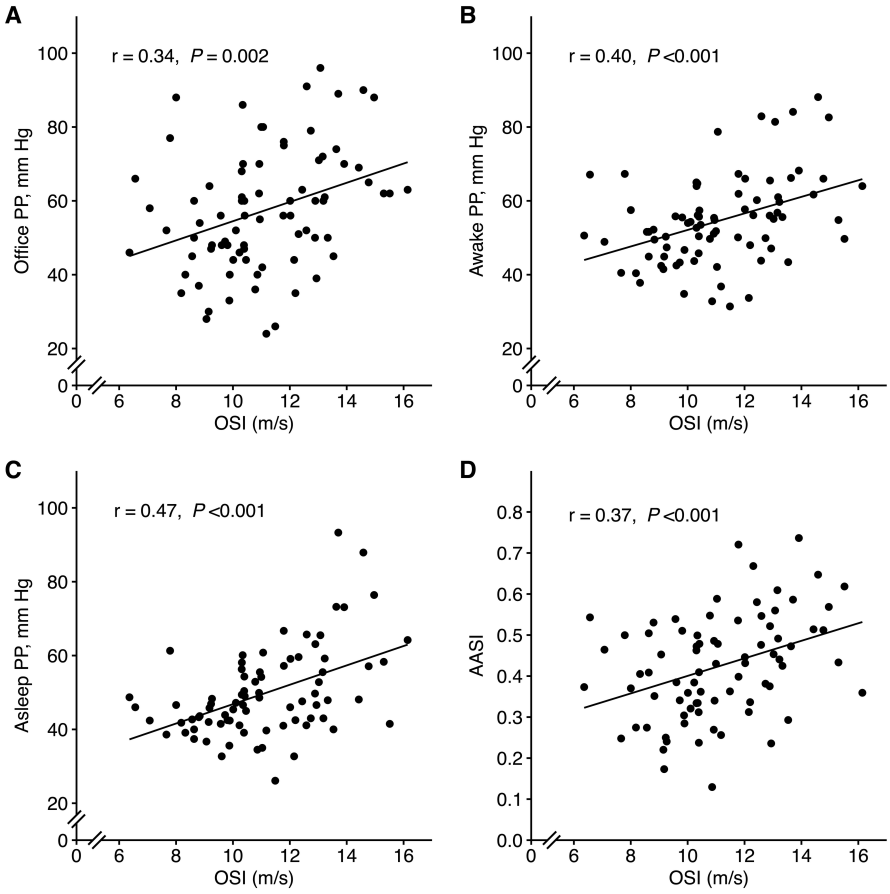

Figure 5. Correlations of overnight stiffness index (OSI) with blood pressure-derived indices of arterial stiffness. (A) Office pulse pressure (PP), (B) awake PP, (C) sleep PP, (D) ambulatory arterial stiffness index (AASI). From (I).

OSI was associated with blood pressure levels, with stronger associations for systolic (awake: r = 0.42, $P < 0.001$; asleep: r = 0.55, $P < 0.001$) than for diastolic blood pressure (awake: r = 0.16, $P = 0.15$; asleep: r = 0.36, $P = 0.001$), and for the sleep period as compared with the awake period. Higher OSI was associated with reduced nocturnal dipping in both systolic (r = –0.32, $P = 0.004$) and diastolic blood pressure (r = –0.30, $P = 0.007$). OSI was independently associated with 24-hour, awake, and asleep systolic ABPM levels after adjusting for confounders, and this association remained following a sensitivity analysis that excluded outliers and influential observations.

Compared with OPPT, OSI showed stronger correlations with ambulatory systolic blood pressure (24-h: r = 0.48 vs. 0.39, $P = 0.012$; awake: r = 0.42 vs. 0.34, $P = 0.046$; asleep: r = 0.55 vs. 0.43, $P = 0.001$), systolic dipping (r = 0.32 vs. 0.23, $P = 0.035$), and asleep diastolic pressure (r = 0.36 vs. 0.24, $P = 0.002$). Although other blood pressure indices demonstrated numerically higher correlations for OSI compared to OPPT, these differences were not statistically significant.

Furthermore, OSI was associated with AHI ($\rho = 0.40$, $P < 0.001$), but this association did not remain significant after adjusting for abovementioned potential confounders (B = 0.63, $\beta = 0.15$, $P = 0.2$, $R^2 = 0.24$).

5.3 Study II

Study participant characteristics are found in Table 3.

Machine learning using the updated PPG feature set, which included 17 new features, revealed that the new feature ”Am b/Am p1” was a principal predictor of both cfPWV and aoPWV (Figure 6).

“Am b/Am p1” also showed strong linear correlations with these measures (Figure 7). “Am b/Am p1” is based on a new way of defining the first peak, “p1”, in the PPG waveform (Figure 1).

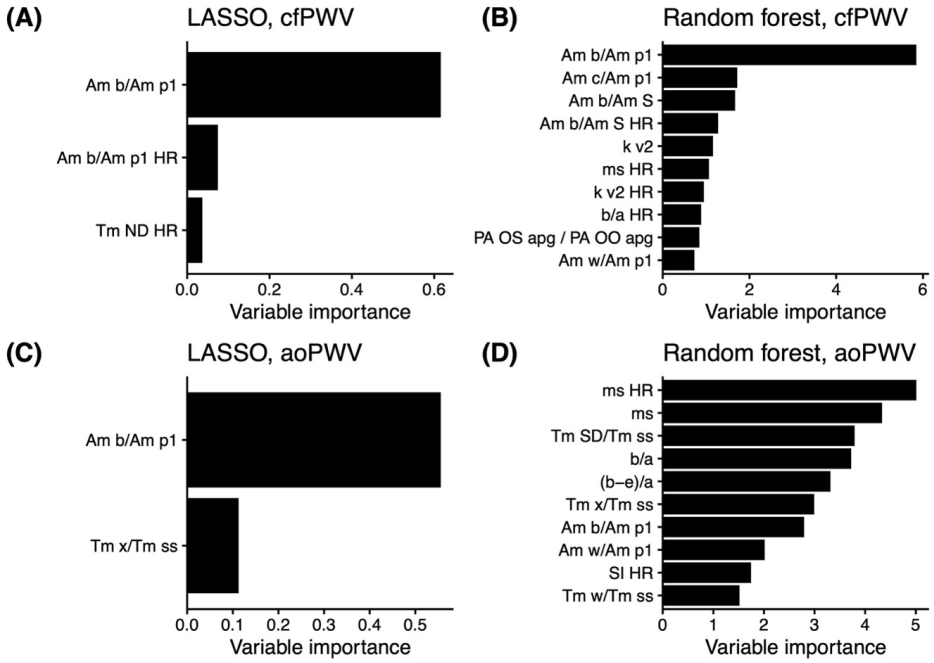

Figure 6. Variable importance from machine learning using the updated photoplethysmography (PPG) feature set in (A) LASSO and (B) random forest predicting cfPWV, and (C) LASSO and (D) random forest predicting aoPWV. Up to 10 features are shown for each model. For PPG features, see Supplementary Table S1 in (II) for details. LASSO, least absolute shrinkage and selection operator; HR, normalised for heart rate. From (II).

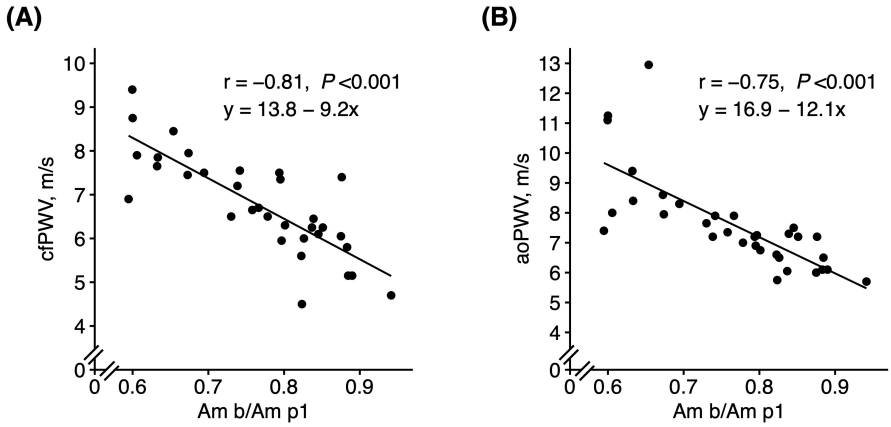

Figure 7. The new photoplethysmography feature "Am b/Am p1" correlated with (A) cfPWV and (B) aoPWV using mean values from visits 1 and 2. Pearson's r with *P* values and simple linear regression lines with formulas are shown. cfPWV, carotid–femoral pulse wave velocity (PWV) by SphygmoCor, aoPWV, aortic PWV by Arteriograph; "Am b/Am p1", an amplitude ratio – see Supplementary Table S1 in (II) for details. From (II).

Linear regression using only "Am b/Am p1" achieved test performance for cfPWV (RMSE 0.76, R^2 0.71), which was comparable to the best-performing complex model (LASSO, RMSE 0.70, R^2 0.74). For aoPWV, linear regression using only "Am b/Am p1" achieved the best test performance among all models (RMSE 0.52, R^2 0.92). Adding NPAT marginally improved cfPWV test performance (linear regression RMSE 0.72, R^2 0.68 versus RMSE 0.76, R^2 0.71 without NPAT) but had no effect on aoPWV test performance (linear regression RMSE 0.52, R^2 0.92 with or without NPAT).

The reference methods showed between-visit repeatability with $r^2 = 0.78$ for cfPWV and $r^2 = 0.81$ for aoPWV, and agreement between cfPWV and aoPWV was $r^2 = 0.60$.

5.4 Study III

In all, 141 patients were included in the final analysis. Patient characteristics are found in Table 3. Thirty-seven (26%) had a family history of premature CAD and the primary outcome, CAD-RADS ≥3, was present in 22 (16%) of the patients.

Referrals for CCTA came from the emergency department (5%), chest pain unit (21%), inpatient ward (24%), and outpatient clinics (50%).

RF-CL models demonstrated moderate discriminatory ability for CAD-RADS ≥3, the PTP model the lowest, and CACS-CL models the highest (Figure 8A).

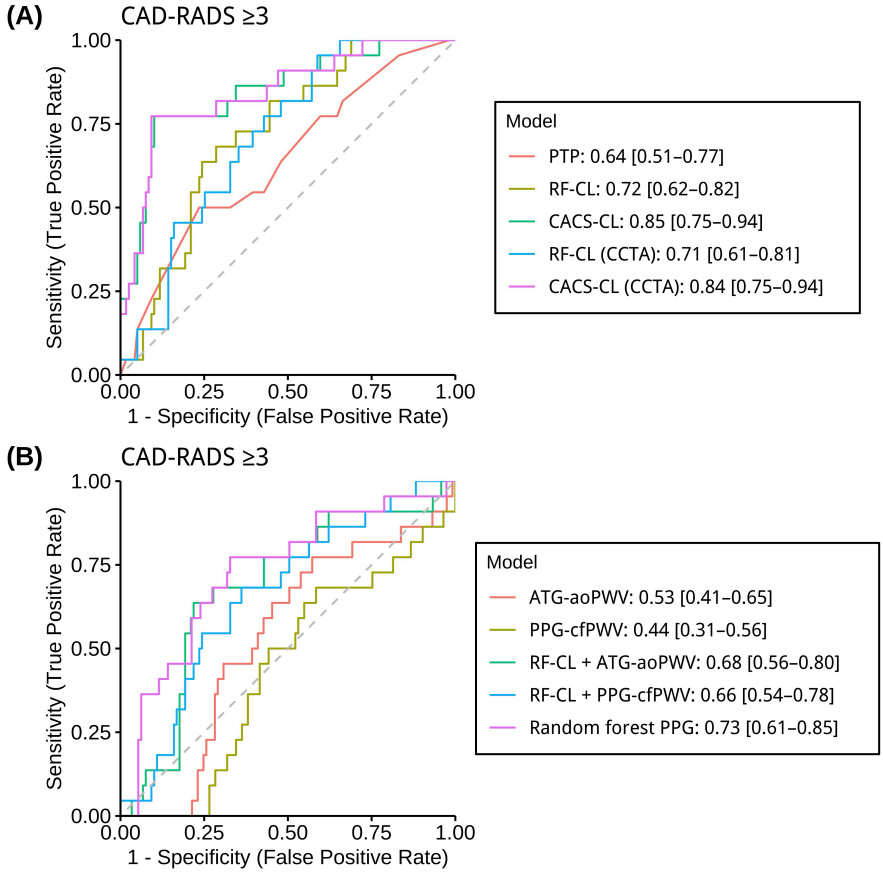

Figure 8. Receiver operating characteristic curves for models predicting CAD-RADS ≥3 for (A) external models and (B) developed models in the present study, showing area under curve value with 95% confidence interval. Developed models were evaluated using repeated cross-validation. PTP, pretest probability; RF-CL, risk factor-weighted clinical likelihood; CACS-CL, coronary artery calcium score-weighted clinical likelihood. "(CCTA)" represents models that were calibrated for coronary computed tomography angiography. ATG-aoPWV, aortic pulse wave velocity (PWV) by Arteriograph (ATG); PPG-cfPWV, carotid–femoral PWV estimated by photoplethysmography (PPG). From (III).

The differences in AUC between RF-CL and CACS-CL (P = 0.012) and between PTP and CACS-CL (P < 0.001) were statistically significant, whereas the difference between PTP and RF-CL (P = 0.058) was not. There were minimal differences between the standard RF-CL and CACS-CL models compared to those that were CCTA-calibrated (data not shown).

Data on ATG-aoPWV were available for 139 subjects, and on PPG, including PPG-cfPWV, for 135 subjects. The arterial stiffness measures aoPWV and PPG-cfPWV

were not independently predictive of CAD-RADS ≥3, and adding them to the RF-CL model did not improve the prediction of CAD-RADS ≥3 (Figure 8B).

In all, 155 PPG features were extracted (Paper II, Supplementary Table S1, with the addition of PPG-cfPWV).

After removal of nine features with low variance, 146 features were evaluated using the Boruta machine-learning algorithm, revealing three features that were significantly important in prediction of CAD-RADS ≥3. These features were the waveform area "Ar OS" (onset "O" to "S") the waveform area ratio "IPA" (the ratio between the PPG areas A_2 and A_1(60), and the time span variable "Tm N" (onset to "N") (Figure 1). The PPG model with the highest discriminatory performance was a random forest model based on these three PPG features, providing an AUC of 0.73 (95% CI 0.61–0.85), which was comparable to and not statistically different from the RF-CL model (AUC 0.72 [0.62–0.82]; *P* = 0.9) (Figure 8A–B).

5.5 Study IV

In total, 102 patients participated, of whom 99 underwent ABPM and were included in the analysis (Figure 4). Patient characteristics are found in Table 3. Heart failure was present in 17 (18%) patients. STEMI (47, 48%) and NSTEMI (non-STEMI) (50, 52%) were equally common, and estimated glomerular filtration rate (eGFR) was 89 ± 15 ml/min/1.73 m².

According to blood pressure phenotype in 96 patients with valid 24-h measurements, 59 (61%) had normotension, 5 (5%) white-coat hypertension, 17 (18%) masked hypertension, and 15 (16%) sustained hypertension. All participants were on at least one antihypertensive medication at the time of ABPM and were therefore considered uncontrolled if having hypertension by ABPM (classified as either sustained uncontrolled hypertension or MUCH). Uncontrolled hypertension was observed in 32 (33%) participants for the 24-h period.

Machine learning analysis for prediction of MUCH and uncontrolled hypertension included 94 patients (registry data was missing for two patients; Figure 4). Sixty-two clinical variables were eligible for machine learning after filtering.

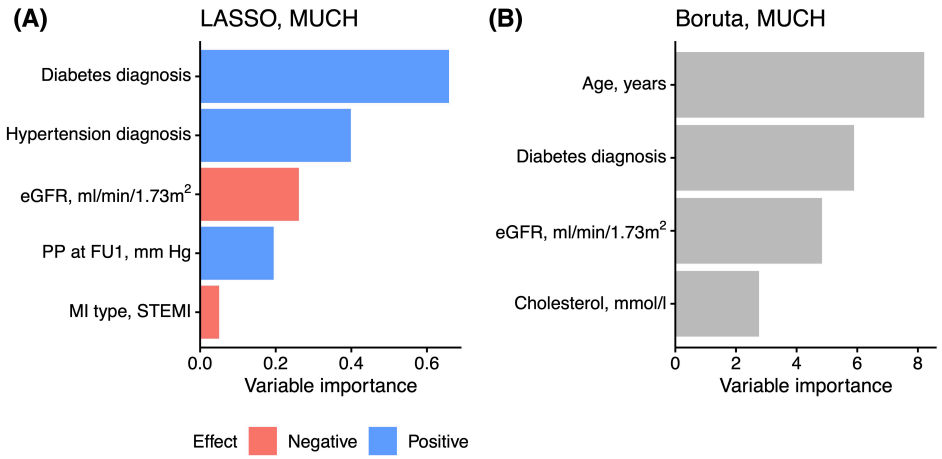

Figure 9. Predictors of masked uncontrolled hypertension (MUCH) identified by (A) LASSO and (B) Boruta. Variable importance scores are shown on relative scales, and for LASSO effect direction is indicated. Myocardial infarction (MI) type refers to STEMI (ST-elevation MI) or NSTEMI (non-ST-elevation MI), and cholesterol denotes total cholesterol. LASSO, least absolute shrinkage and selection operator; eGFR, estimated glomerular filtration rate; PP, pulse pressure; FU1, first follow-up. From (IV).

The discharge diagnoses diabetes and hypertension, eGFR, pulse pressure at first follow-up, MI type, age, and total cholesterol levels were identified as predictors of MUCH by LASSO and Boruta (Figure 9A-B). All 127 combinations of these variables were subsequently evaluated in additional modelling (Table 4).

The highest mean cross-validation AUC was given by a random forest model with the variables discharge diagnoses diabetes and hypertension, eGFR, and age, which provided a sensitivity of 0.94, specificity of 0.66, a positive predictive value of 0.38, and a negative predictive value of 0.98 (Table 4). Comparable discriminatory ability was seen for a logistic regression model using diabetes, hypertension and eGFR as predictors. These predictors were part of most models with the highest discriminatory ability (Table 4).

Table 4. Prediction of masked uncontrolled hypertension post-myocardial infarction

Algorithm	Predictors	CV AUC	Sens	Spec	PPV	NPV
Random forest	Diabetes; Hypertension; eGFR; Age	0.82	0.94	0.66	0.38	0.98
Random forest	Diabetes; eGFR; Age	0.81	0.94	0.57	0.33	0.98
Random forest	Diabetes; Hypertension; eGFR; Age; Cholesterol	0.81	0.88	0.69	0.38	0.96
Random forest	Diabetes; eGFR; Age; Cholesterol	0.81	0.65	0.88	0.55	0.92
Random forest	Diabetes; Hypertension; eGFR; MI type; Age	0.80	0.76	0.73	0.38	0.93
Logistic regression	Diabetes; Hypertension; eGFR	0.80	0.88	0.65	0.36	0.96
LASSO	Diabetes; Hypertension; eGFR	0.80	0.88	0.65	0.36	0.96
LASSO	Diabetes; Hypertension; eGFR; MI type	0.79	0.71	0.77	0.40	0.92
Logistic regression	Diabetes; Hypertension; eGFR; MI type	0.79	0.71	0.77	0.40	0.92
LASSO	Diabetes; eGFR	0.79	0.82	0.68	0.36	0.95
Logistic regression	Diabetes; eGFR	0.79	0.82	0.68	0.36	0.95
Logistic regression	Diabetes; Hypertension; eGFR; Cholesterol	0.79	0.76	0.73	0.38	0.93
LASSO	Diabetes; Hypertension; eGFR; Cholesterol	0.78	0.76	0.73	0.38	0.93
LASSO	Diabetes; eGFR; PP at FU1	0.78	0.71	0.77	0.40	0.92
Logistic regression	Diabetes; eGFR; PP at FU1	0.78	0.71	0.77	0.40	0.92

Prediction of masked uncontrolled hypertension based on all combinations of predictors identified by LASSO and Boruta. The list shows mean repeated cross-validation (CV) receiver operating characteristic (ROC) area under the curve (AUC) for the top five models for each algorithm. Additional ROC curves were constructed using the mean predicted probability for each observation, and the threshold at maximum Youden's index were used to calculate the performance metrics sensitivity (Sens), specificity (Spec), positive predictive value (PPV), and negative predictive value (NPV). Diabetes and hypertension denote diagnoses at discharge. eGFR, estimated glomerular filtration rate; MI, myocardial infarction; LASSO, least absolute shrinkage and selection operator; PP, pulse pressure; FU1, first follow-up. Adapted from (IV).

In prediction of uncontrolled hypertension, the predictors identified by LASSO and Boruta were discharge diagnoses of diabetes and hypertension, level of physical activity, and systolic blood pressure and pulse pressure at the first follow-up. The highest mean cross-validation AUC (0.76) was seen for a random forest model using discharge diagnosis of diabetes, level of physical activity, and systolic blood pressure and pulse pressure at the first follow-up as predictors, yielding a sensitivity of 0.87, specificity of 0.63, positive predictive value of 0.54, and negative predictive value of 0.91.

6 Discussion

6.1 Overnight stiffness index – an improved finger PPG-based measure for assessing cardiovascular risk and arterial stiffness

The novel OSI was associated with future cardiovascular morbidity and mortality as determined by two established cardiovascular risk scores. Additionally, OSI correlated with other markers of cardiovascular risk, including age, and systolic blood pressure dipping.

Furthermore, OSI related to several blood pressure-derived markers of arterial stiffness. The strongest correlation was observed for OSI and pulse pressure during sleep ($r = 0.47$), extending previous studies reporting correlations between daytime SI and pulse pressure (67-69).

OSI was associated with blood pressure levels, most notably systolic blood pressure. This finding extends previous studies that have demonstrated associations between daytime SI and systolic blood pressure (65, 67, 68).

Compared with the previously studied OPPT, OSI, which is the height-corrected OPTT, showed significantly higher correlations with systolic ABP, asleep diastolic blood pressure, and systolic blood pressure dipping. From a physiological perspective, the timing of the reflected peak should be related to body height, and adjusting for height would provide a more precise measure of arterial stiffness. All other blood pressure-derived measures were numerically higher for OSI, although the differences were not statistically significant. This may potentially be due to the limited sample size.

In summary, we found that OSI is an improved PPG-based measure of arterial stiffness that is associated with several indices of cardiovascular risk and arterial stiffness, as well as blood pressure levels. OSI may serve as a useful parameter for cardiovascular risk stratification based on overnight PPG recordings.

6.2 Brief finger PPG measurement for improved arterial stiffness assessment using enhanced features and machine learning

We applied a range of innovative approaches to use the PPG signal for improved arterial stiffness assessment. First, we established an enhanced way of identifying the first systolic peak "p1" in the PPG waveform, by analysing the simultaneous finger blood pressure curve. This has, to our knowledge, not been

done before. Second, we developed several new PPG features, primarily based on "p1", in addition to the established ones. Third, we accounted for the potential influence of heart rate on PPG features related to arterial stiffness by including heart rate-normalised features. Fourth, as repeated measurements were performed, we could assess PPG feature repeatability, and kept only the features with best repeatability in the machine learning analyses.

Machine learning revealed that the new amplitude ratio "Am b/Am p1" was an essential feature in the prediction of arterial stiffness. This feature showed stronger correlations with both cfPWV and aoPWV (r = -0.81 and -0.75, respectively), than previously reported for any individual PPG feature – the "spring constant" with cfPWV (r = -0.72) (70). "Am b" represents the PPG amplitude at the acceleration point "b", and "Am p1" the PPG amplitude of "p1", the first systolic peak, identified with our new method. These features are both located at the beginning of the PPG waveform, and their ratio may characterise a resistance in the aorta during systole.

Our best prediction models demonstrated test performance comparable to the repeatability and agreement for the two reference methods. Moreover, our models showed better predictive performance, as compared to other studies that used biosignals requiring more advanced sensors, such as cfPWV predicted with the carotid artery pressure waveform (RMSE 1.12 m/s) (129), or from the radial artery pressure waveform (RMSE 1.82 m/s) (130).

Adding NPAT did not significantly improve model performance, suggesting that the arterial stiffness information is already well represented in the PPG signal.

In summary, we developed an enhanced way of estimating arterial stiffness using only a brief daytime finger PPG recording, without the need for any other information or equipment. This may facilitate a broader implementation of PPG-based arterial stiffness assessment.

6.3 Arterial stiffness and photoplethysmography in suspected new-onset symptomatic chronic coronary syndrome

Arterial stiffness, assessed as aoPWV by the Arteriograph and estimated from the PPG signal (PPG-cfPWV), did not provide predictive information on obstructive CAD in patients with suspected new-onset symptomatic CCS. Despite the known links between arterial stiffening and atherosclerosis development, arterial stiffness did not reflect coronary atherosclerosis in a

relevant way in this specific clinical application. There may be explanations for this finding.

Compared with other studies which previously have shown predictive value of arterial stiffness assessment in investigation of suspected CAD (91), our study evaluated obstructive stenosis on CCTA, and not by invasive coronary angiography, which previously has been most common (91). CCTA provides high sensitivity and high negative predictive value to rule out obstructive CAD, but it is known to sometimes overestimate the degree of stenosis (131). Furthermore, patients who are scheduled for coronary angiography normally have a higher pretest probability of obstructive CAD, in comparison to subjects who undergo a diagnostic test with CCTA, as in our study. In addition, most of the previous studies predominantly used baPWV (only one out of eight used cfPWV) (91), which limits direct comparisons with our findings. The study using cfPWV had coronary angiography results as outcome (92), which also prevents a direct comparison.

Nevertheless, it remains possible that other direct, or improved indirect measures of arterial stiffness, or studies with larger sample sizes, could demonstrate a value of assessing arterial stiffness in this clinical context. Regardless, the prognostic information gained from an arterial stiffness assessment could be valuable for optimising preventive strategies in these patients.

Interestingly, a machine learning-based evaluation showed that three PPG features in a random forest model demonstrated a discriminatory performance comparable to the RF-CL model (AUC = 0.73 vs. 0.72). The PPG signal reflects vascular structure and haemodynamic function, which seem to provide critical information in this application. Potentially, PPG may also offer a more robust and objective assessment, without the need for collection of risk factor information or interpretation of symptom descriptions.

In summary, arterial stiffness was not predictive of obstructive CAD in patients with suspected new-onset CCS. However, utilising three features from a brief finger PPG recording provided discriminatory ability on par with the RF-CL model, suggesting that PPG could be useful for objective and rapid risk stratification.

6.4 Prediction of masked uncontrolled hypertension post-myocardial infarction

The prevalence of both uncontrolled hypertension (one in three) and MUCH (one in five) was high in patients with a recent MI.

The discharge diagnoses diabetes and hypertension, together with eGFR and age, provided the highest mean cross-validation AUC in a random forest model. Notably, a less complex logistic regression model omitting age but incorporating diabetes, hypertension and eGFR, demonstrated comparable performance, indicating that these predictors alone provide sufficient discriminatory ability.

The central role of these three predictors may be explained by previous knowledge. Diabetes has been shown to be associated with masked hypertension (132), potentially due to increased arterial stiffness, which previously has been associated with masked hypertension (29, 133). Arterial stiffening leads to greater blood pressure variability, which may reduce the reliability of occasional office blood pressure measurements. In line with this, pulse pressure was also identified as an important predictor of MUCH. Kidney dysfunction (low eGFR) has previously been associated with masked hypertension and MUCH (132, 134, 135). Possible mechanisms include a predisposition to nocturnal hypertension (135), and increased arterial stiffness due to accelerated vascular ageing (29). Both kidney dysfunction and diabetes increase sympathetic activity (136, 137), leading to exaggerated blood pressure response during physical activity and stress. The presence of a hypertension diagnosis has also previously been associated with MUCH (132). It may contribute to MUCH prediction because office blood pressure is usually measured during daytime, at the peak effect of antihypertensive treatment, which is commonly taken in the morning (123). Consequently, office blood pressure is more likely to be normal, whereas potentially elevated evening, night-time, or morning blood pressure values contribute to the MUCH phenotype.

The predictors revealed in our study were different (except for pulse pressure) from three previous studies using clinical variables to predict masked hypertension or MUCH (138-140). Key predictors in those studies included office systolic, mean, and diastolic blood pressure, pulse pressure, stroke, dyslipidaemia, left ventricular hypertrophy, heart rate, number of antihypertensive drugs, beta-blocker use, high density lipoprotein cholesterol, male sex, smoking and high–normal clinic blood pressure (138-140). These

differences may be explained through variations in cardiovascular characteristics between patients with established CVD, as in our study, and subjects with lower cardiovascular risk, who participated in the other studies.

The best model predicted MUCH with an AUC of 0.82, which is generally considered to indicate excellent discriminatory ability (141), and provided a high sensitivity and high negative predictive value.

In the prediction of uncontrolled hypertension (*i.e.,* both sustained uncontrolled hypertension and MUCH), the best model provided an AUC of 0.76 , which still represents an acceptable discriminative ability (141). This model included the predictors diabetes, level of physical activity, and systolic blood pressure and pulse pressure at the first follow-up. There was an overlap among predictors, which can be explained by the fact that the majority with uncontrolled hypertension also had MUCH.

In summary, the clinically challenging blood pressure phenotype MUCH was common after a recent MI. Importantly, MUCH may be predicted using the discharge diagnoses diabetes and hypertension, and kidney dysfunction. A machine learning model could aid in identifying MUCH among patients after MI and may be implemented as a clinical decision support tool.

6.5 Limitations

Our studies have several important limitations.

In Study I, OSI was studied in relation to risk estimates derived from cardiovascular risk scores rather than hard endpoints. Furthermore, the blood pressure-derived indices of arterial stiffness (pulse pressure and AASI) with which OSI-associations were studied, are indirect methods of arterial stiffness assessment. However, no direct methods to assess arterial stiffness overnight currently exist. Nevertheless, both pulse pressure and AASI provide cardiovascular prognostic information (54, 55).

In Study II, machine learning was performed using a small sample size and validated on a small test set. In Study III and IV internal validation with repeated cross-validation was conducted. Cross-validation typically provides reasonable estimates of how well models generalise to new data. Ideally, however, our models should be validated in external datasets. Related to this, the comparison of external PTP, RF-CL, and CACS-CL models with those developed in Study III, which were evaluated using cross-validation, does not allow for a comprehensive assessment.

In Study IV, a known limitation is the limited reproducibility of masked hypertension and MUCH (142).

In all studies, the sample sizes were relatively small, and in Study I and IV, there were more men than women. Furthermore, the range of PWV values among participants in Study II was limited, and the number of patients with obstructive CAD and MUCH were also limited in Study III and IV. Taken together, these factors may affect the generalisability of the results and models.

7 Conclusions

1. OSI is an improved overnight finger PPG-based marker of cardiovascular risk and vascular ageing, associated with several indices of cardiovascular risk and arterial stiffness, as well as blood pressure levels.

2. Arterial stiffness can be effectively estimated from a brief finger PPG recording by using enhanced features and machine learning approaches.

3. Arterial stiffness, assessed using a single cuff-based device or estimated from PPG, is not predictive of obstructive CAD in patients with suspected new-onset symptomatic CCS.

4. A machine learning model based on three features from the finger PPG signal demonstrates discriminatory performance comparable to clinical prediction models for obstructive CAD in patients with suspected new-onset symptomatic CCS.

5. Our studies confirm the potential of using PPG for rapid and objective risk stratification, enabling assessment through PPG-based consumer wearable devices.

6. The blood pressure phenotype MUCH is common at follow-up after MI.

7. MUCH after a recent MI and can be predicted using the discharge diagnoses diabetes and hypertension, and kidney dysfunction.

8. A machine learning model could aid in identifying MUCH among patients after MI and may be implemented as a clinical decision support tool.

In summary, this thesis has shown improved methods to assess arterial stiffness with the simple finger PPG method. Machine learning was successfully applied to PPG signals and clinical variables to enhance arterial stiffness estimation, and to identify obstructive CAD in patients with suspected new-onset CCS and MUCH after MI. These findings confirm the potential value of using the widely accessible PPG method and machine learning for cardiovascular risk stratification.

8 Points of perspective

8.1 Leveraging utilisation of the PPG signal in the cardiovascular field

This thesis further establishes PPG as a promising method for cardiovascular assessment and risk stratification. The widespread availability and simplicity of PPG sensors in both medical and consumer wearable devices give PPG-based assessment a tremendous potential (52).

Wearable devices, such as smart rings and smart watches, enable continuous data collection, including during sleep, which may provide more robust assessments (143, 144). In fact, these devices can already assess, for instance, atrial fibrillation, heart rate variability, blood oxygenation, and estimate blood pressure with good accuracy (145). Such devices could easily incorporate measures like OSI from Study I or further improved assessment of arterial stiffness as demonstrated in Study II. Furthermore, modern PPG-based techniques may employ multi-wavelength sensors with higher temporal resolution than that was used in our studies, thereby improving the robustness and quality of the recorded signals.

Using consumer wearables for assessment in broad populations may promote patient engagement and help overcome both patient and physician inertia in cardiovascular assessment. In addition, wearable-based assessment enable collection of larger amounts of data, facilitating the development of better prediction models (112). Furthermore, collecting data in the individual's everyday environment instead of at the clinic will likely provide better prognostic information, as has been shown for out-of-office versus office blood pressure measurements (10).

Interestingly, broader utilisation of peripheral pulse wave analysis-based methods, such as PPG, could in fact be seen as a return to the roots, considering that pulse wave characteristics have historically played an important role in cardiovascular assessment (40).

8.2 Machine learning using PPG or clinical data for improved cardiovascular risk stratification

Machine learning models learn from historical data to predict information that is not directly available. Cardiovascular examples include prediction of outcomes or conditions, the estimation of biosignal parameters, and the assessment of imaging data.

The machine learning models developed in Study II provide estimates from a simple sensor (finger PPG) of a vascular biomarker (PWV) obtained using complex reference equipment. Likewise, in Study III, we used a simple sensor (finger PPG) to predict outcomes derived from highly specialised equipment and procedures (obstructive CAD on CCTA). Recent advances in machine learning and AI, enabling learning directly from raw signals (without the additional step of feature extraction), will further support the optimal utilisation of such data in the future (52, 112, 144).

The MUCH prediction modelling in Study IV exemplifies the prediction of a clinical characteristic that may remain undetected and lead to undertreatment of blood pressure in patients who already face a very high cardiovascular risk. Thus, the potential benefit of introducing this type of model in clinical practice could be substantial. In addition, such models are based on clinical characteristics available in the electronic medical records or clinical registries, which could facilitate simple implementation, since suitable technological platforms already exist. However, certain challenges can be identified with regards to their implementation.

First, to utilise the best-performing models, which in Study IV was a tree-based random forest model, we must accept that the model may not be fully explainable or interpretable, often referred to as "black-box" model (111). Nevertheless, there are ways to gain insight on how also more complex models work, as demonstrated in (III) where we used specific plots to enhance interpretability (146).

Second, issues of responsibility need to be addressed. In general, prediction models implemented as clinical decision support tool software, are subject to regulations for medical devices (147). This may contribute to the underutilisation of prediction models in general, and of more complex models in particular, which cannot easily be translated to tabular scoring system. Models can also be made

available on webpages as online calculators. However, this approach is impractical and prone to errors when data must be entered manually.

Third, the reliability of prediction models must be ensured across different populations and over time. Models require continuous monitoring and may need recalibration or retraining if population characteristics or input data change (148).

In summary, we successfully applied machine learning to PPG for both the estimation of arterial stiffness and the diagnosis of obstructive CAD. Furthermore, we developed machine learning models to identify MUCH. Implementation of such a model may improve blood pressure control after MI, although this may be subject to specific legal requirements.

8.3 Implementation of arterial stiffness assessment in clinical practice

The potential for wider future clinical implementation of arterial stiffness assessment may be addressed through the following observations.

First, as described, most arterial assessment methods are time-consuming and require specialised equipment and training. To date, this has been considered a major obstacle for a widespread implementation in clinical practice. However, the development of new, easier-to-use methods can be expected. Although these methods may not be as precise as traditional ones, they may still provide information sufficient to support clinical decisions (2).

Second, some relatively easy-to-use, established assessment methods already exist, including various cuff-based methods. Despite this, few clinicians perform specific arterial stiffness assessments as part of routine care (149). The added information on vascular health and cardiovascular risk obtained by arterial stiffness assessment, beyond traditional risk factor evaluation, does not currently appear sufficient to drive clinical implementation. Likely, a few well-defined use cases with clearly demonstrated clinical benefits would have led to faster method development and implementation.

Third, substantial educational efforts focused on the concepts of arterial stiffness, vascular ageing, EVA, and their assessment methods are needed. Increased knowledge would help clinicians and patients to embrace new methods, interpret results and take the best clinical actions for the individual being assessed. Such educational initiatives have, among other important

activities, recently been undertaken by the "VascAgeNet – A Network for Research in Vascular Ageing", supported by the European Union (150).

In hypertension, the recent 2024 ESC Guidelines for the management of elevated blood pressure and hypertension (11), suggest that assessment of PWV, among other risk decision tests, may be considered in apparently healthy individuals with elevated blood pressure and with borderline increased 10-year CVD risk (5% – <10% risk). If PWV is increased (>10 m/s for cfPWV), indicating HMOD, pharmacological blood pressure treatment should be initiated for subjects with ≥130/80 mm Hg after three months of lifestyle changes (11). This represents an example of a rather clearly defined use-case for arterial stiffness assessment. Of note, however, although such cut-off values are practical, clinicians should be able to make personalised assessments (151).

Fourth, although there are pathophysiological overlaps between arterial stiffening (mainly due to arteriosclerosis) and atherosclerosis, there may be clinical applications where assessing arterial stiffness provides greater value than applications focusing on atherosclerotic disease. Such applications may be more closely related to the pathophysiology of arterial stiffening or to organs that are susceptible to its adverse effects. These could include the development or management of hypertension, heart failure, kidney failure, dementia, and preeclampsia (9, 152). In this context, in Study III, where we evaluated arterial stiffness assessment in the investigation of obstructive CAD in patients with suspected symptomatic new-onset CCS, we found no added value in this specific application.

Notably, Study III was an example of arterial stiffness assessment in relation to the outcome of an advanced diagnostic examination (being complicated or that carries potential negative consequences). Similar applications may be valuable for arterial stiffness assessment as a complement to primary or secondary prevention settings, which may require long-term follow-up to demonstrate clinical benefit.

Fifth, arterial stiffness may be used for monitoring therapeutic interventions targeting the cardiovascular system, which could also improve patient engagement and motivation. In serial measurements, however, one need to consider factors that may influence the measurement results and cause variability (153).

Sixth, clinical implementations require contemporary, established reference values across broad populations and for different methods (9). Such efforts are ongoing, and recently, The Youth Vascular Consortium database was used to define reference values for arterial stiffness in healthy young individuals between one and 40 years of age (154). In relation to this, the various available assessment methods require standardisation and validation. Recently, updated recommendations on validation of devices measuring PWV have been provided (44).

Seventh, another observation concerns the threshold at which a new vascular biomarker, such as arterial stiffness, should be recommended for clinical practice. One could argue that such a biomarker should demonstrate improved outcomes in randomised controlled trials, among several other criteria, as thoroughly described by Vlachopoulos et al (155). However, not even the use of out-of-office blood pressure (home blood pressure and ABPM) has been evaluated in randomised controlled trials for outcome improvement. Nevertheless, out-of-office blood pressure is widely recommended in current guidelines (156), supported by strong circumstantial evidence. Thus, the questions of when, how and in which clinical applications a new vascular biomarker should be implemented, require continued discussions. Such implementation may be justified by circumstantial evidence while awaiting results from large, well-designed studies. Consideration should also be given to the many individuals who seek additional information about their cardiovascular health, which may be facilitated through consumer devices.

In summary, easy-to-use and accessible methods for arterial stiffness assessment are still largely lacking, although new and simpler methods may emerge. Challenges remain regarding education on the concepts of vascular ageing and arterial stiffness, as well as the establishment of reference values and standardisation of assessment methods. Further studies are needed to evaluate the potential benefits of implementing arterial stiffness assessment in clinical practice.

9 Acknowledgements

I want to express my sincere gratitude to all participants, colleagues and collaborators who have been involved in the studies, and who have made this thesis possible.

I especially would like to thank:

Jonas Spaak, my principal supervisor, for introducing me to the field of vascular biomarkers and for generously sharing your deep scientific knowledge. Your strong support, guidance, and the time you have always taken for me have been truly invaluable.

Thomas Kahan, my co-supervisor, for offering your great expertise and experience. You have provided excellent support throughout my path of becoming a researcher.

Hermine Rietz, **Ludger Grote**, **Jan Hedner**, **Dirk Sommermeyer,** co-authors, for inspiring collaboration and great discussions.

Mikael Karlsson, co-author and collaborator, for pleasant and successful teamwork, and **Johan Hoffman**, co-author, for rewarding discussions.

Henrik Löfmark, for your collaboration in Study III, as co-author and for help with patient recruitment, and for being a valued colleague.

Faris Al-Khalili, for great collaboration and as co-author, and **David Erlinge**, **Bertil Lindahl**, **Tomas Jernberg**, **Jonas Oldgren**, **Stefan James**, for fruitful cooperation as co-authors.

Jeanette Kuhl, my mentor, for your support and greatly appreciated friendship throughout the years.

Tomas Jernberg, head of department, **Johan Engdahl**, director of doctoral studies, **Nina Ringart**, administrative officer, and **Yunzhang Wang**, statistician, at the Department of Clinical Sciences, Danderyd Hospital, for essential support throughout my doctoral training.

Håkan Wallén, my former clinical supervisor and previous director of doctoral studies, for valuable guidance throughout the years.

Peter Giesecke, head of the Department of Cardiology, and **Karin Knudsen Malmqvist**, former head of the Department of Cardiology, for providing a great workplace and a unique environment for research. **Fadi Jokhaji,** head of specialist physicians, for being a trusted colleague and manager. **Viveka Frykman Kull**, former head of specialist physicians and former head of resident physicians, for providing great support in my clinical career, and for encouraging my research activities. **Mika Skeppholm**, former head of resident physicians, for being a wise manager and colleague.

Colleagues **Viktor Taune** and **Ramtin Vedad**, and numerous nurses at the Chest Pain Unit, for great help in recruitment of patients for Study III.

All colleagues and friends at the clinic, for creating an atmosphere combining professionalism and joy. Special thanks to my old roommates **Chalak Amiri**, **Erik Anesäter**, **Helge Brandberg**, **Magnus Lundbäck**, and the great teams in the ischaemia and interventional cardiology departments.

Beatrice Eriksson, **Jenny Holmlund**, and **Nassrin Wandy Karlsson**, for professional administrative support and helpfulness throughout the years.

The late **Gunnar Adolfsson,** my kind-hearted secondary school biology teacher. You asked me to send a message when I had finished my doctoral studies. I hope you receive this greeting somehow.

All my friends, thank you for your encouragement and all good times along the way.

My parents, **Inger** and **Göran**, for being fantastic and supportive in all aspects of life. My brothers, **Rikard** and **Oskar**, for always being there and for your constant support. **My extended family**, for your kindness and encouragement.

My wife, **Maria** for endless unconditional support and love. Without you, none of this would have happened.

My children, **Greta**, **Albert**, and **Julia**, for being such wonderful persons. You truly mean everything.

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