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Acute, ambulatory and central blood pressure measurements in diabetes

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To my cousin Andy

“Found I had a thirst that I could not quell
Lookin´ for the water from the deeper well”

Emmylou Harris

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ABSTRACT

Background: In patients with diabetes, high blood pressure is an established risk factor for cardiovascular disease. The aim of this thesis was to explore the associations between blood pressure levels measured with different techniques and during different circumstances, and the degree of cardiovascular organ damage and subsequent prognosis in patients with diabetes.

Methods: We analysed baseline data from patients with type 2 diabetes who participated in the observational cohort study CARDIPP (Cardiovascular Risk factors in Patients with Diabetes – a Prospective study in Primary care), and longitudinal data from patients registered in the Swedish national quality registry RIKS-HIA (Register of Information and Knowledge about Swedish Heart Intensive care Admissions). Patients in CARDIPP underwent nurse-recorded, 24-hour ambulatory and non-invasive central blood pressure measurements. Patients in RIKS-HIA had their systolic blood pressure measured upon hospitalisation for acute chest pain.

Results: In CARDIPP, nearly one in three patients with office normotension (<130/80 mmHg) were hypertensive during the night (≥120/70 mmHg). This phenomenon, masked nocturnal hypertension, was significantly associated with increased arterial stiffness and increased central blood pressure. Furthermore, nearly one in five CARDIPP patients with office normotension had high central pulse pressure (≥50 mmHg), and there was a significant association between high central pulse pressure and increased carotid intima-media thickness and increased arterial stiffness. Among CARDIPP patients who used at least one antihypertensive drug, those who used beta blockers had significantly higher central pulse pressure than those who used other antihypertensive drugs, but there were no significant between-group differences concerning office or ambulatory pulse pressures. In CARDIPP patients with or without antihypertensive treatment, ambulatory systolic blood pressure levels were significantly associated with left ventricular mass, independently of central systolic blood pressure levels. When RIKS-HIA patients, admitted to hospital for chest pain, were stratified in quartiles according to admission systolic blood pressure levels, the risk for all-cause one-year mortality was significantly lower in patients with admission systolic blood pressure in the highest quartile (≥163 mmHg) than in patients with admission systolic blood pressure in the reference quartile (128-144 mmHg). This finding remained unaltered when the analysis was restricted to include only patients with previously known diabetes.

Conclusions: In patients with type 2 diabetes, ambulatory or central blood pressure measurements identified patients with residual risk factors despite excellent office blood pressure control or despite ongoing antihypertensive treatment. Ambulatory systolic blood pressure predicted left ventricular mass independently of central systolic blood pressure. In patients with previously known diabetes who were hospitalised for acute chest pain, there was an inverse relationship between systolic blood pressure measured at admission and the risk for one-year all-cause mortality.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Såväl hypertoni (högt blodtryck) som diabetes medför ökad risk att drabbas av kardiovaskulär sjukdom (hjärt-kärlsjukdom). När bägge dessa riskfaktorer förekommer samtidigt, ökar den kardiovaskulära risken påtagligt. Det traditionella sättet att mäta blodtrycket är att, under vilobetingelser på en sjukvårdsmottagning, mäta blodtrycket i överarmen. Detta sätt att mäta blodtrycket är emellertid behäftat med ett flertal möjliga felkällor: dels speglar en enstaka mätning inte den blodtrycksnivå som individen exponeras för under hela dygnet, dels är det inte säkert att blodtrycket i överarmen motsvarar blodtrycket nära hjärtat, som sannolikt är mer betydelsefullt för risken att utveckla hjärtsjukdom. De delarbeten som ligger till grund för den här avhandlingen avser att beskriva två alternativa metoder för att mäta blodtrycket, nämligen 24-timmars ambulatorisk blodtrycksmätning samt central blodtrycksmätning, och hur dessa kan användas för att värdera graden av kardiovaskulär organskada bland personer med diabetes. Vidare beskrives hur blodtrycksvärden uppmätta i samband med sjukhusinläggning för akut bröstsmärta kan användas för att förutsäga prognosen hos personer med respektive utan diabetes.

Det är sedan tidigare känt att en del personer som har normalt blodtryck uppmätt på en sjukvårdsmottagning har för högt blodtryck under övriga delen av dagen. Det har emellertid inte tidigare beskrivits hur vanligt det är bland personer med normalt mottagningsblodtryck att ha för högt blodtryck på natten. I **delarbete I** undersökte vi därför 100 personer med typ 2-diabetes och normalt mottagningsblodtryck. Samtliga genomgick en ambulatorisk blodtrycksmätning, där blodtrycket uppmättes med en automatisk mätare var 20:e minut under minst 24 timmar. Vi fann att 30 av de 100 personerna hade förhöjt nattligt blodtryck. Dessa personer hade tecken till ökad stelhet i stora kroppspulsådern, vilket är en etablerad markör för ökad kardiovaskulär risk. Fynden visar att bland personer med typ 2-diabetes är det inte ovanligt att det nattliga blodtrycket är för högt även om mottagningsblodtrycket är normalt. Att detta fenomen, som vi kallade maskerad nattlig hypertoni, även visade sig vara kopplat till ökad kärlstelhet talar för att dessa personer har ökad risk för att drabbas av hjärt-kärlsjukdomar, såsom hjärtinfarkt eller stroke.

Blodtrycksmätning i samband med planerad mottagningsverksamhet bör föregås av ett par minuters vila. Detta är sällan genomförbart på en akutmottagning. Bland personer som sjukhusvårdats för akut kranskärlssjukdom (instabil kärlkramp eller hjärtinfarkt) eller för akut hjärtsvikt har man tidigare kunnat visa att högt blodtryck vid ankomst till sjukhus är associerat med en minskad risk att avlida i anslutning till eller strax efter vårdtillfället på sjukhuset. I **delarbete II** studerade vi om detta även gällde för en stor grupp personer som blivit inlagda på sjukhus på grund av bröstsmärta, men där bakomliggande hjärtsjukdom inte alltid kunnat påvisas. Vi analyserade data från 119 151 personer som registrerats i det nationella kvalitetsregistret RIKS-HIA, varav 21 488 hade tidigare känd diabetes, och fann att ett högre ankomstblodtryck var associerat med en lägre risk att avlida inom ett år efter sjukhusvistelsen. Detsamma gällde i en separat analys av personerna som hade tidigare känd diabetes, och, intressant nog, även bland de personer där man under vårdtillfället inte kunde diagnostisera någon hjärtsjukdom som förklaring till bröstsmärtan. Dessa fynd visar att högt blodtryck, uppmätt i samband med sjukhusinläggning på grund av bröstsmärta, är kopplat till en god prognos. Resultaten belyser att blodtryck uppmätt i samband med bröstsmärta inte speglar den kardiovaskulära risken på samma sätt som ett viloblodtryck gör.

Såväl mottagningsblodtryck som ambulatoriskt uppmätta dygnsblodtryck bygger på att blodtrycket mäts i överarmen. Nya mätmetoder har emellertid möjliggjort beräkningar av det

hjärtnära blodtrycket, det så kallade centrala blodtrycket, med vilket avses blodtrycket i stora kroppspulsådern nära hjärtat. Tekniken bygger på att man utnyttjar det matematiska sambandet mellan formen på pulsvågskurvan i handledsartären, som kan mätas, och motsvarande pulsvågskurva i stora kroppspulsådern. Det centrala blodtrycket kan skilja sig från de blodtrycksvärden som uppmäts i överarmen, och vissa data talar för att risken att drabbas av hjärt-kärlsjukdom är starkare kopplad till centrala blodtrycksvärden än till blodtrycksvärden uppmätta i överarmen. En vanligt förekommande grupp av blodtryckssänkande läkemedel, beta-blockerare, har visat sig sänka det centrala blodtrycket sämre än de sänker blodtrycket i överarmen. Detta har visats i en stor läkemedelsstudie bland person med hypertoni, men det finns inga data som visar om samma sak gäller för personer med diabetes som inte ingår i läkemedelsstudier. I **delarbete III** undersökte vi därför 124 personer med typ 2-diabetes som behandlades med minst ett blodtryckssänkande läkemedel. De som använde en beta-blockerare, ensam eller i kombination med andra läkemedel, hade högre centralt blodtryck än de som använde andra sorters blodtryckssänkande läkemedel. Trots att det förelåg en skillnad avseende det centrala blodtrycket, så var både mottagningsblodtrycket och det ambulatoriska 24-timmarsblodtrycket mycket lika mellan grupperna.

Det har tidigare visats att högt centralt blodtryck identifierar personer med ökad risk att drabbas av hjärt-kärlsjukdom. Hur vanligt det är att ha högt centralt blodtryck trots ett normalt blodtryck uppmätt med konventionell metodik i överarmen, är emellertid inte känt, varför vi i **delarbete IV** mätte det centrala blodtrycket hos 167 personer med typ 2-diabetes som hade normalt blodtryck på mottagningen. Vi kunde påvisa högt centralt blodtryck hos 32 av dessa personer, alltså nära nog hos var femte person med normalt mottagningsblodtryck. Precis som var fallet med personerna med maskerad nattlig hypertoni i delarbete I, fann vi att personerna med högt centralt blodtryck hade tecken till ökad stelhet i stora kroppspulsådern. Vi fann vidare en statistisk koppling mellan förekomst av högt centralt blodtryck och förtjockning av halspulsådrorna, som är en annan etablerad markör för ökad risk att drabbas av hjärt-kärlsjukdomar, såsom hjärtinfarkt eller stroke.

Vänsterkammarhypertrofi (hjärtförstoring) är en vanlig konsekvens av hypertoni, och är även en väl etablerad riskfaktor för hjärtsjukdom. Det har tidigare visats att graden av vänsterkammarhypertrofi, uppmätt genom ultraljudsundersökning, är starkare kopplad till centralt blodtryck än till mottagningsblodtryck. Huruvida graden av vänsterkammarhypertrofi är starkare kopplad till centralt blodtryck än till blodtryck uppmätt under 24-timmars ambulatorisk blodtrycksmätning har emellertid inte studerats hos personer med diabetes. I **delarbete V** undersökte vi därför sambanden mellan graden av vänsterkammarhypertrofi och mottagningsblodtryck, ambulatoriskt uppmätt blodtryck och centralt blodtryck hos 460 personer med typ 2-diabetes. Vi fann att när ambulatoriskt uppmätta blodtryck analyserades tillsammans med centralt blodtryck, så var det endast det ambulatoriskt uppmätta blodtrycket som samvarierade med graden av vänsterkammarhypertrofi. När ambulatoriskt uppmätt blodtryck analyserades tillsammans med mottagningsblodtryck, så var det återigen endast det ambulatoriskt uppmätta blodtrycket som samvarierade med graden av vänsterkammarhypertrofi. Fynden talar för att ambulatoriskt uppmätt blodtryck erbjuder information om graden av vänsterkammarhypertrofi utöver vad som kan erhållas utifrån antingen mottagningsblodtryck eller centralt blodtryck.

Sammanfattningsvis visar fynden i denna avhandling att ett normalt mottagningsblodtryck hos en person med typ 2-diabetes inte utsluter möjligheten att antingen det nattliga blodtrycket eller det centrala blodtrycket är för högt. Vidare har vi visat att personer med typ 2-diabetes

som använder beta-blockerare kan ha högre centralt blodtryck än personer med typ 2-diabetes som använder andra slags läkemedel mot högt blodtryck, trots att mottagningsblodtryck och ambulatoriskt uppmätt blodtryck inte skiljer sig åt mellan grupperna. Vid en direkt jämförelse mellan mottagningsblodtryck, centralt blodtryck och ambulatoriskt uppmätt blodtryck hos personer med typ 2-diabetes, visade sig framför allt det ambulatoriska blodtrycket ha en oberoende association med graden av vänsterkammarhypertrofi. Högt blodtryck uppmätt i samband med akut sjukhusinläggning på grund av bröstsmärta var, till skillnad från vad vi tidigare vet om mottagningsblodtryck uppmätt i vila, kopplat till lägre risk för förtida död hos personer med eller utan diabetes. När man ska använda blodtrycksvärden för att värdera graden av organskada eller den framtida prognosen hos patienter med diabetes, måste man alltså ta hänsyn till både den mätmetod som använts, och till de förhållanden som rådde i samband med blodtrycksmätningen.

ABBREVIATIONS AND ACRONYMS

ABCD, Appropriate Blood Pressure Control in Diabetes

ACCORD, Action to Control Cardiovascular Risk in Diabetes

ACE, Angiotensin Converting Enzyme

ADVANCE, Action in Diabetes and Vascular disease: preterax and diamicron-MR Controlled Evaluation

AGE, Advanced Glycation End products

ARB, Angiotensin Receptor Blocker

ASCOT, Anglo-Scandinavian Cardiovascular Outcomes Trial

CAFE, Conduit Artery Function Evaluation

CARDIPP, Cardiovascular Risk factors in Patients with Diabetes – a Prospective study in Primary care

CAREFUL, Cardiovascular Reference Population

CI, Confidence Interval

DCCT, Diabetes Control and Complications Trial

DPP-4, Dipeptidyl-Peptidase 4

EDIC, Epidemiology of Diabetes Interventions and Complications

ESH, European Society of Hypertension

GLP-1, Glucagon-Like Peptide 1

HDL, High-Density Lipoprotein

HOPE, Heart Outcomes Prevention Evaluation

HOT, Hypertension Optimal Treatment

HR, Hazard Ratio

ICCU, Intensive Cardiac Care Unit

IDACO, International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes

IFG, Impaired Fasting Glucose

IGT, Impaired Glucose Tolerance

IMT, Intima-Media Thickness

LDL, Low-Density Lipoprotein

LIFE, Losartan Intervention For Endpoint reduction

LVH, Left Ventricular Hypertrophy

LVMI, Left Ventricular Mass Index

NADPH, Reduced Nicotinamide Adenine Dinucleotide Phosphate

NDR, National Diabetes Register

OGTT, Oral Glucose Tolerance Test

OR, Odds Ratio

PKC, Protein Kinase C

Q, Quartile

RIKS-HIA, Registry of Information and Knowledge about Swedish Heart Intensive care Admissions

T, Tertile

UKPDS, United Kingdom Prospective Diabetes Study

WHO, World Health Organization

LIST OF PAPERS

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

I. Wijkman M, Länne T, Engvall J, Lindström T, Östgren C J, Nystrom F H: **Masked nocturnal hypertension—a novel marker of risk in type 2 diabetes.** *Diabetologia* 2009; 52: 1258–1264.

II. Stenestrand U†, Wijkman M, Fredrikson M, Nystrom F H: **Association between admission supine systolic blood pressure and 1-year mortality in patients admitted to the intensive care unit for acute chest pain.** *JAMA* 2010; 303: 1167-1172.

III. Wijkman M, Länne T, Engvall J, Lindström T, Östgren C J, Nystrom F H: **β-blocker treatment is associated with high augmentation index and with high aortic, but not brachial, pulse pressure in type 2 diabetes.** *Journal of Clinical Metabolism & Diabetes* 2010; 1: 9-15.

IV. Wijkman M, Länne T, Engvall J, Lindström T, Östgren C J, Nystrom F H: **Central pulse pressure elevation is common in patients with type 2 diabetes and office normotension, and is associated with markers of atherosclerosis.** *Submitted.*

V. Wijkman M, Länne T, Grodzinsky E, Östgren C J, Engvall J, Nystrom F H: **Ambulatory systolic blood pressure predicts left ventricular mass in type 2 diabetes, independently of central systolic blood pressure.** *Submitted.*

INTRODUCTION

Hypertension

Diagnosis, epidemiology and etiology

Hypertension, defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, is estimated to affect about 972 million adult people worldwide[1]. The highest systolic blood pressure levels are currently found in low- and middle-income countries[1]. Based on expected demographic changes, the number of people with hypertension is likely to increase further in the forthcoming decades[2]. Hypertension is associated with an increased risk for cardiovascular disease, such as stroke[3] and myocardial infarction[4]. A meta-analysis of observational epidemiological studies revealed a close relationship between systolic or diastolic blood pressure and the risk of either fatal stroke or fatal coronary heart disease, with no evidence of a threshold level of blood pressure down to 115/75 mmHg, and with no difference between men and women[5]. Globally, higher than optimal blood pressure was estimated to account for seven million deaths in 2000, or almost 13% of all deaths in that year[6], and is the single potentially modifiable risk factor that contributes most to world-wide, all-cause mortality[7].

In the vast majority of patients with hypertension, approximately 90% in an unselected hypertensive population, no specific underlying mechanism is found. This condition is referred to as essential or primary hypertension. Essential hypertension is considered a multifactorial, partly genetically inherited condition, influenced by environmental factors. Several pathophysiologic factors have been suggested to contribute to the development of essential hypertension. A diet rich in sodium but low in potassium has been proposed to be an important factor that predisposes to the development of hypertension[8]. Autonomic imbalance, with increased sympathetic tone and decreased parasympathetic tone, may induce both heart rate elevation, cardiovascular remodelling, increased peripheral resistance, and increased activity of the renin-angiotensin-aldosterone system, all of which may contribute to blood pressure elevation and target organ damage[9]. Other plausible mechanisms that may contribute to the development of essential hypertension are increased arterial stiffness, insulin resistance and mild renal damage[10]. Secondary forms of hypertension include hypertension seen in patients with renal or endocrine disorders, such as renal parenchymatous disease, renal artery stenosis, primary hyperaldosteronism, hypercortisolism, phaeochromocytoma, or rare genetic disorders causing disturbed renal electrolyte handling. Hypertension can also be induced or aggravated by drugs such as oral contraceptives, non-steroid anti-inflammatory drugs, and some anti-depressants.

Office blood pressure measurements

By convention, the unit of measurement of blood pressure is millimeters of mercury (mmHg), instead of pascal, which is the official unit for pressure measurements in other scientific circumstances. This is because the traditional method of blood pressure measurement depended on the sphygmomanometer being connected to a mercury column. Nowadays, however, due to the environmental hazards associated with mercury handling, mercury sphygmomanometers are being replaced by mechanical anaeroid sphygmomanometers, or by automated oscillometric devices. Detailed gudielines concerning optimal office blood pressure measurement techniques have been published by the ESH (European Society of Hypertension)[11]. In brief, these guidelines recommend that office blood pressure is measured

following a five minute wait with the patient sitting comfortably in a relaxed position, the arm supported at heart level, and with an appropriately sized cuff. At the first occasion, blood pressure should be measured in both arms, and if there is reason to suspect orthostatic hypotension, blood pressure should also be measured with the patient in the standing position. Before the actual blood pressure measurement is performed, the radial or brachial artery of the patient should be palpated, and the cuff should be inflated to approximately 30 mmHg above the point at which no pulse can be palpated, and then slowly deflated. The blood pressure level at which the pulse is again palpable gives an estimate of the systolic blood pressure level. Thereafter, a stethoscope is placed over the brachial artery, the cuff is inflated to approximately 30 mmHg above the estimated systolic blood pressure and then slowly deflated at a tempo of approximately two to three mmHg per heartbeat. The observer should now note the first appearance of "faint, repetitive, clear tapping sounds that gradually increase in intensity" (Korotkoff phase I) as the systolic blood pressure, and the point at which all sounds disappear (Korotkoff phase V) as the diastolic blood pressure. Ideally, the average of at least two blood pressure measurements should be used at each visit, with the blood pressure rounded to the nearest two mmHg interval. For confirmation of a diagnosis of hypertension, blood pressure values taken on several visits over a period of a few weeks should be used. According to office blood pressure measurements, blood pressure status can be classified as optimal, normal, high normal or hypertension grade 1-3, respectively (Table1)[12].

	Systolic		**Diastolic**
Optimal	<120 mmHg	and	<80 mmHg
Normal	120-129 mmHg	and/or	80-84 mmHg
High normal	130-139 mmHg	and/or	85-89 mmHg
Grade 1 hypertension	140-159 mmHg	and/or	90-99 mmHg
Grade 2 hypertension	160-179 mmHg	and/or	100-109 mmHg
Grade 3 hypertension	≥180 mmHg	and/or	≥110 mmHg
Isolated systolic hypertension	≥140 mmHg	and	<90 mmHg

Table1. Classification of office blood pressure levels according to the ESH[12].

Ambulatory blood pressure measurements

Due to measurement imprecision and short-term biological variability, a single office blood pressure measurement may underestimate the strength of the association between the blood pressure level and the risk for cardiovascular disease. This effect is called the regression dilution bias. One way to overcome this problem is to use an automated device which measures the blood pressure repeatedly during 24 hours, since the larger number of measurements minimises the influence of individual random measurement errors. Furthermore, the blood pressure altering influence of the encounter with the person measuring the blood pressure (the so called white coat effect) is eliminated. The automated measurements approach also reduces the risk of digit preference, i.e. the preference of reporting blood pressure values that end with zero. Ambulatory blood pressure thresholds for definition of hypertension, as proposed by the ESH[12], are given in Table 2 together with the

thresholds that were associated with similar 10-year cardiovascular risks as an office blood pressure of 130/85 mmHg according to data from the IDACO (International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes) investigators[13]. As of today, there are no diabetes-specific treatment targets for ambulatory blood pressure levels.

	ESH thresholds for hypertension diagnosis	IDACO thresholds for normal blood pressure
24-hour blood pressure	125-130/80 mmHg	125/75 mmHg
Day-time blood pressure	130-135/85 mmHg	130/85 mmHg
Night-time blood pressure	120/70 mmHg	110/70 mmHg

Table 2. Arbitrary thresholds for diagnosis of ambulatory hypertension according to the ESH[12], and outcome-driven thresholds for ambulatory blood pressure normality according to the IDACO investigators[13].

Several studies have shown that, compared with office blood pressure levels, ambulatory blood pressure levels are more closely associated with the risk for cardiovascular disease. For instance, in a cohort consisting of 5292 patients with untreated hypertension at baseline, ambulatory systolic blood pressure was associated with increased risk for cardiovascular and all-cause mortality during a median follow-up period of eight years, independently of office systolic blood pressure and other traditional cardiovascular risk factors[14]. Furthermore, in a population-based cohort of 1700 persons without previously known cardiovascular disease at baseline, ambulatory systolic blood pressure predicted cardiovascular and all-cause mortality, independently of office systolic blood pressure, age and smoking status during a median follow-up period of 10 years[15]. A meta-analysis of prospectively designed studies showed that, following adjustment for traditional cardiovascular risk factors including office blood pressure levels, the hazard ratio (HR) for cardiovascular death was 1.19 (95% CI: 1.13-1.26), 1.12 (95% CI 1.07-1.18) and 1.22 (95% CI 1.16-1.27) per 10 mmHg increase in 24-hour, day-time and night-time ambulatory systolic blood pressures, respectively[16]. For the purpose of refined risk stratification, low ambulatory blood pressure levels have been associated with relatively low cardiovascular risk in patients with treatment-resistant hypertension according to office blood pressure measurements[17], as well as in patients with treated hypertension regardless of office blood pressure levels[18]. In patients with type 2 diabetes, ambulatory pulse pressure predicted all-cause mortality during a mean follow-up period of four years, independently of office pulse pressure[19]. In another cohort of patients with type 2 diabetes, either of ambulatory 24-hour, day-time or night-time systolic blood pressure predicted the risk of having a myocardial infarction, stroke or sudden cardiac death, independently of office systolic blood pressure and of other traditional cardiovascular risk factors[20]. A statistically significant trend towards increasing all-cause mortality during a mean follow-up time of seven years was also seen with increasing tertiles of 24-hour ambulatory, but not office, pulse pressure in patients with type 2 diabetes[21].

Ambulatory 24-hour blood pressure measurements, as well as home blood pressure measurements, also allow the identification of patients with masked hypertension, i.e. patients who are normotensive in the office but hypertensive according to blood pressure measurements out of office. Masked hypertension, according to either home or ambulatory blood pressure measurements, has been associated with higher LVMI (left ventricular mass index)[22-24] and with increased carotid IMT (intima-media thickness)[22, 24, 25]. The prognostic

implications of masked hypertension were first described in a Swedish cohort of 70-year old men not treated with antihypertensive drugs, in which the presence of masked hypertension was associated with an increased risk for cardiovascular disease, independently of traditional cardiovascular risk factors[26]. In a community-based cohort, masked hypertension was subsequently shown to predict a composite outcome of cardiovascular mortality and non-fatal stroke, regardless of whether patients were classified as belonging to low or high cardiovascular risk categories according to traditional cardiovascular risk parameters[27]. The authors of a recent meta-analysis concluded that masked hypertension is associated with an increased risk for cardiovascular events (HR: 1.92, 95% CI 1.51-2.44) but that comparisons between different studies are complicated by the application of various definitions of the phenomenon, various measurement techniques and various characteristics of the study populations[28]. In studies which specifically enrolled patients with type 2 diabetes, masked hypertension has been associated with increased prevalence of nephropathy, retinopathy and coronary heart disease[29] and with higher carotid IMT[30], higher urinary albumin to creatinine ratio[30, 31], higher left ventricular posterior wall thickness[30, 31] and with echocardiographic markers of left ventricular diastolic dysfunction[32].

A unique feature of ambulatory blood pressure monitoring, which home blood pressure monitoring does not permit, is the opportunity to measure also the nocturnal blood pressure. Several individual studies have shown that the cardiovascular risk is more closely associated with nocturnal blood pressure levels than with day-time blood pressure levels. Night-time ambulatory systolic blood pressure has, for instance, been shown to predict cardiovascular mortality, independently of day-time ambulatory systolic blood pressure and other traditional cardiovascular risk factors[14]. Furthermore, in placebo-treated patients with isolated systolic hypertension who participated in the Systolic hypertension in Europe trial, night-time but not day-time ambulatory systolic blood pressure predicted cardiovascular and all-cause mortality within a median follow-up period of four years, independently of office systolic blood pressure and traditional cardiovascular risk factors[33]. In a pooled analysis from the IDACO consortium, nocturnal blood pressure levels predicted both cardiovascular and all-cause mortality over a median follow-up period of 10 years, independently of day-time blood pressure levels, whereas day-time blood pressure levels did not predict cardiovascular or all-cause mortality independently of night-time blood pressure levels[34]. It was recently shown that patients with ambulatory day-time normotension but ambulatory nocturnal hypertension were at increased risk for premature mortality, and that among these patients, the majority were normotensive according to office blood pressure measurements[35]. This suggests that the presence of high blood pressure during the night may be associated with a poor prognosis even if blood pressure levels are normal according to office and ambulatory day-time measurements. Despite this, the definition of masked hypertension had previously been restricted to out-of office BP values obtained during the wake part of the day, rather than during the night. Therefore, we undertook the analyses presented in paper I.

The close association between nocturnal blood pressure levels and cardiovascular prognosis may be of therapeutic relevance. For instance, in a sub-study of 38 Swedish patients, who had been included in the HOPE (Heart Outcomes Prevention Evaluation) study on the basis of peripheral arterial disease, nocturnal blood pressure was lowered significantly more in patients randomised to treatment with the ACE (angiotensin converting enzyme) inhibitor ramipiril, administered in the evening, than in patients randomised to placebo, despite there being no significant between-group difference concerning reductions of office blood pressure[36]. It has been suggested that such a selective lowering of nocturnal blood pressures contributed to the outcome of the entire HOPE study, in which ramipril reduced the risk for

cardiovascular death, myocardial infarction and stroke compared with placebo, despite an only modest office blood pressure lowering effect[37].

Blood pressure measurements during stressful conditions

Thus, there is convincing evidence that high blood pressure, measured either in the office or during ambulatory blood pressure monitoring, is associated with an increased risk for premature morbidity and mortality. However, the predictive value of the blood pressure response to stress remains controversial. Traditionally, an exaggerated blood pressure response during exercise has been considered as a marker for increased cardiovascular risk. This is supported by the results of a Norwegian study, in which an early rise in systolic blood pressure to ≥200 mmHg during a bicycle exercise test was significantly associated with an increased risk for cardiovascular death in 520 healthy men with mildly elevated clinic blood pressure[38]. It was also shown in an American study in which 6578 men and women with dyslipidaemia but without previously known cardiovascular diseases performed a treadmill exercise test, that a maximal blood pressure >200/95 mmHg during exercise was significantly associated with an increased risk for cardiovascular death despite adjustments for classical cardiovascular risk factors (HR 1.66, 95% CI 1.14-2.40 compared with patients with maximal systolic blood pressure <160/80 mmHg)[39].

Other studies, however, have suggested that a greater blood pressure response during exercise is a marker of good prognosis. In a prospective cohort study, 937 patients with coronary artery disease underwent a bicycle exercise test. Following the exclusion of 29 patients, whose blood pressure fell during exercise, the remaining study participants were divided into quartiles (Q) according to the size of the systolic blood pressure response during exercise (Q1: 0-22 mmHg, Q2: 23-36 mmHg, Q3: 37-50 mmHg, Q4: 51-114 mmHg). Five-year mortality was significantly lower in Q4 compared with Q1 (HR 0.50, 95% CI 0.33-0.76) despite adjustments for classical cardiovascular risk factors, as was the risk for the individual outcomes of stroke/TIA, myocardial infarction and hospitalisation for heart failure[40]. Similar results were presented in a Swedish study in which 386 75-year-old study participants underwent a bicycle exercise test. Following the exclusion of four patients, whose blood pressure fell during exercise, the remaining study participants were divided into tertiles (T) according to the size of the systolic blood pressure response during exercise (T1: 0-30 mmHg, T2: 31-55 mmHg, T3: >55 mmHg). Compared with study participants in T3, study participants in T1 were significantly more likely to die within a median follow-up time of 11 years (HR 2.01, 95% CI 1.28-3.14)[41].

In the light of the robust relationships between high blood pressure at rest and increased risk for cardiovascular disease, it may seem surprising that an exaggerated blood pressure response during exercise has been associated with a good cardiovascular prognosis in several studies, and it is also surprising that different authors report differing results. A pathophysiological approach, however, may explain part of these discrepancies. Physical activity induces vasodilatation in the arteries supplying the skeletal muscles, leading to decreased peripheral resistance. This would lead to a drop in systemic arterial pressure, had it not been for a simultaneous vasoconstriction in the splanchnical region, which enhances the venous return to the heart and, together with an increased heart rate, leads to an augmentation of the cardiac output, which in a healthy individual overcomes the effects of the reduced peripheral resistance. Thus, the net effect of exercise on blood pressure in a healthy individual is an increased systemic blood pressure[42]. In patients with underlying cardiac disease, however, this rise may be blunted by a decreased ability to increase cardiac output. Therefore,

a less pronounced exercise-induced blood pressure rise may be a marker of compromised myocardial function, which is unmasked by the exercise provocation. In patients without underlying heart disease, however, a more pronounced exercise-induced blood pressure rise may be explained by endothelial dysfunction, with which follows an inability to dilate the peripheral arteries, and which may be a marker of increased cardiovascular risk. Indeed, an association between impaired endothelial function and exaggerated blood pressure response during exercise testing has been described[43], and patients with diabetes are more likely to react with an exaggerated systolic blood pressure response during a tread-mill test[44]. In summary, among the studies discussed here, an exaggerated blood pressure response during exercise has been associated with a poor prognosis in populations with a low probability of having underlying cardiac disease[38, 39], whereas in populations in which a high prevalence of cardiac disease can be suspected, an exaggerated blood pressure response during exercise was instead associated with a good prognosis[40, 41].

Another stressful condition, during which high blood pressure is associated with a good prognosis, is hospitalisation due to acute illness. In a large multinational registry comprising 22 645 patients who had been hospitalised with an acute coronary syndrome (unstable angina pectoris, non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction), the hazard for six-month post-discharge mortality increased with lower systolic blood pressure levels at presentation (the HR associated with a 20 mmHg decrease in systolic blood pressure was 1.1, 95% CI 1.06-1.17)[45]. However, it had not previously been shown if these associations between high admission systolic blood pressure and good prognosis remained in patients presenting in the emergency room with chest pain, regardless of underlying disease. Particularly, there were no data concerning such possible relationships in patients with diabetes. This paucity of data encouraged us to perform the analyses presented in paper II.

Central blood pressure measurements

The ejection of the left ventricular stroke volume during systole constitutes the driving force that creates the flow of blood through the arterial tree. The blood flow through arteries can be described in terms of a pulse wave which travels from the heart towards the periphery. The amplitude of the pulse wave equals the pulse pressure, i.e. the difference between the peak (systolic) and the lowest (diastolic) blood pressures. As the pulse wave travels throughout the arterial tree, it will be reflected. Reflections emerge due to structural properties of the larger arteries (bifurcations and atherosclerotic plaques), and due to increased vasomotor tone in the arterioles (increased peripheral resistance). The sum of the wave reflections will be a backward travelling pulse wave, which may superimpose on the forward travelling pulse wave, and thereby amplify its amplitude. Since the velocity with which the pulse waves travel is lower in the central aorta than in the peripheral arteries, and since the reflection sites are closer to the peripheral arteries than to the central aorta, the amplification effect will be larger in the peripheral arteries than in the central aorta. Accordingly, the pulse pressure will widen gradually as the pulse wave travels from the heart towards the periphery, a phenomenon referred to as spatial amplification[46]. This means that brachial blood pressure levels may differ significantly from central aortic blood pressure levels close to the heart. Since the ratio between central and brachial blood pressure levels exhibit considerable inter-individual variability, there may be considerable central blood pressure overlap between individuals with similar brachial blood pressure[47]. Spatial amplification is higher in younger patients and falls with increasing age[47, 48]. This is probably due to a more marked age-related change in arterial

wall properties in the aorta than in the peripheral arteries[49], which results in a more pronounced age-related elevation of the systolic blood pressure in the central aorta than of the systolic blood pressure in the brachial artery. Patients with diabetes have lower spatial amplification than patients without diabetes[47], which means that for any given brachial systolic blood pressure, central blood pressure is likely to be higher in a patient with diabetes than in a patient without diabetes.

The ideal method to determine the central blood pressure would be invasive, direct catheter-based measurements. Obviously, such an approach cannot be used for large scale epidemiologic research purposes. However, several non-invasive techniques for central blood pressure measurements have been developed lately. The most commonly used method in clinical studies, and the method which has been used for all central blood pressure estimations in this thesis, is the SphygmoCor device developed by AtCor Medical[50]. This method is based on computerised analyses of the arterial pulse wave form, obtained at the level of the radial artery, which is scanned for 10 seconds with a Millar pressure tonometer. The radial pulse wave is calibrated to the peripheral blood pressure, usually obtained from the upper arm. From the average radial pulse wave form, the corresponding ascending aortic pulse wave form can then be derived with the use of a validated generalised transfer function[51-53]. Central blood pressure levels can then be calculated based on the derived central pulse wave form. By analysing the shape of the central pulse wave form, the relative contribution of the reflected pulse wave (the augmentation pressure) to the central pulse pressure can also be quantified, by calculating the central augmentation index (AIx) as shown in Figure 1.

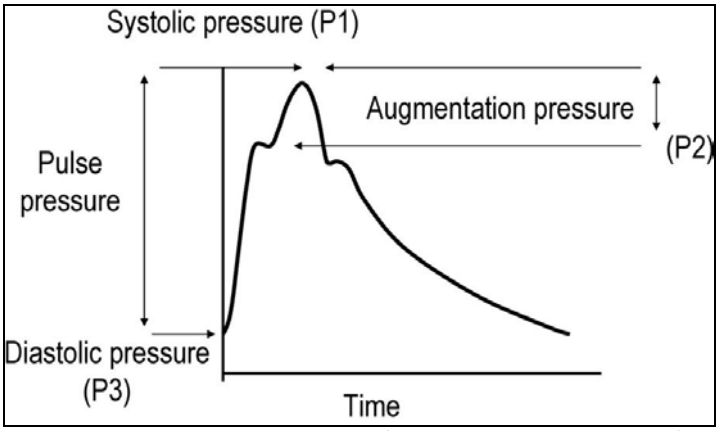

Figure 1. A typical central pulse wave. P1 refers to the systolic pressure. P2 refers to the pressure at the inflection point, where the returning pulse wave merges with the outward travelling pulse wave. P3 refers to the diastolic pressure. The central pulse pressure is calculated as P1 – P3. The augmentation pressure is calculated as P1 – P2. The augmentation index (AIx) is calculated as ((P1-P2) / (P1-P3)) * 100.

Central blood pressure measurements may be of importance for evaluating the effect of pharmacological antihypertensive treatment. It has been shown in small short-term studies that beta blocking drugs lower central blood pressure to a lesser degree than other commonly used antihypertensive drugs such as calcium channel blockers, diuretics and ACE inhibitors[54] and angiotensin receptor blockers (ARBs)[55], and that ACE inhibitors lower central blood pressure more than they lower brachial blood pressure[56]. In terms of target organ damage, it has been shown in a randomised trial that combined treatment with the ACE inhibitor perindopril and the diuretic indapamide reduced LVMI to a larger degree than mono therapy

with the beta blocker atenolol, and that this difference was associated with central, but not brachial pulse pressure reduction[57]. The less pronounced impact of beta blockers on central blood pressure levels has been suggested as a possible explanation of the results of the LIFE (Losartan Intervention for Endpoint Reduction) trial, in which the ARB losartan offered greater protection than atenolol against stroke in patients with hypertension and LVH (left ventricular hypertrophy), despite an extremely small inter-group difference in achieved brachial blood pressure[58]. It has also been proposed that the results of the HOPE study might have been due to a more pronounced lowering of central than brachial blood pressure by ramipril, since ramipril in that study reduced the risk of cardiovascular death, myocardial infarction and stroke compared with placebo, despite an only modest brachial blood pressure lowering effect[37]. It was not, however, until the CAFE (Conduit Artery Function Evaluation) study[59] was undertaken, that this concept was tested in the setting of a large randomised clinical trial. The CAFE study was a subgroup evaluation of the larger ASCOT (Anglo-Scandinavian Cardiovascular Outcomes Trial), in which treatment with the calcium channel blocker amlodipine (with the possible addition of perindopril) was compared with atenolol-based treatment (with the possible addition of the diuretic bendroflumethiazide) in patients with hypertension and additional cardiovascular risk factors. The main finding in ASCOT was that amlodipine-based treatment was associated with fewer strokes and fewer deaths than atenolol-based treatment[60]. In CAFE, 1042 ASCOT patients who were assigned to amlodipine-based treatment and 1031 ASCOT patients who were assigned to atenolol-based treatment were evaluated with applanation tonometry and central blood pressure levels were calculated. Interestingly, central systolic blood pressure differed significantly between the two groups, being higher in patients assigned to atenolol-based treatment (mean between-group difference: 4.3 mmHg, 95% CI 3.3-4.5) whereas brachial systolic blood pressure did not differ significantly between the two groups (mean between-group difference: 0.7 mmHg, 95% CI -0.4-1.7)[59]. This finding might be explained by a vasodilating effect of amlodipine, which would decrease peripheral resistance and thus move the reflection point, at which backward travelling waves are created, towards the periphery. Alternatively, the beta blocker-induced heart rate lowering might prolong the systolic ejection phase so much that the reflected waves reach the heart already during systole, thus augmenting central systolic pressure. The latter mechanism might explain why beta blocker-induced heart rate lowering is associated with an increased risk for myocardial infarction and cardiovascular death in patients with hypertension[61]. Whether a similar association between beta blocker use and high central, but not brachial, blood pressure exists in patients with type 2 diabetes treated in usual care, had not been demonstrated. This was the rationale for performing the analyses presented in paper III.

Given the proximity of the central aorta to susceptible target organs such as the heart, the carotid arteries and the brain, it is plausible to believe that central blood pressure is a more appropriate marker of risk than brachial blood pressure. Indeed, several studies have revealed a closer relationship between the degree of cardiovascular target organ damage and central blood pressure levels than with brachial blood pressure levels[62-65]. However, other studies have suggested that central and brachial blood pressure levels are similarly associated with markers of cardiac hypertrophy[66, 67]. Although the associations between blood pressure levels and target organ damage may help us understand important pathophysiological concepts, the clinical utility of central blood pressure measurements should be evaluated by their ability to predict the cardiovascular prognosis. In a recent meta-analysis of observational prospective studies, the relative risk of any cardiovascular event was 1.088 (95% CI 1.040-1.139, *n*=3285) for an increase of central systolic blood pressure by 10 mmHg and 1.137 (95% CI 1.063-

1.215, *n*=4778) for an increase of central pulse pressure by 10 mmHg, but neither the relative risk associated with higher central systolic blood pressure nor the relative risk associated with higher central pulse pressure differed significantly from the relative risks associated with its brachial counterparts, respectively[68]. Following that meta-analysis, one subsequent report showed that in 1272 Chinese people recruited from the community, central systolic blood pressure predicted cardiovascular mortality independently of brachial systolic blood pressure and traditional cardiovascular risk factors (HR per 10 mmHg increase in central systolic blood pressure: 1.34, 95% CI 1.107-1.612), whereas central pulse pressure did not predict cardiovascular mortality independently of brachial pulse pressure and traditional cardiovascular risk factors[64]. Thus, the available data suggest that central blood pressure levels correlate with markers of target organ damage and predict cardiovascular events, although not necessarily better than conventional brachial blood pressure measurements obtained in the usual clinic setting. So far, central blood pressure parameters have been compared with ambulatory blood pressure parameters in only one prospectively designed study with hard end-points. In that study, ambulatory 24-hour systolic blood pressure predicted cardiovascular mortality independently of central systolic blood pressure and traditional cardiovascular risk factors (HR for one SD increment in 24-hour systolic blood pressure: 1.71, 95% CI 1.16-2.52) in 1014 healthy Taiwanese people recruited from the community[69]. There are currently no defined treatment goals for central blood pressure, but central pulse pressure ≥50 mmHg has been suggested as an appropriate cut-off value for the identification of patients with increased cardiovascular risk[70]. The prevalence of such an elevated central pulse pressure in patients with type 2 diabetes and well controlled brachial blood pressure had not been previously described, and therefore we undertook the analyses presented in paper IV.

Risk stratification

Current European guidelines for the management of hypertension emphasise that treatment decisions should be based on total cardiovascular risk rather than on blood pressure levels only[12, 71]. Total cardiovascular risk can be assessed by a structured work-up of hypertensive patients, which takes into account blood pressure levels, classical cardiovascular risk factors such as age, smoking, dyslipidaemia, obesity and family history of premature cardiovascular disease, as well as the presence of established cardiovascular and renal disease and of diabetes mellitus. Additionally, it is recommended that the presence of hypertension-related target organ damage is evaluated. The presence of target organ damage reflects structural alterations of the cardiovascular organs in response to chronic blood pressure elevation, and can be considered an intermediate step between risk factors and established cardiovascular disease. Examples of target organ damage recommended by the ESH include micro-albuminuria, LVH, increased carotid IMT, presence of carotid plaques, increased arterial stiffness, and decreased ankle/brachial blood pressure index[12]. A large proportion of hypertensive patients who were considered at low or medium cardiovascular risk according to routine diagnostic procedures, exhibited signs of either LVH or carotid abnormalities when examined with ultrasonography[72], suggesting that routine examinations that does not include ultrasonographic screening for target organ damage may underestimate the cardiovascular risk profile of patients with hypertension. On the other hand, although additional measurement of target organ damage has been shown to increase the sensitivity of conventional cardiovascular risk prediction, this is also associated with a decreased specificity[73]. Therefore, the appropriate utilisation of markers of cardiovascular risk is crucial in order to estimate the risk of cardiovascular disease in an individual patient with hypertension. Of particular interest

within the context of this thesis are LVH, arterial stiffness, and carotid IMT, as discussed in detail below.

Left ventricular hypertrophy

Increased left ventricular mass is a compensatory response of the heart to increased afterload, and left ventricular mass increases with increasing blood pressure levels. Electrocardiographic criteria for diagnosis of LVH have been proposed, and may be used to identify patients with severe LVH, but have low sensitivity and thus cannot be used to rule out the presence of LVH. Therefore, the gold standard for identification of LVH is echocardiography. Since left ventricular mass increases with body size, echocardiographically determined left ventricular mass is usually indexed to either calculated body surface area, as recommended by the ESH[12], or to height to the power of 2.7, which has been proposed as a more appropriate indexation method in populations with a high prevalence of obesity[74]. To further adjust for sex-associated differences in left ventricular mass, the ESH recommend sex-specific cut-off points to diagnose LVH ($\geq$125 g/m^2 in men and $\geq$110 g/m^2 in women)[12]. Left ventricular geometry can be further subdivided into concentric hypertrophy (LVH and high left ventricular wall to radius ratio), eccentric hypertrophy (LVH and normal left ventricular wall to radius ratio), and concentric remodelling (no LVH but high left ventricular wall to radius ratio). In particular, concentric LVH has been associated with an increased risk for cardiovascular disease, cardiovascular mortality and all-cause mortality in patients with essential hypertension, whereas patients with eccentric LVH had higher risk than patients without LVH but lower risk than patients with concentric LVH[75]. In the Framingham Heart Study, only age and echocardiographically determined left ventricular mass were strongly associated with both the risks for cardiovascular disease, cardiovascular mortality and all-cause mortality in both men and women without previously known cardiovascular disease[76].The association between LVH and cardiovascular risk is likely explained by an increased myocardial oxygen consumption of the hypertrophic myocardium, making patients with LVH more susceptible to cardiac ischaemia. Structural myocardial alterations associated with LVH may also predispose to fatal arrhythmias. Furthermore, in hypertensive populations, the presence of LVH is likely to exclude patients with white-coat hypertension, who are less likely to develop signs of target organ damage. Antihypertensive treatment may lead to LVH regression, and treatment-induced regression of LVH is associated with a reduced risk for cardiovascular disease[77]. There seems to exist differences between different blood pressure lowering drugs in terms of their ability to induce LVH regression. This was demonstrated in a meta-analysis, in which treatment with either calcium channel blockers, ACE inhibitors or ARBs were associated with larger reductions in left ventricular mass than treatment with beta blockers, despite similar reductions in blood pressure[78]. It had not been shown previously whether the degree of left ventricular hypertrophy in patients with type 2 diabetes correlated with ambulatory blood pressure levels independently of central blood pressure levels, which prompted us to perform the analyses presented in paper V.

Arterial stiffness

With ageing, arteries become stiffer[79]. The stiffening process involves structural and functional rearrangements of the elastic material in the arterial wall, and is the result of an interaction between classical cardiovascular risk factors and genetic susceptibility[80]. In a person with increased arterial stiffness, both the forward travelling pulse wave and the sum of its reflected, backwards travelling pulse waves will travel at increased velocity, and the accumulated reflected pulse wave will reach the central aorta earlier than in a person with

lower arterial stiffness. This means that in a person with markedly increased arterial stiffness, the reflected pulse wave will return to the central aorta earlier, prior to the closure of the aortic valve (i.e. during systole), thus augmenting afterload by increasing the central systolic blood pressure and widening the central pulse pressure. This is in contrast to what happens in a person with lower arterial stiffness, in which the reflected pulse wave will reach the central aorta after the closure of the aortic valve (i.e. during diastole), thus instead augmenting the coronary perfusion by increasing the central diastolic blood pressure. Since the age-dependent increase of arterial stiffness is more pronounced in the central than in the peripheral arteries, the central pulse pressure will be selectively increased with aging and the magnitude of the spatial amplification in the peripheral arteries will be attenuated. This is the likely pathophysiological explanation of the clinically well-established notion that increased brachial pulse pressure is a more robust marker of risk in the elderly than in the young[81]: for any given brachial pulse pressure, the central pulse pressure is higher in a (supposedly older) person with high arterial stiffness than in a (supposedly younger) patient with low arterial stiffness[82]. The influence of age on spatial amplification is illustrated in Figure 2.

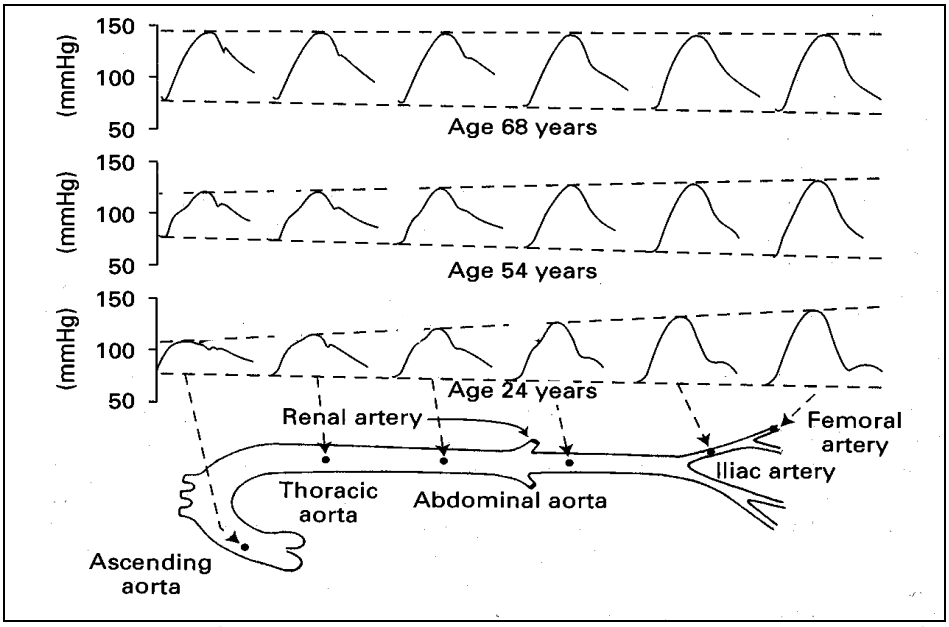

Figure 2. When moving from the ascending aorta towards the periphery, pulse pressure is gradually amplified due to the effect of wave reflection. This phenomenon, spatial amplification, is more evident in younger than in older persons. Illustration from Nichols WW, O´Rourke MF. McDonalds blood flow in arteries. Theoretical, experimental and clinical principles. 5th ed. Oxford University Press; 2005, p. 88.

Aortic pulse wave velocity is the gold standard for arterial stiffness measurements[83], and is an established marker of increased cardiovascular risk. The aortic pulse wave velocity can be measured by performing electrocardiogram-gated applanation tonometric recordings of the femoral and carotid pulse waves[83]. The pulse wave transit time is calculated by subtracting the time between the ECG R-wave and the arrival of the pulse wave to the carotid measurement site from the time between the ECG R-wave and the arrival of the pulse wave to the femoral measurement site. The surface distance between the two measurement sites is measured, and the aortic pulse wave velocity can be calculated by dividing the surface distance with the pulse wave transit time.

Of particular interest within the context of this thesis is that in patients with type 2 diabetes, aortic pulse wave velocity predicted cardiovascular mortality independently of age, sex and brachial blood pressure[84] and that in patients with essential hypertension, aortic pulse wave velocity predicted cardiovascular mortality independently of age, previous cardiovascular disease and diabetes[85]. In a recent meta-analysis of 17 studies comprising data on 15 877 patients, the relative risk for cardiovascular mortality that was associated with an increase of aortic pulse wave velocity by one m/s was 1.15 (95% CI 1.09-1.21)[86]. In patients with hypertension, an increase of aortic pulse wave velocity by five m/s has been shown to be equivalent, in terms of cardiovascular risk, to that of ageing 10 years[85]. Reference values for 11 092 patients without overt cardiovascular disease, without diabetes and without antihypertensive medication have been established, and show that the aortic pulse wave velocity rises progressively with both age and blood pressure[87]. For instance, patients younger than 30 years and with office blood pressure <120/80 mmHg had a mean aortic pulse wave velocity of 6.1 m/s, whereas patients aged 70 years or older and with office blood pressure ≥160/100 mmHg had a mean aortic pulse wave velocity of 14.0 m/s[87]. The ESH recommend in their guidelines that an aortic pulse wave velocity >12m/s should be considered as a marker of subclinical organ damage[12]. For comparison, this cut-off value corresponds to a PWV of 9.6 m/s after adjustment for the slightly differing methodologies that were applied when the reference values were constructed[87].

Carotid intima-media thickness

The carotid IMT can be measured non-invasively with ultrasonography. Increased IMT represents both vascular hypertrophy (medial thickening) and atherosclerosis (intimal thickening), making it an integrated marker of early arterial damage. Increased IMT is associated with an increased risk for cardiovascular disease. In a meta-analysis, the hazard ratio associated with a 0.1 mm increase in carotid IMT was 1.10 (95% CI: 1.08-1.13, *n*=30 162) for myocardial infarction and 1.13 (95% CI: 1.10-1.16, *n*=34 335) for stroke, following adjustment for traditional markers of cardiovascular risk[88]. Antihypertensive treatment, particularly with calcium channel blockers, reduces the progression of carotid IMT[89]. Treatment-induced reduction of carotid IMT has not, however, been associated with a better cardiovascular prognosis in a large prospective analysis of patients with treated hypertension[90].

Treatment

The over-all aim of pharmacological antihypertensive therapy is to prevent strokes and myocardial infarctions, and to reduce the risk of developing congestive heart failure and renal failure. Life style interventions such as diet modification and exercise lower blood pressure levels modestly, at least in a short term setting, but has not been shown to reduce the risk for cardiovascular disease[91]. There are some data from randomised trials, however, in support of a protective effect of dietary sodium reduction against cardiovascular disease[92, 93].

Five major drug classes are commonly used as first-line drugs to treat hypertension: beta blockers (which inhibit renin release and lower the heart rate), thiazide diuretics (which induce natriuresis), dihydropyridine calcium channel blockers (which induce vasodilatation), and ACE inhibitors and ARBs (both of which block the renin-angiotensin-aldosterone system). Antihypertensive treatment with any of these drugs reduces the risk of coronary heart disease or stroke[94, 95]. It has been estimated that a pharmacologically induced reduction of the systolic blood pressure of 10 mmHg, or of the diastolic blood pressure of 5 mmHg,

corresponds to a 41% reduced risk for stroke and a 22% reduced risk for coronary artery disease[95]. The relative risk reduction associated with antihypertensive therapy is similar in men and women[94] and is similar in people with or without previously known cardiovascular disease[95]. Specifically, beta blockers seem to offer extra protection, beyond that expected by blood pressure reduction alone, in patients with a recent myocardial infarction, but seem to be less effective than other drugs in preventing strokes, whereas calcium channel blockers seem to be more effective than other drugs in preventing strokes, but less effective than other drugs in preventing heart failure[95]. The treatment target for most patients with hypertension is <140/90 mmHg[12], and in patients with diabetes the treatment target is usually considered to be either <130/80 mmHg[96], or systolic blood pressure "well below" 140 mmHg[71].

Diabetes mellitus

Diagnosis, epidemiology and etiology

Diabetes mellitus is a diagnosis which encompasses a group of metabolic disorders with differing pathophysiologic backgrounds, but all sharing the pathognomonic characteristic of hyperglycaemia. The global prevalence of diabetes mellitus among adults was recently estimated to 347 million people[97], and conservative estimates based on expected demographic changes have suggested that the global prevalence of diabetes will rise with approximately 50% during the next 20 years[98]. The diagnosis diabetes mellitus is based on elevated plasma glucose levels. If a patient presents with typical diabetes symptoms, such as polyuria, polydipsia, unexplained weight loss or coma, a casual capillary plasma glucose ≥12.2 mmol/L (venous plasma glucose ≥11.1 mmol/L) is sufficient to diagnose diabetes mellitus. In patients without such typical symptoms, the diagnostic criteria are based on plasma glucose measurements performed either in the fasting state or two hours after the ingestion of a 75 gram oral glucose load, a so called OGTT (Oral Glucose Tolerance Test). The current diagnostic criteria for diabetes mellitus and other categories of hyperglycaemia, endorsed by the WHO (World Health Organization)[99], are presented in Table 3. The states of slightly elevated plasma glucose levels, which exceed the reference thresholds but which fall below the diagnostic cut-off values, are termed IFG (Impaired Fasting Glucose) if glucose levels were measured in the fasting state and IGT (Impaired Glucose Tolerance) if glucose levels were measured following an OGTT. From a pathophysiologic point of view, diabetes mellitus is usually classified as either type 1 or type 2 diabetes. Type 1 diabetes is an autoimmune disorder, characterised by autoimmune destruction of the insulin-secreting pancreatic beta-cells, a process which usually leads to absolute insulin deficiency[100]. It is currently not known which factors that primarily trigger the autoimmune response. Type 2 diabetes is by far the most common form of diabetes and is believed to account for approximately 90% of the diabetes cases in the world[101]. Type 2 diabetes has been described as a genetically determined failure of the pancreatic beta-cells to compensate for insulin resistance[102]. Patients with type 2 diabetes are often obese, with a predominantly intra-abdominally located fat mass, which predisposes for insulin resistance. Insulin resistance leads to decreased glucose uptake in the skeletal muscles, increased glycogenolysis and increased gluconeogenesis in the liver and increased lipolysis in the adipose tissue. Initially, the insulin resistance can be compensated for by increased insulin secretion, but with time the insulin secreting pancreatic beta-cells fail to secrete sufficient amounts of insulin for glucose homeostasis to be maintained, which leads to slowly progressing hyperglycaemia until the diagnostic criteria for IFG and/or OGTT and, eventually, diabetes mellitus are finally met. A third form of diabetes mellitus is gestational diabetes mellitus, defined as diabetes diagnosed during pregnancy and which wanes off after delivery. Other specific forms of diabetes mellitus include drug-induced diabetes caused by

glucocorticoids or other diabetogenic drugs, diabetes secondary to diseases of the pancreas such as pancreatitis, haemochromatosis or cystic fibrosis, diabetes secondary to other specific endocrine disorders such as Cushing´s syndrome or acromegaly, and diabetes secondary to rare genetic defects of beta-cell function or insulin action[99].

	Capillary plasma glucose (mmol/L)	Venous plasma glucose (mmol/L)
Diabetes mellitus		
Fasting	≥7.0	≥7.0
2 hour oral glucose tolerance test (OGTT)	≥12.2	≥11.1
Impaired Fasting Glucose (IFG)	6.1 – 6.9	6.1 – 6.9
Impaired Glucose Tolerance (IGT)	8.9 – 12.1	7.8 – 11.0

Table 3. Diagnostic criteria for diabetes mellitus and other categories of hyperglycaemia according to the WHO[99].

Complications

Prolonged hyperglycaemia causes damage to susceptible cell types through several mechanisms, such as accumulation of AGEs (advanced glycation end products), increased activity in the polyol metabolic pathway and activation of PKC (protein kinase C)[103]. Increased protein glycation leads to accumulation of AGEs both intracellularly and in the extracellular matrix, and glycated circulating plasma proteins activate AGE receptors which induce inflammatory processes. Prolonged hyperglycaemia also causes glucose to be metabolised to fructose via sorbitol through the polyol pathway, which consumes NADPH, thus leading to intracellular depletion of reduced glutathione and increased oxidative stress. Furthermore, hyperglycaemia leads to activation of PKC via increased levels of diacylglycerol, which leads to reduced vasodilatory capacity, increased vasoconstriction and decreased fibrinolysis. Among the cell types that are most susceptible to hyperglycaemia-induced damage are the endothelial cells of the retinal capillaries, the mesangial cells of the kidneys, and Schwann cells of peripheral neurons[103], which explains the development of the classical microvascular complications of diabetes: retinopathy[104], nephropathy[105] and neuropathy[106]. However, diabetes is also associated with an increased risk for coronary heart disease[4], stroke[3] and peripheral arterial disease[107], which are collectively referred to as macrovascular diabetes complications. Patients with type 2 diabetes are also known to have higher LVMI and higher left ventricular wall to radius ratio than patients without diabetes, and these difference seem to be independent of differences in blood pressure[108]. Furthermore, many patients with type 2 diabetes without previously known cardiovascular disease have been shown to have higher left ventricular mass than could be expected solely by their sex, body size and left ventricular stroke work[109]. If diabetes is accompanied by hypertension, the risk of developing macrovascular complications increases even further[110]. Other established risk factors for coronary heart disease in patients with type 2 diabetes are increased LDL cholesterol, decreased HDL cholesterol, hyperglycaemia and smoking[110], similar to what is observed in the general population. Due mainly to macrovascular complications, diabetes is associated with a more than two-fold increase in the risk for premature cardiovascular mortality but also for premature all-cause mortality[111]. The association between diabetes and premature mortality is stronger in women than in men[112]. Globally, diabetes was estimated to account for 4 million deaths in 2010, or almost 7% of all deaths in that year[113]. The over-all

aim of pharmacologic therapy of diabetes is to prevent or postpone the development of micro- and macrovascular complications. Life style modifications, such as to prevent the development of obesity, to reduce excessive salt intake and not to smoke, should be encouraged but should not delay the initiation of appropriate pharmacological treatment.

Glucose lowering treatment

In patients with type 1 diabetes, insulin therapy is almost always necessary for immediate survival. Insulin can be delivered subcutaneously either via multiple daily injections with insulin pens or syringes, or with a continuous subcutaneous insulin infusion with the help of an insulin pump. The randomised DCCT (Diabetes Control and Complications Trial) compared an intensive insulin regimen, which was subject to individual dose adjustments according to the results of at least four self-measured blood glucose values per day, with a less strict insulin regimen which instead aimed at controlling hyper- and hypoglycaemic symptoms, in 1441 relatively young patients with type 1 diabetes but without severe diabetes complications. Patients were followed for a mean of seven years. The results showed that intensive glucose control prevented the development and progression of retinopathy, nephropathy and neuropathy, respectively, although at the cost of an increasing number of hypoglycaemic events[114]. At the end of the study, intensive therapy was only non-significantly associated with a decreased risk for macrovascular diabetes complications. However, after the trial was terminated, the study participants were followed in the observational EDIC (Epidemiology of Diabetes Interventions and Complications) study, and it was found that after 11 years, participants who had previously been randomised to the intensive treatment group had a 57 % lower risk of myocardial infarction, stroke or cardiovascular death compared with patients who had previously been randomised to less strict glucose control[115].

In most patients with type 2 diabetes, insulin therapy is not necessary for immediate survival, but may be necessary for achieving good glycaemic control and avoiding complications. The optimal insulin regimen for patients with type 2 diabetes remains under debate. According to a recent meta-analysis, biphasic or prandial insulin regimens may lower HbA1c more effectively early after insulin initiation[116], but these differences are likely to wane over time, as more complex insulin regimens are likely to be needed in order to achieve good glycaemic control[117]. However, early in the course of type 2 diabetes, hyperglycaemia can often be treated with oral glucose lowering drugs together with lifestyle modifications, but without insulin. The first-hand choice among the oral glucose lowering drugs is metformin, which works mainly by suppressing the hepatic glucose output and by reducing the insulin resistance in the skeletal muscles[118]. Sulphonylureas, which work by stimulating the insulin secreting capability of the pancreatic beta-cells, are commonly used as second-line drugs or in patients who do not tolerate metformin. Pioglitazone, an agonist of the peroxisome proliferator-activated gamma receptor, works by promoting adipocyte differentiation and enhance fatty acid uptake, and has been shown to reduce the composite of myocardial infarction, stroke and all-cause mortality in patients with type 2 diabetes and established macrovascular disease, but was also associated with an increased risk for peripheral oedema and heart failure in these patients[119] and is therefore used only cautiously. Newer agents which enhance the actions of the incretin system, such as GLP-1 (glucagon-like peptide 1) receptor agonists, GLP-1 analogues and DPP-4 (dipeptidyl-peptidase 4) inhibitors are promising but evidence concerning their potential abilities to prevent micro- or macrovascular complications is currently lacking.

The value of achieving good glycaemic control in type 2 diabetes was first shown in the UKPDS (United Kingdom Prospective Diabetes Study), in which 3867 patients with newly diagnosed type 2 diabetes were randomised to either intensive glucose control with sulphonylureas or insulin, or to conventional life style modification treatment. Additionally, 742 patients were randomised to either intensive glucose control with metformin or to conventional life style modification treatment. Patients were followed for a median of 10 years. At the end of the trial, treatment with sulphonylurea or insulin was associated with a significantly decreased risk of retinopathy or nephropathy, but neither all-cause nor diabetes-related mortality were significantly lower in patients treated with sulphonylurea or insulin than in conventionally treated patients[120]. Metformin treatment, however, was associated with a significantly decreased risk for not only retinopathy or nephropathy, but also for both diabetes-related and all-cause mortality, respectively, when compared with conventional treatment[121]. When an observational follow-up study was conducted, patients who had previously been randomised to intensive treatment had decreased risk of diabetes-related mortality and of all-cause mortality, regardless of whether metformin or sulphonylureas/insulin had been used during the randomised trial[122], suggesting that early improvement of glucose control with any of these three drug regimens may prevent macrovascular disease in patients with type 2 diabetes. Attempts to completely normalise hyperglycaemia in patients with longer duration of type 2 diabetes and a with a higher prevalence of previous cardiovascular disease than the participants in the UKPDS have, however, not been successful: in the randomised ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, a strategy which aimed at lowering HbA1c to levels within the normal, non-diabetic range was associated with an increased risk for all-cause mortality[123].

Lipid lowering treatment

In insulin resistant patients with type 2 diabetes, and in patients with type 1 diabetes and poor glycaemic control, the lipid profile is often characterised by elevated triglycerides, elevated apolipoprotein B levels, decreased HDL (high-density lipoprotein) cholesterol levels and elevated small dense LDL (low-density lipoprotein) cholesterol particles, although total LDL levels may be normal[124]. Randomised placebo-controlled trials have shown that statin treatment reduces the risk of macrovascular diabetes complications, regardless of pre-treatment cholesterol levels[125, 126], and a meta-analysis has shown that statin-induced LDL lowering is closely correlated to reduced risk of major cardiovascular disease in patients with either type 1 or type 2 diabetes regardless of whether there was a history of previous cardiovascular disease or not[127].

Blood pressure lowering treatment

Hypertension is common in diabetes, and approximately one third of cardiovascular deaths in patients with diabetes may be attributable to co-existent hypertension[128]. In patients with type 1 diabetes, hypertension usually develops as a consequence of diabetic nephropathy, which reduces the ability of the kidneys to excrete sodium and water, whereas in type 2 diabetes, insulin resistance and obesity may contribute to the development of hypertension by promoting sympathetic nervous system over-activity and increased renal sodium retention. In the UKPDS, systolic blood pressure levels predicted both micro- and macrovascular complications and all-cause mortality[129], and data from the Swedish NDR (National Diabetes Register) have shown that in patients with type 2 diabetes without previously known congestive heart failure, the hazard ratio associated with any increase of systolic blood pressure by 10 mmHg was 1.08 (95% CI: 1.04-1.13) for coronary heart disease and 1.20 (95%

CI: 1.13-1.27) for stroke[130]. Several randomised clinical trials have shown that intensified blood pressure control is associated with improved cardiovascular prognosis in patients with type 2 diabetes. In the UKPDS, 1148 patients with newly diagnosed type 2 diabetes were randomised to what was then called either "tight" (goal <150/85 mmHg) or "less tight" (goal: <180/105 mmHg) blood pressure treatment. Mean achieved blood pressure was 144/82 mmHg in the tightly controlled group and 154/87 mmHg in the less tightly controlled group. Compared with less tight blood pressure control, tight blood pressure control was associated with a relative risk reduction of 34% for the composite macrovascular end-point (stroke, myocardial infarction, peripheral arterial disease or sudden death) and of 35% for the risk of needing retinal photocoagulation treatment of diabetic retinopathy, over a median follow-up time of eight years[131]. In the diabetes subgroup (n=1501) of the HOT (Hypertension Optimal Treatment) study, targeting office diastolic blood pressure levels ≤80 mmHg rather than ≤90 mmHg was associated with a relative risk reduction of 51% for the composite outcome of myocardial infarction, stroke and cardiovascular death[132]. Achieved mean blood pressures in the different randomisation arms were not presented specifically for patients with diabetes in that publication, however. In the normotensive subgroup of the ABCD (Appropriate Blood Pressure Control in Diabetes) trial, 480 patients with type 2 diabetes and base-line blood pressure <140/90 mmHg were randomised to either intensive treatment (goal: diastolic blood pressure 10 mmHg below baseline) or moderate treatment (initially placebo, but if blood pressure eventually exceeded 160/90 mmHg, active treatment was initiated with target systolic blood pressure ≤160 mmHg and target diastolic blood pressure 80-89 mmHg). Those patients who were randomised to intensive treatment (mean achieved blood pressure: 128/75 mmHg) had a significantly lower stroke event rate (1.7% vs 5.4%) compared with those patients who were randomised to moderate office blood pressure reduction (mean achieved blood pressure: 137/81 mmHg), and a significantly slower progression of diabetic retinopathy during a mean follow-up period of five years[133]. The ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation) trial, although not specifically designed to compare different treatment targets, provides additional information concerning the value of strict blood pressure control in patients with type 2 diabetes. In ADVANCE, 11 140 patients with type 2 diabetes and with established macrovascular disease or with additional cardiovascular risk factors were randomised to either placebo or to active treatment with perindopril plus indapamide, given in addition to previous treatment, and were followed for a mean of four years[134]. Mean baseline blood pressure was 145/81 mmHg, and during the study, mean blood pressure was 5.6/2.2 mmHg lower in the actively treated than in the placebo-treated patients. Active treatment was associated with a significantly decreased risk for cardiovascular mortality and with decreased risk for coronary events, compared with placebo treatment. Surprisingly, however, stroke risk was not significantly affected by treatment. In the original study publication, mean achieved blood pressures were not specified, but in subsequent analyses it has been reported that it was on average 140/76 mmHg in the placebo group and 134/74 mmHg in the actively treated group[135]. Targeting even lower blood pressure levels might be associated with additional stroke prevention, as shown in the ACCORD blood pressure trial, in which 4733 patients with type 2 diabetes and additional risk factors were randomised to either intensive therapy, with the aim of reducing the systolic blood pressure <120 mmHg, or to standard therapy, with the aim of reducing the systolic blood pressure to <140 mmHg. Patients randomised to intensive therapy (mean achieved blood pressure: 119.3/64.4 mmHg) had significantly fewer strokes than patients randomised to standard therapy (mean achieved blood pressure: 133.5/70.5 mmHg), but neither the risk for cardiovascular mortality nor the risk for coronary events differed significantly between the groups[136]. The hypothesis that very low achieved blood pressures

would be associated with an increased risk for coronary heart disease in susceptible patients, such as in patients with diabetes, has not been confirmed by a recent meta-analysis of 73 913 patients with diabetes who participated in hypertension treatment trials, which showed that lower achieved blood pressure levels were associated with reduced risk for stroke, whereas no significant association was found between lower achieved blood pressure levels and the risk for myocardial infarction[137]. Another meta-analysis included 13 randomised trials of patients with type 2 diabetes or IFG, in which patients in one group achieved systolic blood pressure ≤135 mmHg and patients in the other group achieved systolic blood pressure ≤140 mmHg, with a between-group difference in achieved systolic blood pressure of at least three mmHg[138]. Patients who achieved systolic blood pressure ≤135 mmHg had significantly lower odds ratio (OR) for stroke (OR: 0.83, 95% CI 0.73-0.95) than patients who achieved systolic blood pressure ≤140 mmHg, but there was no such association between lower achieved systolic blood pressure and the risk for myocardial infarction. The risk of serious adverse events were, however, higher in patients who achieved systolic blood <135 mmHg than in patients who received systolic blood pressure <140 mmHg. A stratified analysis showed that those patients who achieved systolic blood pressure ≤130 mmHg had an even lower risk for stroke (OR: 0.55, 95% CI 0.38-0.75) compared with patients who achieved systolic blood pressure ≤140 mmHg, without an increased risk for myocardial infarction. However, it should be emphasised that since both of these meta-analyses were based on comparisons between achieved blood pressure levels rather than on comparisons between patients randomised to intensive or less intensive blood pressure reductions, the results should be cautiously interpreted.

To conclude, the UKPDS helped establishing that blood pressure control is important for the prevention of both micro- and macrovascular diabetes complications[131]. Subsequent clinical trials of hypertension treatment in diabetes have aimed at determining the optimal blood pressure treatment goals, with the HOT study results showing that patients with type 1 or type 2 diabetes benefit from more ambitious blood pressure goals than patients without diabetes[132], and with the ABCD trial results showing that reducing blood pressure to less than 130/80 mmHg is beneficial for patients with type 2 diabetes[133], and with the ACCORD study results[136] suggesting that targeting even lower blood pressure values might protect patients with type 2 diabetes against stroke without increasing the risk for coronary events, but at the price of increased risk for adverse events. Current guidelines from the ADA (American Diabetes Association) recommend a blood pressure goal of <130/80 mmHg for all patients with diabetes[96], whereas the ESH recently revised their guidelines and recommend that in patients with diabetes, systolic blood pressure should be lowered "well below" 140 mmHg[71]. Significant improvements in terms of blood pressure control has been noted lately in Swedish patients with either type 1 or type 2 diabetes[139] but despite this, a majority of patients with type 2 diabetes have been found to have higher than optimal office blood pressure levels[140].

AIMS

The general aim of this thesis has been to explore how blood pressure levels obtained with different measurement techniques and during different circumstances correlate with the degree of organ damage and prognosis in patients with diabetes. Specific aims were:

- to explore the prevalence of the novel concept of masked nocturnal hypertension, defined as ambulatory nocturnal hypertension despite office normotension, and its association with arterial stiffness, in patients with type 2 diabetes.
- to explore the prognostic impact of a high admission systolic blood pressure in patients admitted to intensive cardiac care units for chest pain.
- to explore the associations between beta blocker treatment and office, ambulatory and central pulse pressures in patients with type 2 diabetes who received antihypertensive treatment.
- to describe the prevalence of central pulse pressure elevation in patients with type 2 diabetes and office normotension.
- to explore the associations between central pulse pressure elevation, arterial stiffness and carotid intima-media thickness in office normotensive patients with type 2 diabetes.
- to explore whether ambulatory systolic blood pressure levels predict left ventricular mass index independently of central systolic blood pressure levels in patients with type 2 diabetes.

MATERIALS AND METHODS

Study populations

Two different study populations were studied in the papers that constitute this thesis: the participants of the CARDIPP (Cardiovascular Risk factors in Patients with Diabetes – a Prospective study in Primary care) study, and patients registered in the Swedish national quality registry RIKS-HIA (Registry of Information and Knowledge about Swedish Heart Intensive care Admissions). CARDIPP is an observational prospective community-based cohort study launched in 2005. The general aim of the study is to explore the prevalence and impact of cardiovascular risk factors in patients with type 2 diabetes. CARDIPP comprises data on an extended annual follow up of 761 patients with type 2 diabetes, aged 55-65 years, consecutively recruited by specially trained nurses from 22 different primary health care centres in the counties of Östergötland and Jönköping, Sweden. Patients with concomitant severe physical or mental disease (for instance terminal cancer or dementia) were not eligible for inclusion. The investigation included a standard medical history, covering data on known diabetes duration and on-going medication. All patients also underwent office and ambulatory blood pressure measurements, central blood pressure measurements, aortic PWV measurements, ultrasonographic evaluation of the carotid arteries and echocardiography, as described in detail below. Blood specimens were drawn in the morning following a 10 hour over-night fast. Routine blood tests such as HbA1c, plasma glucose and serum lipids were analysed. HbA1c was analysed according to the Swedish Mono-S HPLC standard, which yields values approximately one percent unit below the DCCT standard[141]. The participating study centres are located in different demographic areas and are differing in size but the management and care of type 2 diabetes were organised similarly and all centres adhered to the same national guidelines of diabetes care. Additionally, 199 persons aged 50-70 years, without previously known or newly detected diabetes and without a family history or own diagnosis of aortic aneurysms, were recruited from the population of Linköping. All participants who accepted participation in this project, which was entitled CAREFUL (Cardiovascular Reference Population), underwent the same study protocol as the participants of the CARDIPP study. Results from the CAREFUL cohort have been published[142], but are not included in this thesis. RIKS-HIA is a Swedish national quality registry. As described in detail previously[143], all patients admitted to Swedish ICCU´s (Intensive Cardiac Care Units) are registered in RIKS-HIA. Data such as age, sex, smoking status, electrocardiographic findings, and previous medication are entered by the admitting nurse. Laboratory findings, results from diagnostic and prognostic tests such as coronary angiography, echocardiography and exercise stress testing, together with outcomes and complications of therapeutic interventions are registered during the stay at the ward. The discharging physician registers diagnoses and medication at discharge.

In Paper I, we analysed data from all 414 participants in the CARDIPP study who had completed the baseline study analyses by November 2008 and for which complete data concerning nocturnal blood pressure levels and aortic pulse wave velocity were available. *In Paper II*, we analysed data from all 119 151 patients registered in RIKS-HIA from May 1997 to the end of December 2006 who were admitted with chest pain and who had a potential follow-up time of at least one year, and who had a pulse pressure ≥10 mmHg at admission. Of these, 21 488 had previously diagnosed diabetes. Mortality data were obtained from the Swedish National Death Registry. *In Paper III*, we analysed data from all 228 participants in the CARDIPP study who had completed the baseline study analyses by December 2006 and for which complete data concerning office, ambulatory and central blood pressure and

echocardiographically determined LVMI were available. *In Paper IV*, we analysed data from all 688 participants in the CARDIPP study for which complete baseline data concerning office and central pulse pressure, aortic PWV and carotid IMT were available. *In Paper V*, we analysed data from all 460 participants in the CARDIPP study for which complete baseline data concerning office, ambulatory and central blood pressure and LVMI were available, and in which the success rate of the ambulatory blood pressure measurements was 70% or higher.

Blood pressure measurements

In paper I, III, IV and V, office blood pressure was the average of three seated measurements taken one minute apart by specially trained nurses at the participating primary health care centres. Normal office blood pressure was defined as office blood pressure <130/80 mmHg with or without antihypertensive treatment. *In paper I and III*, office blood pressure is referred to as clinic blood pressure. *In paper II*, systolic blood pressure at admission was defined as the blood pressure first obtained at the presentation to the ICCU, measured with the patient resting in the supine position. *In paper I, III and V*, ambulatory blood pressure measurement devices (Spacelab 90217, Spacelabs Inc., Redmond, Washington, USA) were set to measure the BP at 20-minute intervals for 24 hours. Night time was defined as the period between the time when the patient reported going to bed and the time when the patient reported getting out of bed the following morning. *In paper V*, only participants with ≥70% successful ambulatory blood pressure measurements were included.

Applanation tonometry

In paper I, III, IV and V, the radial artery pressure waveform was recorded for 10 seconds with a Millar pressure tonometer and the Sphygmo-Cor system (Model MM3, AtCor Medical, Sydney, Australia). The radial pulse wave was calibrated to brachial blood pressure, measured with an automated oscillometric device. From the average radial pulse wave form, the corresponding ascending aortic pulse wave form was derived, using a validated generalised transfer function[51-53] incorporated in the software (SphygmoCor software, version 7.0), which also provided the calculated central blood pressure and the calculated central AIx. For the analysis of aortic PWV, sequential electrocardiogram-gated recordings of the carotid and femoral pulse waves, respectively, were performed. The pulse wave transit time was calculated by subtracting the time between the ECG R-wave and the arrival of the pulse wave to the carotid measurement site from the time between the ECG R-wave and the arrival of the pulse wave to the femoral measurement site. The surface distance was defined as the distance between the suprasternal notch and the femoral measurement site, subtracted by the surface distance between the suprasternal notch and the carotid measurement site. Aortic PWV was calculated by dividing the surface distance with the pulse wave transit time. All applanation tonometric investigations were performed at the University Hospital in Linköping or at the County Hospital Ryhov, Jönköping, Sweden.

Echocardiography

Echocardiography was performed with the patient in the left semi-lateral position, and left ventricular mass was determined according to the method described by Devereux[144]. Basic measurements of the dimensions of the left ventricle in diastole and systole, and intra-ventricular septum thickness and posterior wall thickness in diastole were done in M-mode. The Penn convention was then used for the calculation of left ventricular mass. All echocardiographic investigations were performed at the University Hospital in Linköping or

at the County Hospital Ryhov, Jönköping, Sweden. *In paper I, III and V*, indexation was made for body surface area (expressed with the unit g/m^2) and LVH was defined as LVMI ≥125 g/m^2 in men and LVMI ≥110 g/m^2 in women according to the ESH guidelines for risk stratification of patients with hypertension[12]. *In paper V*, left ventricular mass was additionally indexed for height in meters to the power of 2.7 (expressed with the unit g/m$^{2.7}$) in order to make comparisons with other studies more feasible.

Carotid ultrasonography

In paper III and IV, carotid IMT was measured in B-mode, using Philips ATL HDI 5000 (Philips Ultrasound, Seattle, USA) with a 4-7 MHz linear transducer. Three consecutive longitudinal images, frozen in diastole, were analysed with software for off-line measurement of IMT (Artery Measurement System II; Image and Data Analysis, Gothenburg, Sweden). A section of 10 mm in proximity of the carotid bulb was measured manually by tracing a cursor along the echo wedges. A mean value from the right and left carotid arteries was calculated. All carotid investigations were performed at the University Hospital in Linköping or at the County Hospital Ryhov, Jönköping, Sweden.

Statistics

All statistical tests were two-sided. Statistical significance was defined as $p < 0.05$. No adjustments were made for multiple comparisons. In all papers, between-group differences were tested for statistical significance with independent t-tests for numerical variables and with either the Chi-square test or with Fisher´s exact test for categorical variables. Strengths of correlations between numerical variables were tested with bivariate correlation analyses and presented as Pearsons´s correlation coefficients (r). Results of multiple regression analyses are presented as standardised regression coefficients (β) of the independent variables of the models. *In paper II*, survival analyses were performed with Cox proportional hazards models. Hazard ratios between quartiles of systolic blood pressure were compared using the Mantel-Cox method (log-rank test). The assumption of proportional hazards was tested with the Nelson-Aalen method. *In paper V*, the degrees of multicollinearity between related independent variables were evaluated by calculating variation inflation factors. *In paper I, III, IV and V*, and in the preliminary analyses of *paper II*, SPSS software (SPSS, Chicago, IL, USA) was used for statistical analyses. The final analyses of *paper II* were performed with Stata software (Stata-Corp, College Station, TX, USA).

Ethics

All patients in CARDIPP gave written informed consent for participation in the study. The RIKS-HIA registry, and the merging of its data with other registries, was approved by the National Board of Health and Welfare and the Swedish Data Inspection Board. All patients for whom data were entered into RIKS-HIA gave informed consent for participation in the registry (patients could request to be excluded) as well as for the long-term follow-up. All studies were approved by local ethical review boards and followed the principles expressed in the Declaration of Helsinki.

RESULTS AND DISCUSSION

Paper I

Results

By the time of writing this manuscript, complete data for ambulatory nocturnal blood pressure and aortic PWV were available in 414 CARDIPP participants, 100 of which were office normotensive (office blood pressure <130/80 mmHg). Among the patients with office normotension, there were 30 patients with nocturnal hypertension (mean night-time ambulatory blood pressure ≥120/70 mmHg), and thus the prevalence of masked nocturnal hypertension was 30/414=7.2% in the entire cohort and 30/100=30% in the subgroup with office normotension. The study design is illustrated in Figure 3.

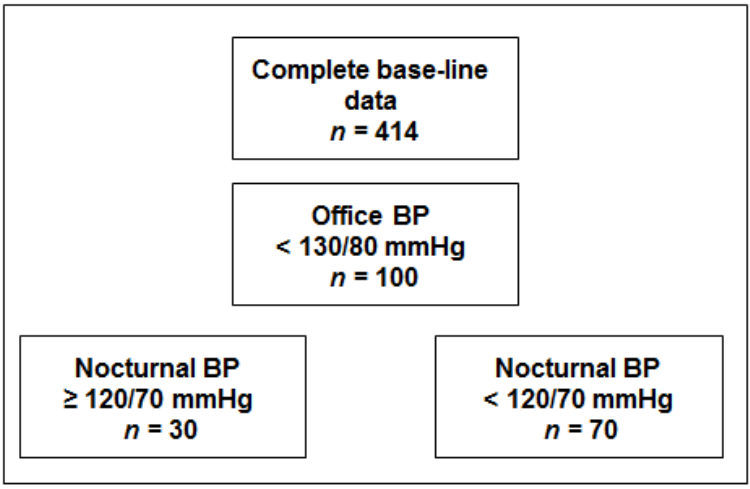

Figure 3. Study design of Paper I.

As shown in Table 4, patients with office normotension and nocturnal hypertension had significantly higher aortic pulse wave velocity and central blood pressure than patients with office normotension and nocturnal normotension. Day-time blood pressure was significantly higher in the patients with nocturnal hypertension than in the patients with nocturnal normotension, but there was only a statistically non-significant trend towards higher office blood pressure in the patients with nocturnal hypertension.

	Nocturnal hypertension	Nocturnal normotension	*p*
	***n*=30**	***n*=70**	
Office SBP (mmHg)	121.8±4.9	119.4±6.9	0.08
Office DBP (mmHg)	72.1±6.0	70.7±6.0	0.31
Night-time SBP (mmHg)	125.7±8.9	106.1±6.6	<0.01
Night-time DBP (mmHg)	72.4±5.9	61.2±4.9	<0.01
Day-time SBP (mmHg)	132.5±11.1	125.0±8.8	<0.01
Day-time DBP (mmHg)	78.7±6.6	74.9±6.0	<0.01
Central SBP (mmHg)	117.6±13.9	110.4±16.4	0.04
Central DBP (mmHg)	74.0±9.1	69.7±9.6	0.04
Aortic PWV (m/s)	10.2±1.8	9.4±1.7	0.03

Table 4. Haemodynamic and vascular characteristics in 100 patients with type 2 diabetes and office normotension, with or without nocturnal hypertension. Data are means±SD. DBP, diastolic blood pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

Among the 414 patients, there were 164 patients who did not use any antihypertensive medications (beta blockers, calcium channel blockers, diuretics or ACE inhibitors/ARBs), 48 of which had office blood pressure <130/80 mmHg. In this group, we found nocturnal hypertension in 15 patients. Thus, the prevalence of masked nocturnal hypertension was 15/164=9.1% in the entire cohort that did not use antihypertensive medications, and 15/48=31% in the subgroup with office normotension. Untreated patients with masked nocturnal hypertension had significantly higher aortic PWV (10.6±2.2 m/s vs. 9.0±1.5 m/s; $p<0.01$), central aortic systolic BP (118.3±16.4 mmHg vs. 106.5±12.5 mmHg; $p<0.01$) and central aortic diastolic BP (74.6±7.4 mmHg vs. 68.6±8.8 mmHg; $p=0.03$) than untreated patients with office normotension and night-time normotension.

Discussion

The most important finding of this study was that nocturnal hypertension was found in 30% of patients with office normotension. This phenomenon, masked nocturnal hypertension, has to the best of our knowledge not been described previously in diabetes. It was associated with increased arterial stiffness, measured as increased aortic pulse wave velocity, and with higher central blood pressure. Office blood pressure, however, was not significantly higher in patients with masked nocturnal hypertension than in patients with nomotension both in the office and during the night. Taken together, these data indicate that ambulatory blood pressure measurements can be used to identify patients who, despite office normotension, are hypertensive during the night, and suggest that masked nocturnal hypertension is not an innocent condition, due to its association with other markers of increased risk.

Blood pressure is usually lower during the night than during the day, and a decreased nocturnal blood pressure decline (the so-called "non-dipping" phenomenon) has been associated with increased risk for cardiovascular mortality in patients with or without high ambulatory blood pressure levels[145]. The clinical entity of masked nocturnal hypertension is

different from “non-dipping” in that it requires nocturnal blood pressure to be high, whereas a person can have normal or even low nocturnal blood pressure, and still be a “non-dipper”, if day-time blood pressure is low enough. However, there is evidence that in patients with type 2 diabetes, actual blood pressure means are more important determinants than the presence or absence of a “non-dipping” blood pressure pattern for the severity of hypertension-related target organ damage[146]. Therefore, we believe that masked nocturnal hypertension is a more relevant marker of risk than “non-dipping”. However, we cannot tell from the results of the present study whether masked nocturnal hypertension is indeed associated with a poor prognosis, only that it is associated with markers of increased cardiovascular risk. We also cannot tell whether tailored blood pressure treatment that targets nocturnal blood pressure elevations specifically (i.e., bed-time administration of antihypertensive drugs) would be associated with an improved prognosis. Future studies will have to be designed to answer these important questions. Furthermore, based on our results we cannot establish whether there is a causal relationship between masked nocturnal hypertension and increased arterial stiffness.

Our results do not reveal the mechanisms underlying masked nocturnal hypertension. Previously, high nocturnal blood pressure levels have been proposed as an adaptive mechanism by which individuals with impaired capacity to excrete enough amounts of sodium in the urine during the day can, by pressure-dependent nocturnal natriuresis, maintain 24-hour sodium balance. Data to support this hypothesis include the observation that individuals who excrete only a small proportion of their total 24-hour urinary sodium during the day, have higher nocturnal blood pressure levels than patients who excrete a larger proportion of their total 24-hour urinary sodium during the day[147]. It has also been shown that in patients with chronic renal failure, the time it takes until the mean arterial nocturnal blood pressure falls below 90% of the mean arterial day-time blood pressure was negatively associated with the renal function, so that in patients with more advanced renal failure, blood pressure remained high for a longer period during the night[148]. Whether nocturnal hypertension caused renal dysfunction and an increased nocturnal sodium excretion, or whether renal dysfunction contributed to the development of nocturnal hypertension could not be clarified from those observational data, but decreased kidney function and impaired renal electrolyte handling seem to be associated with high nocturnal blood pressure. Obstructive sleep apnea may also contribute to nocturnal blood pressure elevation, but we have no data on its prevalence in the CARDIPP cohort.

Paper II

Results

The study cohort comprised 119 151 patients, 21 488 of which had previously known diabetes. Patients were divided in quartiles (Q1-Q4) according to their systolic blood pressure at admission (the blood pressure first obtained at the ICCU). Important patient characteristics according to quartiles are shown in Table 5. Admission systolic blood pressure was <128 mmHg in Q1, 128-144 mmHg in Q2, 145-162 mmHg in Q3, and ≥163 mmHg in Q4. The total range of admission systolic blood pressures in the entire cohort was 40 – 290 mmHg.

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
	***n*=29 802**	***n*=32 165**	***n*=27 522**	***n*=29 662**
Age (years)	66.6±15	65.8±14	67.8±13	69.9±12
Women, *n* (%)	10 735 (36)	11 556 (36)	10 898 (40)	13 494 (45)
BMI (kg/m^2) [a]	26.0±4.4	26.7±5.4	26.9±4.6	27.1±4.7
Smoking, *n* (%) [b]	15 860 (58)	16 708 (56)	13 489 (53)	13 912 (51)
Diabetes, *n* (%) [c]	5002 (17)	5581 (17)	5045 (18)	5860 (20)
Systolic blood pressure (mmHg)	113.0±12	136.9±5.2	154.5±4.8	183.1±16
Diastolic blood pressure (mmHg)	68.5±12	78.4±11	85.1±13	94.0±16
Heart rate (bpm)	78.8±27	76.3±22	76.6±20	77.6±20

Table 5. Patient characteristics according to quartiles of admission systolic blood pressure. BMI, body mass index; bpm, beats per minute. Data are either means ±SD or *n* (%).
[a]Complete data available for 57 308 patients.
[b]Ex-smokers and current smokers combined.
[c]Known diabetes at admission.

Quartile 2 was used as the reference, since this blood pressure range was considered to be closest to a normal blood pressure level. The HRs for one-year mortality were 1.46 (95% CI 1.39-1.52) for patients in Q1, 0.83 (95% CI 0.79-0.87) for patients in Q3 and 0.76 (95% CI 0.72-0.80) for patients in Q4, following adjustment for age, sex, smoking, diastolic blood pressure, use of antihypertensive medications and nitroglycerin at admission, and use at discharge of antihypertensive medications, statins, other lipid-lowering medications and antiplatelet and anticoagulant medications (*n*=118 607 with data on all covariates). Survival curves for all patients with complete data on all covariates are shown in Figure 4 according to quartiles of admission systolic blood pressure.

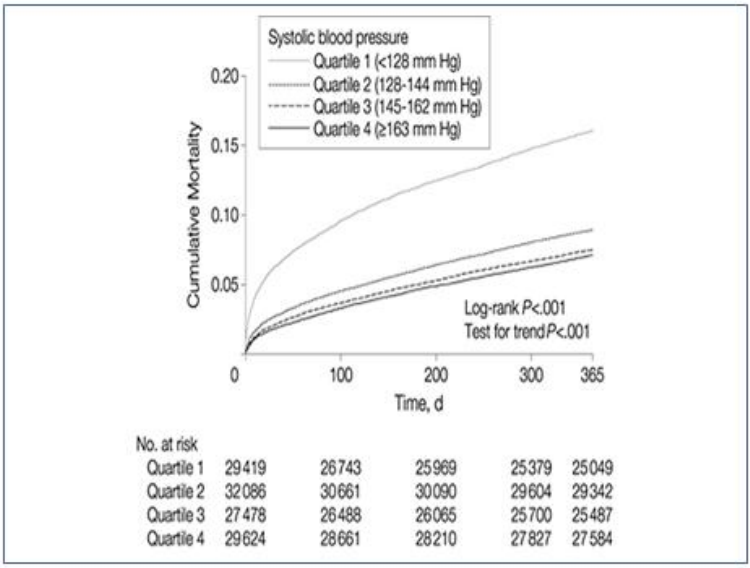

Figure 4. Cumulative one-year mortality by quartiles of admission systolic blood pressure.

Following exclusion of patients who died in hospital, the risk of dying within one year remained significantly lower in Q4 than in Q2. The same general finding of a better prognosis for patients in Q4 compared with patients in Q2 was found in other subgroups as well, such as in the patients who eventually were discharged with a final diagnosis of myocardial infarction or angina (HR for one-year mortality was 0.75, 95% CI 0.71-0.80 for patients in Q4 compared with patients in Q2; *n*=56 585 with data on all covariates) as well as in the 27 482 patients who eventually were discharged with only the diagnosis chest pain - i.e., no cardiac disease had been found to explain their chest pain - (HR for one-year mortality was 0.81, 95% CI 0.68-0.97 for patients in Q4 compared with patients in Q2).

In Table 6, cumulative one-year mortality hazard ratios, adjusted for age, sex, smoking, diastolic blood pressure, use of antihypertensive medications and nitroglycerin at admission, and use at discharge of antihypertensive medications, statins, other lipid-lowering medications and antiplatelet and anticoagulant medications are shown for the patients with previously known diabetes. Again, high systolic blood pressure was associated with a lower risk for one-year mortality. Treatment with any antihypertensive drug at admission was associated with an increased risk for one-year mortality, whereas treatment with any antihypertensive drug (except for diuretics) at discharge was associated with a decreased risk for one-year mortality.

	HR (95% CI)	*p*
Quartile 1	1.47 (1.35-1.61)	<0.01
Quartile 2	1	-
Quartile 3	0.88 (0.80-0.96)	<0.01
Quartile 4	0.83 (0.75-0.91)	<0.01
Smoking	1.12 (1.06-1.18)	<0.01
Sex	0.85 (0.80-0.91)	<0.01
Age	1.07 (1.06-1.07)	<0.01
Diastolic blood pressure	1.00 (1.00-1.00)	0.55
Medication use at admission		
ACE inhibitor	1.13 (1.03-1.23)	<0.01
ARB	1.21 (1.08-1.36)	<0.01
Beta blocker	1.27 (1.17-1.37)	<0.01
Calcium channel blocker	1.12 (1.02-1.23)	0.01
Diuretic	1.56 (1.42-1.71)	<0.01
Nitroglycerin	1.17 (1.10-1.25)	<0.01
Medication use at discharge		
ACE inhibitor	0.86 (0.79-0.94)	<0.01
ARB	0.83 (0.73-0.94)	<0.01
Beta blocker	0.72 (0.66-0.78)	<0.01
Calcium channel blocker	0.76 (0.69-0.84)	<0.01
Diuretic	1.30 (1.19-1.43)	<0.01
Statin	0.72 (0.67-0.77)	<0.01
Other lipid lowering drug	0.95 (0.84-1.07)	0.40
Aspirin	0.77 (0.71-0.84)	<0.01
Other antiplatelet drug	1.01 (0.95-1.07)	0.76
Anticoagulant	0.75 (0.67-0.83)	<0.01

Table 6. Cumulative one-year mortality hazard ratios for patients with previously known diabetes, hospitalised with acute chest pain. For blood pressure quartiles, comparisons are made with Q2 as reference. Adjustments, see text. Smoker=sum of ex-smokers and current smokers. Sex=0 for women, 1 for men.

Discussion

The main finding of this study was that, in patients with or without previously known diabetes who were hospitalised for acute chest pain, a higher blood pressure at admission was associated with a lower risk of dying within one year. Results were similar regardless of whether patients were discharged with a diagnosis of ischaemic heart disease or whether they were discharged with no other diagnosis than chest pain. This suggests that in patients hospitalised with acute chest pain, admission blood pressure values can be used for the purpose of long-term risk stratification already before the underlying diagnosis is known.

In an American registry of patients hospitalised with acute heart failure, the risk for in-hospital mortality increased with lower admission systolic blood pressure as did the risk for post-discharge mortality[149]. In our study population, however, the main finding was unaffected by exclusion of patients who died in hospital, suggesting that our findings could not be attributable to a poor prognosis of patients in cardiogenic chock with expected poor short-term prognosis and low blood pressure at admission.

Strengths of this study include the large number of patients included, and that no patients were lost to follow-up. Furthermore, patients admitted to ICCU´s were included in the RIKS-HIA registry consecutively, without any specific inclusion and exclusion criteria, which make it likely that the data we present are valid in the every-day clinical setting. Study limitations include that blood pressures were measured in a non-standardised way, and thus may not be as exact as when measured by specially trained personnel. It may also be argued that a low blood pressure at admission may be due to generalised chronic diseases such as anaemia or cachexia, factors for which we are unable to adjust. Thus, our results do not reveal the mechanisms that may explain the association between high admission systolic blood pressure and low one-year mortality. Nonetheless, this does not diminish the potential clinical usefulness of the admission systolic blood pressure for prognostic purposes.

It is important to point out that our results should not be interpreted as a suggestion not to lower an elevated blood pressure in a patient with acute chest pain. Likewise, it should be stressed that the blood pressure levels we report were measured at admission, and should not be confused with blood pressure levels at discharge, since uncontrolled hypertension at discharge following an acute coronary event has previously been associated with a poor prognosis[150]. Finally, it could be suggested that patients with high blood pressure at presentation were those who were most likely to tolerate increased doses of antihypertensive drugs with cardiovascular protective effects, which might partly explain their more favorable prognosis. It was recently shown, for instance, that in patients who were hospitalised for acute heart failure, the magnitude of the systolic blood pressure reduction from admission to discharge was associated with decreased risk for one-year post-discharge mortality as well as with the number of newly introduced blood pressure lowering drugs[151]. However, since we adjusted for use of antihypertensive medications at discharge, this does not seem to entirely explain our results.

Paper III

Results

By December 2006, complete data concerning office, 24-hour ambulatory and central blood pressure and LVMI were available in 228 CARDIPP participants, 124 of which were treated with at least one antihypertensive drug (beta blockers, calcium channel blockers, diuretics or ACE inhibitors/ARBs). Among the patients who used at least one antihypertensive drug, 67 used beta blockers and 57 used any other of the above-mentioned antihypertensive drugs. The study design is illustrated in Figure 5.

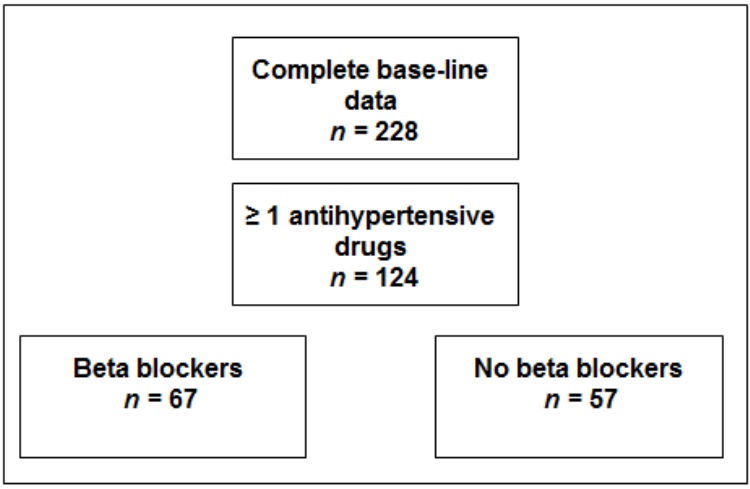

Figure 5. Study design of Paper III.

As shown in Table 7, patients treated with beta blockers had significantly higher central pulse pressure than patients treated with other antihypertensive drugs, despite there being no significant inter-group difference concerning pulse pressure measured in the office or during 24-hour ambulatory blood pressure measurement. Similarly, central AIx was significantly higher in patients treated with beta blockers than in patients treated with other antihypertensive drugs. We also found significantly higher LVMI in patients treated with beta blockers than in patients treated with other antihypertensive drugs. There was no significant inter-group difference, however, concerning aortic PWV or carotid IMT.

	No beta blockers	Beta blockers	*p*
	***n*=57**	***n*=67**	
Clinic PP (mmHg)	58.9±13.1	60.4±16.3	0.59
Clinic SBP (mmHg)	139.7±16.7	139.0±18.6	0.83
Clinic DBP (mmHg)	80.8±10.1	78.7±10.9	0.26
Ambulatory PP (mmHg)	54.8±10.6	55.2±9.1	0.80
Ambulatory SBP (mmHg)	132.3±12.3	130.3±13.5	0.40
Ambulatory DBP (mmHg)	77.5±9.2	75.1±8.7	0.14
Central PP (mmHg)	45.1±10.2	49.6±12.2	0.03
Central SBP (mmHg)	119.8±13.8	125.1±16.6	0.06
Central DBP (mmHg)	74.7±8.9	75.5±10.9	0.67
Ambulatory heart rate (bpm)	75.9±10.2	65.9±9.2	<0.01
Central AIx (%)	25.8±8.8	30.7±8.4	<0.01
Aortic PWV (m/s)	10.5±2.6	10.5±1.8	0.99
Carotid IMT (mm)	0.72±0.16	0.72±0.25	0.98
LVMI (g/m^2)	117.4±27.4	129.5±29.7	0.02

Table 7. Haemodynamic, cardiac and vascular characteristics in 124 patients with type 2 diabetes, using at least one antihypertensive drug, according to the use of beta blockers. Data are means±SD. Ambulatory blood pressure parameters refer to mean 24-hour values. AIx, augmentation index; bpm, beats per minute; DBP, diastolic blood pressure; IMT, intima-media thickness; LVMI, left ventricular mass index; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

When the analyses were restricted to only patients without a history of angina pectoris, previous myocardial infarction or previous coronary artery bypass surgery (*n*=99), patients treated with beta blockers (*n*=47) still had significantly higher central pulse pressure (beta blocker: 49.9±12.1 mmHg, no beta blocker: 45.3±10.5 mmHg; *p*=0.05) and higher central AIx (beta blocker: 31.4±8.2%, no beta blocker: 26.1±8.7%; *p*<0.01) than patients treated with other antihypertensive drugs, despite there being no significant inter-group difference concerning pulse pressure measured in the office (beta blocker: 61.6±16.3 mmHg, no beta blocker: 59.4±13.4 mmHg; *p*=0.47) or during ambulatory blood pressure measurement (beta blocker: 55.1±9.1 mmHg, no beta blocker: 55.0±10.8 mmHg; *p*=0.98). However, LVMI was only non-significantly higher in patients treated with beta blockers than in patients treated with other antihypertensive drugs (beta blocker: 124.3±27.3 g/m^2, no beta blocker: 116.4±24.7 g/m^2; *p*=0.14).

Discussion

The principal finding in this study was that in patients with type 2 diabetes, patients with a blood pressure lowering drug regimen that included a beta blocker had significantly higher

central pulse pressure and central AIx than patients using blood pressure lowering drug regimens that did not include beta blockers. Despite this, office and ambulatory pulse pressures did not differ significantly between patients treated with beta blockers and patients treated with other antihypertensive drugs.

Central pulse pressure elevation is usually thought of as a consequence of arterial stiffening. In our study, however, aortic PWV was similar in patients treated with beta blockers and in patients treated with other antihypertensive drugs. Carotid IMT, another marker of atherosclerosis, was also similar between groups, suggesting that patients had a similar degree of atherosclerotic burden regardless of beta blocker treatment status. The two comparator groups were, however, unbalanced in terms of a previous history of ischaemic heart disease, which is a study limitation. Most likely, this is explained by the fact that patients using beta blockers may have had them prescribed as primary or secondary prevention for ischaemic heart disease, rather than as antihypertensive drugs. We tried to explore whether the uneven distribution of ischaemic heart disease was a source of bias, by excluding all patients with either angina pectoris, previous myocardial infarction or previous coronary artery bypass surgery, and then repeating the analyses, and found that the principal finding of the study remained unaltered. Since the study population was rather small, however, this post-hoc subgroup analysis may have been underpowered, and we therefore also performed a multivariable regression analysis in all patients, and found a negative association between previous myocardial infarction and central pulse pressure levels, suggesting that the uneven distribution of previous myocardial infarctions may, if anything, have diluted the magnitude of our findings. Other study limitations include that we cannot determine whether our findings can be attributed to an association between beta blockers and a high central pulse pressure, or to an association between other antihypertensive drug classes and a low central pulse pressure.

Our results suggest that the selective reduction of brachial rather than central blood pressure parameters, which has been attributed to beta blockers in randomised clinical trials[59], may be of importance also in patients with type 2 diabetes treated in usual care. The clinical implication of this study is that patients treated with different blood pressure lowering regimens may have different central pulse pressure levels, despite having similar brachial pulse pressures as measured either in the office or during ambulatory blood pressure measurements.

Paper IV

Results

Complete data concerning office and central blood pressure, carotid IMT and aortic PWV were available in 688 CARDIPP participants. Among these, 167 patients had office normotension, defined as nurse-recorded office blood pressure <130/80 mmHg, 32 of which had central pulse pressure ≥50 mmHg. The remaining 135 patients with office normotension had central pulse pressure <50 mmHg. As shown in Table 8, central systolic blood pressure, office pulse pressure and, obviously, central pulse pressure, were significantly higher in the group with office normotension and high central pulse pressure than in the group with office normotension and normal central pulse pressure. The two markers of atherosclerosis of interest for this paper, carotid IMT and aortic PWV, were both significantly higher in the group with high central pulse pressure than in the group with normal central pulse pressure (Table 8).

	Central PP ≥50 mmHg	**Central PP <50 mmHg**	***p***
	***n*=32**	***n*=135**	
Office SBP (mmHg)	120.7±8.0	118.6±6.7	0.13
Office DBP (mmHg)	70.0±6.0	71.3±5.9	0.29
Office PP (mmHg)	50.7±8.0	47.4±8.1	0.039
Central SBP (mmHg)	131.2±12.7	106.9±11.2	<0.01
Central DBP (mmHg)	73.4±9.1	70.6±8.7	0.11
Central PP (mmHg)	57.8±9.1	36.3±6.7	<0.01
Carotid IMT (mm)	0.76±0.2	0.71±0.1	0.041
Aortic PWV (m/s)	11.0±2.5	9.5±1.8	<0.01

Table 8. Office and central blood pressure levels, and markers of atherosclerosis, in 167 patients with type 2 diabetes and office normotension (office blood pressure <130/80 mmHg) with or without central pulse pressure ≥50 mmHg. Data are means±SD. DBP, diastolic blood pressure; IMT, intima-media thickness; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.

In two different bivariate correlation analyses, in which all 167 patients with clinical normotension were included, central pulse pressure correlated significantly with carotid IMT (r=0.20, p=0.01) and with aortic PWV (r=0.34, p<0.01). The scatter plots in Figure 6 illustrate the relationships between central pulse pressure and carotid IMT and aortic PWV, respectively.

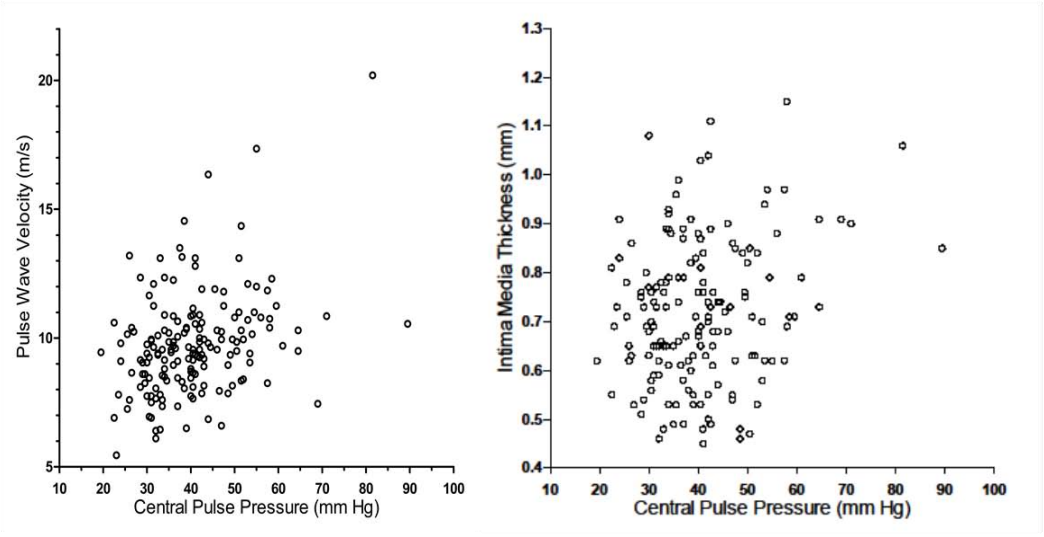

Figure 6. Scatter plots showing, in 167 patients with type 2 diabetes and office normotension, the relationships between central pulse pressure and aortic pulse wave velocity (left, r=0.34, p<0.01) and carotid IMT (right, r=0.20, p=0.01), respectively.

When a multivariable regression model, in which carotid IMT was the dependent variable and in which CPP elevation (entered as a dummy variable where 0 indicated CPP <50 mmHg and 1 indicated CPP≥ 50 mmHg), age, sex (0=male, 1=female) and separate dummy variables for each major antihypertensive drug class (diuretics, beta blockers, ACE inhibitors/ARBs, calcium channel blockers) and for statin treatment (0=not treated, 1=treated) were forced-entered as independent variables and applied on all 167 patients with clinical normotension, CPP elevation status predicted carotid IMT positively (standardised regression coefficient β=0.16), significantly (p=0.046) and independently of all other covariates. When instead PWV was used as the dependent variable in an otherwise identical multivariable regression model, CPP elevation predicted PWV positively (standardised regression coefficient β=0.29), significantly (p <0.01) and independently of all other covariates.

Discussion

The most important finding of this study was that almost one in five patients with type 2 diabetes and excellent office blood pressure control had elevated central pulse pressure. We also found an independent association between central pulse pressure elevation and markers of both structural (increased carotid IMT) and functional (increased aortic PWV) atherosclerotic changes. Furthermore, when treated as a continuous variable, central pulse pressure was significantly associated with both of these markers. This suggests that additional investigation with central pulse pressure measurements may help clinicians to identify patients with type 2 diabetes who, despite excellent office blood pressure control, have markers of increased cardiovascular risk.

As for masked nocturnal hypertension in Paper I, we cannot establish whether there is a causal relationship between central pulse pressure elevation and markers of increased atherosclerosis, and the mechanisms that might explain the rather high prevalence of central pulse pressure elevation in our cohort remain to be elucidated. It has been shown previously, however, that the amplification factor that describes the peripheral amplification of the pulse pressure from the aorta to the brachial artery, is decreased in patients with diabetes[47], which in our opinion is in line with our findings. However, to the best of our knowledge, the prevalence of central pulse pressure elevation in patients with type 2 diabetes and excellent office blood pressure control has not been described in any other cohort previously. Importantly, we cannot tell, based on our cross-sectional data, whether central pulse pressure elevation is associated with an increased risk for macrovascular diabetes complications in otherwise normotensive patients, although based on previous findings from the Strong Heart Study[70] we believe that this could reasonably be assumed. Whether these patients would benefit from more aggressive risk factor control, remains to be determined in clinical trials.

Paper V

Results

Complete data for office, ambulatory and central blood pressure and LVMI were available in 509 CARDIPP participants, 460 of which had a success rate of ≥70% of the ambulatory blood pressure readings. These 460 participants were included in this analysis. Five different multivariable regression models were constructed, in which LVMI was the dependent variable and age, sex, body mass index, ambulatory 24-hour heart rate, duration of known diabetes and presence or absence of any antihypertensive medication (any of the following medications: beta blockers, ACE inhibitors, ARBs, calcium channel blockers or diuretics) were used as independent variables together with office systolic blood pressure (model 1) and with the addition of either 24-hour ambulatory systolic blood pressure (model 2), day-time ambulatory systolic blood pressure (model 3), night-time ambulatory systolic blood pressure (model 4) or central systolic blood pressure (model 5). Two sets of each model were constructed, where left ventricular mass was indexed either for body surface area or for height to the power of 2.7. The standardised regression coefficients for all systolic blood pressure variables are presented in Table 9. Office systolic blood pressure predicted LVMI independently and significantly in model 1, but lost its statistical significance and was replaced by 24-hour ambulatory systolic blood pressure in model 2, by day-time ambulatory systolic blood pressure in model 3, and by night-time ambulatory systolic blood pressure in model 4. In model 5, office systolic blood pressure remained a significant and independent predictor of LVMI, whereas central systolic blood pressure did not predict LVMI significantly and independently in that model. Four additional multivariable regression models were constructed, in which LVMI was again the dependent variable and age, sex, body mass index, ambulatory 24-hour heart rate, duration of known diabetes and presence or absence of any antihypertensive medication (same drug classes as above) were used as independent variables together with central systolic blood pressure (model 6) and with the addition of either 24-hour ambulatory systolic blood pressure (model 7), day-time ambulatory systolic blood pressure (model 8) or night-time ambulatory systolic blood pressure (model 9). Again, two sets of each model were constructed, where left ventricular mass was indexed either for body surface area or for height to the power of 2.7. The standardised regression coefficients for all systolic blood pressure variables are presented in Table 9. Central systolic blood pressure predicted LVMI independently and significantly in model 6, but lost its statistical significance and was replaced by 24-hour ambulatory systolic blood pressure in model 7, by day-time ambulatory systolic blood pressure in model 8 and by night-time ambulatory systolic blood pressure in model 9. In general, the models accounted for a larger proportion of the variance of left ventricular mass indexed for height to the power of 2.7 (model´s R^2 ranged between 0.34-0.36) than of the variance of left ventricular mass indexed for body surface area (model´s R^2 ranged between 0.22-0.25).

	LVMI (g/m^2)			LVMI ($g/m^{2.7}$)		
	β	***p***	**Model´s R^2**	***β***	***p***	**Model´s R^2**
Model 1			0.23			0.35
Office SBP (mmHg)	0.13	<0.01		0.13	<0.01	
Model 2			0.25			0.36
Office SBP (mmHg)	0.001	0.99		0.03	0.59	
Ambulatory 24-hour SBP	0.20	<0.01		0.16	<0.01	
Model 3			0.25			0.36
Office SBP (mmHg)	0.02	0.80		0.04	0.47	
Ambulatory day SBP	0.17	<0.01		0.14	<0.01	
Model 4			0.25			0.36
Office SBP (mmHg)	0.03	0.54		0.05	0.31	
Ambulatory night SBP	0.18	<0.01		0.15	<0.01	
Model 5			0.23			0.35
Office SBP (mmHg)	0.10	0.04		0.11	0.02	
Central SBP (mmHg)	0.06	0.25		0.05	0.31	
Model 6			0.22			0.34
Central SBP (mmHg)	0.10	0.02		0.09	0.02	
Model 7			0.25			0.36
Central SBP (mmHg)	0.02	0.76		0.02	0.71	
Ambulatory 24-hour SBP	0.19	<0.01		0.17	<0.01	
Model 8			0.25			0.36
Central SBP (mmHg)	0.02	0.63		0.02	0.61	
Ambulatory day SBP	0.17	<0.01		0.16	<0.01	
Model 9			0.25			0.36
Central SBP (mmHg)	0.02	0.63		0.02	0.61	
Ambulatory night SBP	0.18	<0.01		0.17	<0.01	

Table 9. Standardised regression coefficients for left ventricular mass indices, models 1-9. All models adjusted for age, sex, body mass index, ambulatory heart rate, antihypertensive medication, and known diabetes duration. DBP, diastolic blood pressure; LVMI, left ventricular mass index; SBP, systolic blood pressure.

Discussion

In this study we report that in 460 patients with type 2 diabetes, ambulatory systolic blood pressure predicted LVMI independently of central systolic blood pressure. This suggests that, for the purpose of predicting LVMI, central blood pressure levels may be of little additional value if ambulatory blood pressure levels are known. Our findings suggest a plausible

mechanism which might explain the recent finding that ambulatory systolic blood pressure predicted cardiovascular mortality independently of central systolic blood pressure in 1014 healthy Taiwanese people[69]. Another noteworthy finding is that central blood pressure did not predict LVMI independently of office blood pressure, which is in contrast to what has previously been demonstrated in another study of patients with type 2 diabetes[62], although that study was considerably smaller, focused on pulse pressure rather than on systolic blood pressure, and included only selected patients free from known cardiac disease. Our finding that all ambulatory systolic blood pressure measures (24-hour, day-time and night-time) predicted LVMI independently of nurse-recorded blood pressure levels also contradict what has previously been reported[152, 153]. Whether there exist diabetes-specific factors that contribute to the central or office blood pressure-independent association between ambulatory systolic blood pressure levels and LVMI, remains to be elucidated in future studies.

METHODOLOGICAL CONSIDERATIONS

The results of this thesis should be interpreted within the context of its methodological limitations and strengths. Some important methodological issues are discussed below.

Study design and data collection

All data presented in this thesis are based on observational studies. This means that it can be difficult to differentiate between causes and consequences, and that it cannot be established whether the associations we report are causally mediated or not. In *Paper I, III, IV* and *V,* patients were recruited to the CARDIPP study by specially trained nurses working with diabetes in primary health care. In *Paper II,* patients were included in the national quality registry RIKS-HIA. Although patients in all studies were recruited consecutively, we have no data concerning the clinical characteristics of patients who declined to participate (*Papers I-V*) or concerning patients that were not included due to concomitant severe physical or mental disease (*Paper I, III, IV* and *V*). Thus, although we believe that CARDIPP participants are representative of middle aged patients with type 2 diabetes treated in primary care and that patients registered in RIKS-HIA are representative of patients with chest pain treated at ICCU´s, we cannot exclude some degree of inclusion bias which would limit the generalisability of our results. The results in *Paper I, III, IV* and *V* are based on cross-sectional data, which precludes us from drawing any conclusions concerning the predictive value of the risk factors we describe. In all large registries, such as RIKS-HIA in *Paper II*, there is a risk of misclassifications and erroneous data input. However, validations of the RIKS-HIA registry were performed by a specially trained monitor who visited participating hospitals, and found an overall 94% agreement between registry information and individual patient records[154], suggesting that the quality of the RIKS-HIA registry is good.

Ambulatory blood pressure measurements

It has been suggested that the ambulatory blood pressure measurement device itself may have influenced the sleeping pattern of study participants, but we do not believe that this explains the high prevalence of masked nocturnal hypertension in *Paper I*, since studies performed by others have not been able to show an effect on nocturnal blood pressure levels by the measurement device itself, although it may cause brief arousals and alter the depth of sleep[155]. It has also been suggested that one single ambulatory blood pressure measurement is not sufficient to determine the true diurnal blood pressure pattern of an individual patient, since there may be high intra-individual variability concerning the nocturnal blood pressure pattern. However, it was recently shown that short-term reproducibility of nocturnal BP patterns is higher in patients with type 2 diabetes than in patients without diabetes[156], suggesting that in the majority of patients with type 2 diabetes, a single ambulatory blood pressure measurement is sufficient.

Central blood pressure measurements

The methods used in this thesis to estimate central blood pressure levels have been used extensively in clinical trials and epidemiological research. Nonetheless, some inherent methodological limitations need to be considered. Ideally, the blood pressure levels used for calibration of the radial pulse wave should be measured intra-arterially in the radial artery, but since such an approach would require invasive catheter insertion, non-invasively obtained brachial blood pressure is usually considered a surrogate for invasively obtained radial blood pressure. This introduces a potential source of error, since brachial non-invasively measured

blood pressure may not necessarily be the same as radial intra-arterial blood pressure. A second potential source of error is introduced by the application of a generalised transfer function. Although the generalised transfer function has proven to yield accurate estimates of invasively obtained central blood pressure levels[51-53], these validation studies have been performed in small numbers of patients with a clinical indication for invasive central arterial catheter insertion, and it has been suggested that the generalised transfer function may not work as well in certain other patient groups, such as in patients with diabetes[157]. As of today, however, no generally accepted diabetes-specific transfer function has been developed, and therefore we relied on using the methodology which has to date been most widely used in clinical research.

SUMMARY

Antihypertensive treatment has been shown to reduce the risk for micro- and macrovascular diabetes complications. However, the clinical outcome cannot always be predicted from the magnitude of the reduction in office blood pressure[135]. Furthermore, the cardiovascular risk often remains high in patients with diabetes despite intensive antihypertensive treatment[158]. Thus, there is a need to improve risk stratification in patients with diabetes, particularly in patients with normal office blood pressure and in patients who are already treated with antihypertensive medications. In this thesis, blood pressure measurements have therefore been performed during varying circumstances, ranging from extremely stressful (during acute hospitalisation for chest pain) to extremely peaceful (sleeping during the night at home), and in different anatomic locations (the brachial artery and the proximal aorta). The results demonstrate that in patients with type 2 diabetes and excellent office blood pressure control, subgroups of patients with high nocturnal blood pressure or with high central pulse pressure could be identified. These patients exhibited markers of more advanced atherosclerosis. Furthermore, patients with type 2 diabetes treated with beta blockers had significantly higher central pulse pressure than patients treated with other antihypertensive drugs, despite there being no significant inter-group difference concerning office or ambulatory pulse pressure. Together, these findings suggest that if only office blood pressure levels are used for risk stratification and for treatment evaluation, many patients with high residual risk will not be detected. Therefore, additional evaluation with either ambulatory or central blood pressure measurements may be of value in patients with type 2 diabetes. We also compared ambulatory with central blood pressure levels concerning their abilities to independently predict the degree of left ventricular hypertrophy, and found that when entered into the same regression model, ambulatory but not central blood pressure levels predicted LVMI significantly and independently. We also found that in patients with previously known diabetes, blood pressures measured during hospitalisation for acute chest pain were inversely associated with the risk for one-year mortality, which shows that the relationship between prognosis and systolic blood pressure levels measured in the acute setting is inverted compared with the relationship between prognosis and systolic blood pressure levels measured at rest.

CONCLUSIONS

- Nearly one in three patients with type 2 diabetes and office normotension have ambulatory nocturnal hypertension.
- This phenomenon, masked nocturnal hypertension, is associated with increased arterial stiffness.
- In patients admitted to intensive cardiac care units for chest pain, a high systolic blood pressure at admission is associated with a lower one-year mortality rate than is a normal systolic blood pressure at admission.
- Patients with type 2 diabetes who use beta blockers have a higher central pulse pressure than patients with type 2 diabetes who use other antihypertensive drugs.
- Patients with type 2 diabetes who use beta blockers have similar office and ambulatory pulse pressures as patients with type 2 diabetes who use other antihypertensive drugs.
- Nearly one in five patients with type 2 diabetes and office normotension have elevated central pulse pressure levels.
- Elevated central pulse pressure is associated with increased arterial stiffness and with higher carotid intima-media thickness in office normotensive patients with type 2 diabetes.
- Ambulatory systolic blood pressure levels predict left ventricular mass index independently of central systolic blood pressure levels in patients with type 2 diabetes.

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