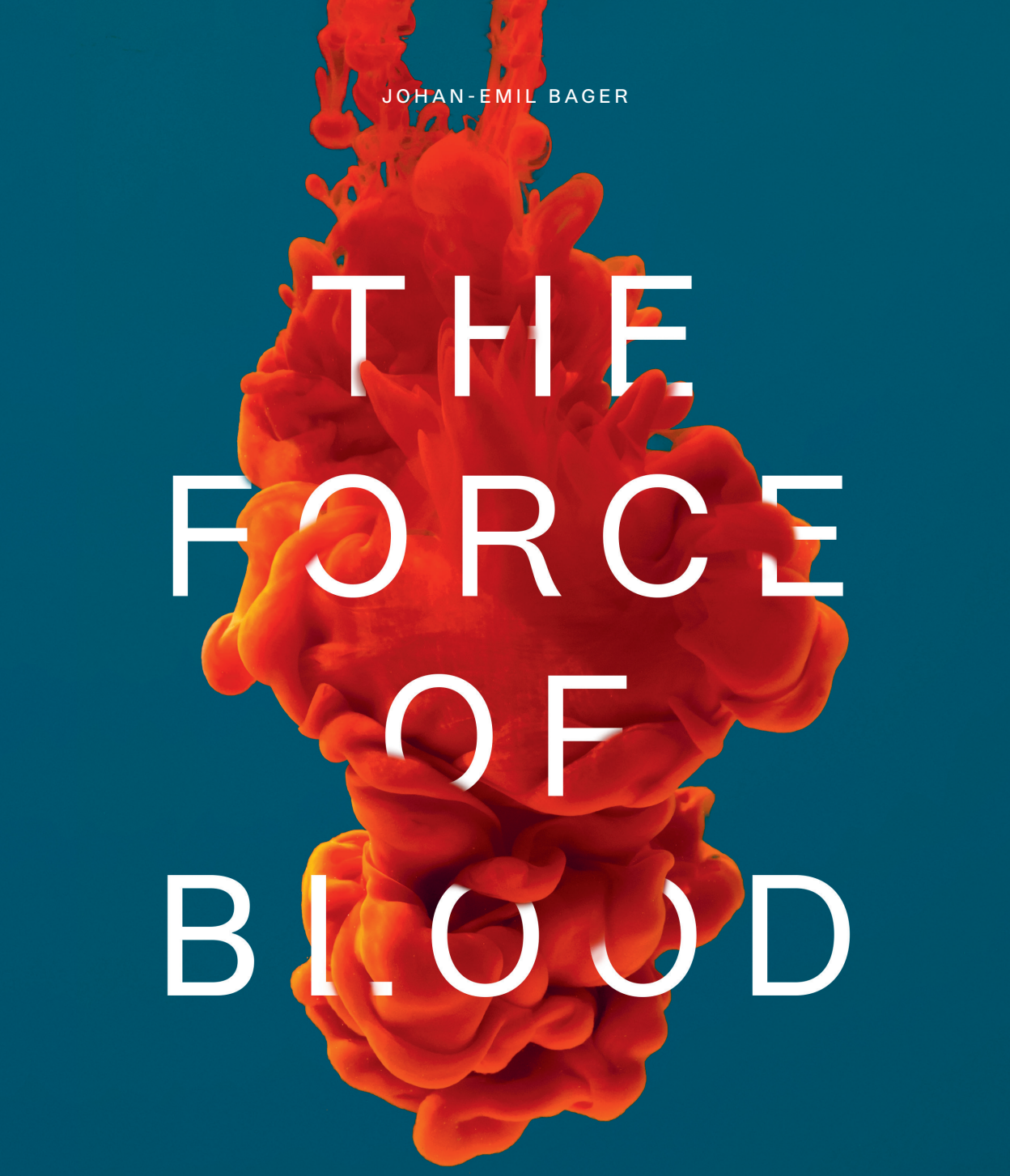
JOHAN-EMIL BAGER



THE FORCE OF BLOOD

Epidemiological studies of blood pressure in stroke, atrial fibrillation and primary care

♡ *For Kristina, August and Milla* ♡

Osler once wrote that a man's
life is a gift of his blood pressure.
If life is a gift, your love is the prize.

The Force of Blood – Epidemiological studies of blood pressure in stroke, atrial fibrillation and primary care

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THE FORCE OF BLOOD

Epidemiological studies of blood pressure in stroke,
atrial fibrillation and primary care

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Abstract

Aim: The overarching aim of this thesis was to investigate the prevalence, temporal trends and associations to cardiovascular outcomes of blood pressure levels in patients in Västra Götaland.

Methods and findings: In **Study I,** Cox regression analysis was used to investigate associations between blood pressure and mortality in 799 patients with acute ischemic stroke who were identified in the quality register of a stroke ward at Sahlgrenska University Hospital. Early change in blood pressure (BP) was found to be a significant predictor of mortality in patients with acute ischemic stroke.

In **Study II**, 31 704 patients with hypertension, but without cancer, diabetes or manifest cardiovascular disease, were included from the primary care register QregPV. 5 041 were above age 75. The Kaplan-Meier estimator and Cox regression analysis were used to study the incidence and risk of stroke or myocardial infarction (MI) at different systolic blood pressure (SBP) levels. Older patients with SBP in the 110 – 129 mmHg range had a lower risk of stroke or MI, compared to those with SBP 130 – 139 mmHg.

In **Study III**, the risk of haemorrhagic stroke at different baseline SBP levels was analyzed with Cox regression in 3 972 patients with hypertension, atrial fibrillation (AF) and newly initiated oral anticoagulants (OAC), who were identified in the Swedish Primary Care Cardiovascular Database of Skaraborg. Baseline SBP in the 145 – 180

mmHg range, prior to initiation of OAC, was associated with a more than doubled risk of haemorrhagic stroke, as compared to an SBP of 130 mmHg. This suggests that lowering SBP to below 145 mmHg, prior to initiation of OAC, decreases the risk of haemorrhagic stroke in patients with hypertension and AF.

Study IV comprised 259 753 patients with hypertension, but without diabetes mellitus or ischemic heart disease. The study described longitudinal trends of SBP and low-density lipoprotein cholesterol (LDL-C); and risk-factor control from 2010 to 2017 in three important, modifiable risk factors: BP<140/90 mmHg, LDL-C <2.6 mmol/L and smoking status. Mean SBP decreased from 140.5 to 137.1 mmHg and BP control improved from 2010 to 2017. Smoking frequency decreased from 15.7% to 12.3 %, but mean LDL-C and LDL-C control changed little. In 2017, 90.0% of patients with hypertension were still exposed to at least one uncontrolled, modifiable risk factor for cardiovascular disease.

Keywords: epidemiology, blood pressure, hypertension, stroke, myocardial infarction, atrial fibrillation, anticoagulants, LDL cholesterol, primary health care

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Sammanfattning på svenska

Bakgrund och mål

Högt blodtryck, hypertoni, är den främsta behandlingsbara orsaken till sjukdom och död i världen. Mer än en miljard människor har högt blodtryck, vilket definieras som ett blodtryck högre än 140/90 mmHg. Förekomsten av hypertoni ökar med åldern. Synen på hypertoni har förändrats mycket under det senaste seklet, under vilket högt blodtryck har gått från att betraktas som ett oförargligt mätvärde till ett farligt tillstånd som erfordrar behandling. Hypertoni är nu erkänd som en betydande riskfaktor för ett flertal allvarliga hjärt- och kärl-sjukdomar, såsom stroke, hjärtinfarkt, hjärtsvikt, aortadissektion, förmaksflimmer och perifer kärlsjukdom. Blodtrycksbehandling minskar risken att insjukna i dessa kardiovaskulära sjukdomar. Behandling av högt blodtryck sker oftast med läkemedel, vilket är den behandlingsmetod som har bäst vetenskapligt stöd. Eftersom blodtryck kan mätas i siffror med enkla metoder så är praxis att blodtrycksbehandling ges med ett numeriskt blodtrycksmål i åtanke. Enkelt uttryckt så är blodtrycksmålet 130/80 mmHg för de flesta patienter med hypertoni. För vissa patientgrupper är det vetenskapliga stödet för behandling till vissa blodtrycksnivåer svagare än för andra. Exempelvis saknas det välgjorda studier om vilket blodtrycksmål som är mest lämpligt för patienter

som samtidigt har hypertoni, förmaksflimmer och blodförtunnande behandling. Blodtrycksmål för äldre patienter utan tidigare kardiovaskulär sjukdom har, till följd av varierande resultat i olika studier, också varit föremål för diskussion. Ett annat omdebatterat ämne är blodtryckets betydelse vid akut hjärninfarkt.

Det övergripande målet för den här avhandlingen var att studera förekomst och förändring över tid av olika blodtrycksnivåer samt dessas koppling till kardiovaskulär sjukdom, särskilt stroke, hos patienter i Västra Götalands län. Delarbete III studerade sambandet mellan blodtrycksnivå och stroke hos patienter med hypertoni, förmaksflimmer och blodförtunnande behandling. Delarbete II studerade kopplingen mellan blodtrycksnivå och stroke eller hjärtinfarkt hos äldre patienter som inte tidigare hade haft stroke eller hjärtinfarkt. Delarbete I studerade sambandet mellan blodtrycksnivå eller blodtrycksförändringar och död eller neurologisk funktionsnivå hos patienter med akut hjärninfarkt. Delarbete IV studerade förändringen i blodtryck över tid samt förekomsten av välreglerad blodtrycksnivå, välreglerad blodfettsnivå och rökning hos patienter med hypertoni i Västra Götalands län.

Metod och resultat

Alla delarbeten i avhandlingen var observationsstudier baserade på registerdata. Delarbete I – III undersökte samband mellan exponering (blodtryck) och utfall (död, hjärtinfarkt, stroke). Delarbete IV var ett deskriptivt arbete.

Delarbete I omfattade 799 patienter med akut hjärninfarkt från ett stroke-avdelningsregister på Sahlgrenska Universitetssjukhuset. Vi undersökte sambandet mellan blodtrycksnivå vid ankomst till akutmottagningen eller blodtrycksförändring under det första dygnet och risken för död eller risken för lägre, neurologisk funktionsnivå. Det huvudsakliga fyndet i arbetet var sambandet mellan blodtrycksförändring under första dygnet och död, se Figur 18. Patienter som sjönk i blodtryck under det första dygnet hade lägre risk för död vid en, tre och tolv månader efter insjuknandet i hjärninfarkt. För varje mmHg som blodtrycket sjönk så minskade risken för död med 1 %. Ett blodtrycksfall om exempelvis 10 mmHg medförde därmed 10 % lägre risk för död. Den lägre risken för död hos patienter med sjunkande blodtryck under det första dygnet beror sannolikt inte på blodtryckssänkningen i sig. Snarare är det en bakomliggande process, kanske återupprättad genomblödning i området kring hjärninfarkten, som föranleder både blodtryckssänkningen och den lägre risken för död på sikt.

I Delarbete II undersökte vi kopplingen mellan olika blodtrycksintervall och risken för hjärtinfarkt eller stroke hos 31 704 patienter, av vilka 5 041 var äldre än 75 år, med hypertoni och som inte hade haft hjärtinfarkt eller stroke tidigare. Patienterna i studien identifierades via primärvårdsregistret QregPV. Det huvudsakliga fyndet i delarbetet var ett samband hos de äldre patienterna mellan 40 % lägre risk för hjärtinfarkt eller stroke och ett systoliskt blodtryck (övertryck) i intervallet 110 – 129 mmHg, jämfört med ett systoliskt blodtryck i 130 – 139 mmHg, se Figur 20. Ett systoliskt blodtryck i intervallet 130 – 139 mmHg betraktas som ett välreglerat blodtryck, vilket innebär att resultaten i artikeln kan tala för att det är gynnsamt för äldre patienter, utan tidigare hjärtinfarkt eller stroke, att ha ett blodtryck lägre än 130 mmHg.

I Delarbete III studerade vi sambandet mellan olika blodtrycksnivåer och risken för hjärnblödning hos 3 972 patienter med hypertoni, förmaksflimmer och blodförtunnande behandling. Vi identifierade patienterna via primärvårdsregistret SPCCD-SKA. Patienter med systoliskt blodtryck i intervallet 145 – 180 mmHg hade mer än dubbelt så hög risk för hjärnblödning, jämfört med patienter med 130 mmHg i systoliskt blodtryck, se Figur 21. Resultaten kan tala för att ytterligare blodtryckssänkande behandling kan minska risken för hjärnblödning hos patienter med hypertoni och förmaksflimmer som står i färd att påbörja behandling med blodförtunnande läkemedel och har ett systoliskt blodtryck som är 145 mmHg eller högre.

I Delarbete IV undersökte vi förändringar från 2010 till 2017 i riskfaktorer som ökar risken för kardiovaskulär sjukdom, som stroke och hjärtinfarkt, hos patienter med hypertoni, men utan tidigare hjärtsjukdom eller diabetes, i Västra Götalands län. Vi följde blodtrycksnivåer och blodfettsnivåer samt beräknade andelen av patienter som nådde välreglerad blodtrycksnivå (<140/90 mmHg) eller välreglerad blodfettsnivå (LDL-kolesterol <2,6 mmol/L) eller var rökare. Medelvärdet för systoliskt blodtryck minskade under tidsperioden från 140,5 mmHg till 137,6 mmHg, se Tabell 5. Andelen med välreglerat blodtryck ökade och andelen rökare minskade, se Figur 23. Trots dessa förbättringar så var 90 % av patienterna med hypertoni i Västra Götaland fortfarande exponerade för minst en otillräckligt reglerad, påverkbar, kardiovaskulär riskfaktor. Vi drog slutsatsen att blodtrycks- och blodfettssänkande läkemedel fortfarande är underutnyttjade hos patienter med hypertoni och att ökat användande borde leda till minskad risk för kardiovaskulära sjukdomar hos patientgruppen i fråga.

Begränsningar

Samtliga delarbeten i avhandlingen har metodologiska svagheter, vilka bör betänkas när resultaten från dem tolkas. Delarbeten I – III var sambandsstudier, men eftersom de är baserade på observationsdata så kan de enbart antyda, men inte fastställa, orsakssamband mellan exponering och utfall. I dessa sambandstudier användes statistiska modeller för att så långt som möjligt justera

för påverkan av förväxlingsfaktorer, men det utesluter inte kvarvarande förväxlingseffekter. För delarbete II – IV, som var baserade på registerdata från primärvårdspatienter, så var andelen saknade mätvärden hög för många variabler. När mätvärden saknas i stor utsträckning så riskerar det att medföra systematiska fel i studien. För alla vetenskapliga studier gäller att läsaren bör ha i åtanke att påvisade samband mellan exponering och utfall kan bero på tre saker: 1) Systematiska fel i studien; 2) Slump; eller 3) Ett sant samband mellan exponeringen och utfallet.

List of studies

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Bager J-E, Hjalmarsson C, Manhem K, Andersson B. Acute blood pressure levels and long-term outcome in ischemic stroke
Brain and Behavior. 2018;8(6):e00992.

II. Bager J-E, Hjerpe P, Manhem K, Björck S, Franzén S, Rosengren A, Adamsson Eryd S. Treatment of hypertension in old patients without previous cardiovascular disease
J Hypertens. 2019;37(11):2269-2279.

III. Bager J-E, Hjerpe P, Schiöler L, Bengtsson Boström K, Kahan T, Ödesjö H, Jood K, Hasselström J, Ljungman C, Manhem K, Mourtzinis G. Blood pressure levels and risk of haemorrhagic stroke in patients with atrial fibrillation and oral anticoagulants: Results from the Swedish Primary Care Cardiovascular Database
J Hypertens. Electronically published ahead of print; doi: 10.1097/HJH.0000000000002838

IV. Bager J-E, Mourtzinis G, Andersson T, Nåtman J, Rosengren A, Björck S, Manhem K, Hjerpe P. Trends in blood pressure, blood lipids and smoking from 259 753 patients in a large Swedish primary care register: Results from QregPV
Accepted for publication in Eur J Prev Cardiol.

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Abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
ATC	Anatomic therapeutic chemical classification system
BCE	Before common era
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
ΔBP	Change (delta) in blood pressure
DBP	Diastolic blood pressure
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ER	Emergency room
HR	Hazard ratio
ICD-10	International statistical classification of diseases, 10th revision
LISA	Longitudinal Integrated Database for Health Insurance and Labour Market Studies
MAP	Mean arterial pressure
MI	Myocardial infarction
mRS	Modified Rankin scale
NIHSS	National Institutes of Health Stroke Scale
OAC	Oral anticoagulant
RAS	Renin-angiotensin-aldosterone-system
PP	Pulse pressure
QregPV	Quality register for primary care (“primärvård”)
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SPCCD-SKA	The Swedish Primary Care Cardiovascular Database of Skaraborg
SPRINT	Systolic blood pressure intervention trial
TIA	Transient ischemic attack

Preface

This thesis has several ambitions. It can be viewed as a very short introduction to epidemiology in observational studies. It also offers a literature review of clinical hypertension, with emphasis on blood pressure levels and cardiovascular outcomes. More than anything, however, it is my record, my journal, my synthesis of what I hope I have learned during my years as a doctoral student.

From a personal viewpoint, this thesis concerns epidemiology as much as it does hypertension. Although epidemiology can be seen as a scientific tool, it is also very much a science in itself – a science that it has been my privilege to become at least superficially acquainted with and which has unlocked doors to a scientific understanding that was well beyond my grasp prior to this academic voyage.

Consequently, I have given the introductory chapter of this thesis a dual focus. The first part, on epidemiology in observational studies, comprises the basics of the nomenclature and methodology used in my research. It is the chapter I would have very much liked to read myself *before* I started writing my first paper. The second introductory chapter, on clinical hypertension, is a straight-forward review of what blood pressure and hypertension is; what the current literature suggests in terms of hypertension treatment; and what some of the knowledge gaps are in clinical hypertension research.

Chapter 1

Introduction

1

"Medicine is a science of uncertainty
and an art of probability"

– Sir William Osler

1.1 Epidemiological studies

This thesis is based on observational studies. All observational studies are epidemiological studies. Epidemiology literally means the study (*-logia*) of that which is upon (*epi-*) people (*dêmos*). Historically, it was the study of infectious epidemics (although the term predates germ theory), but it has evolved into the science of measuring any disease occurrence, regardless of cause. Epidemiological studies can be either descriptive or analytical.

Descriptive epidemiological studies measure disease occurrence in a specific group of people, often called a *population* in epidemiologic nomenclature, but they are not intended to test a *hypothesis* (see Analytical epidemiology below). Descriptive epidemiology is always observational and can be used, for instance, to quantify how many people in a certain population are afflicted by a certain disease during a certain time span. Descriptive epidemiological studies are also important for generating hypotheses which may be tried in analytical, epidemiological studies. Neither analytical nor descriptive epidemiological studies can, for practical reasons, study everyone in a population. Instead they generally focus on a smaller group, a *sample*. See Figure 1. After analysis of this sample,

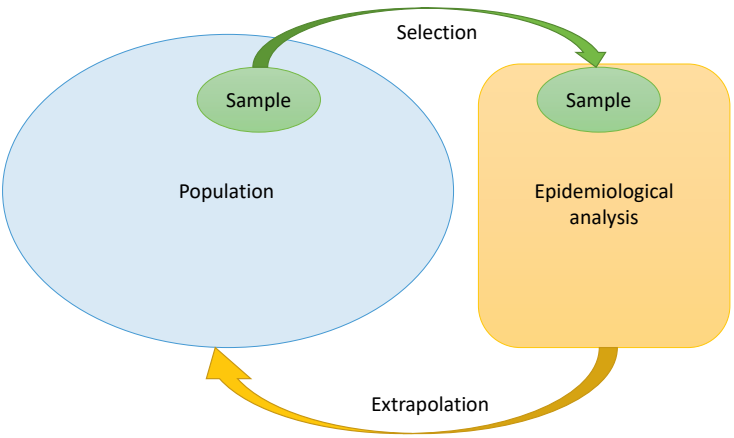


FIGURE 1

Sampling from a population, sample analysis and extrapolation of sample findings back onto the population.

epidemiologists then draw conclusions about the sample and extrapolate to the population which the sample came from. This

sampling process is analogous to how a polling institute measures the sympathies for the political parties in parliament among, say, 1 000 people and presents the results in a newspaper as representative of all eligible voters.

Unlike descriptive studies, analytical, epidemiological studies are not content with merely describing a phenomenon. They aspire to say something about the causal relation between an *exposure* and an *outcome* and they do this by testing a *hypothesis*. An exposure can be anything that may affect us, such as medication, air pollution or a biological phenomenon like one's weight or blood pressure. An outcome is something that happens to a person, like being diagnosed with hypertension, getting married or graduating from college. A hypothesis in medical science specifies three things: 1) an exposure; 2) how the presence of the exposure affects an outcome, compared to the absence of the exposure and; 3) a population in which to test the hypothesis. An example could be: people[population] who smoke[exposure] have more myocardial infarctions[outcome] than people who do not smoke. Or: men in their forties[population] who own power tools[exposure] visit the emergency room[outcome] more often than men in their forties who do not own power tools. Rothman articulated the need to compare exposure categories succinctly in his textbook:

"To measure a causal effect, we have to contrast the experience of exposed people with what would have happened in the absence of exposure."(1)

Analytical, epidemiological studies attempt to measure causal effects, and can be either interventional or observational. The most well-known example of an interventional, epidemiological study is the *randomized, controlled trial*. In a randomized, controlled trial (RCT) some participants are randomly assigned to be exposed to an intervention, perhaps cinnamon bubblegum, while the rest of the trial participants are not. All trial participants are then observed for a period of time, and the investigators register the good and bad outcomes (usually mostly the latter) they experience. If the participants who were exposed to the intervention – the cinnamon bubblegum

group – suffered fewer bad things, perhaps parking tickets, then the investigators might very well be tempted to proclaim that their amazing cinnamon bubblegum causes a lower risk of parking tickets. If the study was well-designed and properly conducted, they may be right in claiming a causal relationship between chewing cinnamon gum and getting fewer parking tickets. In interventional studies – such as the randomized, controlled trial – the researchers thus assign the exposure to some of the trial's participants, whereas in observational studies, the distribution of the exposure is not controlled by the researchers.

The studies which this thesis is based on are not interventional. They are observational and do not involve any cinnamon bubble gum. Three of them (I – III) are analytical cohort studies and one is descriptive (IV). The etymological origin of *cohort* is the Roman empire, where a cohort was the word for a tenth of a Roman legion. The legion was the largest unit in the Roman army and comprised around 5 000 soldiers. A cohort would consequently constitute around 500 soldiers. An epidemiological cohort is to the overall population what the Roman cohort was to the legion – a subgroup, much like the sample in Figure 1. More precisely, an epidemiological cohort is a group of people with a set of specified characteristics that are observed at a point in time or for a period of time.(2) Examples of studied cohorts may be women aged 30 – 45 with a history of migraine, in 2016. Or patients older than 30 with hypertension and diabetes, from 2010 – 2017.

The participants in a randomized, controlled trial are, by definition, involved in a closed cohort study, but the term cohort is usually used in the context of observational cohort studies. Cohort studies can feature either closed or open populations. In closed cohort studies, a specific group of participants are recruited for a limited amount of time and then followed. After recruitment has completed and follow-up has begun, no further participants can be added to the cohort which will consequently shrink over time, as its participants either die or opt out of study participation. The dynamic, or

open, cohort instead comprises a population with a specific set of attributes, such as the residents of Sweden or patients with hypertension. Dynamic cohorts can both increase and decrease in number as people are born, move, die or develop disease.

Methodology in epidemiological studies

The most important property of any epidemiological study is its *internal validity*. A study with high internal validity features the study population it purports to feature; measures exposure, outcome and other important variables accurately and similarly across categories of exposure; and addresses potential *bias* properly. When these criteria are not met, the end result is a biased study. Bias comprises systematic errors such as *confounding* and *misclassification* (see below), which distort the results of the study. All studies can be expected to contain some bias, but less is better. Internal validity is thus a measure of the amount of bias in a study. It represents methodological stringency and how well the definitions and measurements of a study hold up to scrutiny. A high degree of bias results in poor internal validity, which renders any study meaningless.(3)

Randomized, controlled trials are the gold standard for establishing a causal relationship between an exposure and an outcome. This is in part because properly conducted RCTs are the shining beacons of internal validity. Their participants are systematically included and measurements of exposure and outcome are immaculately registered. In the RCT, participants are also randomly assigned to an exposure, such as the cinnamon gum in the example above. The purpose of the random assignment of an exposure is to attain similar comparison groups. The random assignment process will ensure that characteristics like age, sex, income, smoking habits and preexisting medical conditions will be evenly distributed across the comparison categories, provided that enough participants are included. Characteristics of the participants, such as smoking, which are evenly distributed across comparison groups will affect

the outcome similarly for both exposure categories. If, by contrast, the comparison groups are *not* similar, a measured difference in outcome might be caused by a difference in the characteristics of the groups, rather than by the studied exposure. For example, if we wanted to investigate the connection between cinnamon gum and myocardial infarction and were to study this by non-randomly assigning cinnamon gum use to 100 people and regular, menthol control gum use to 100 more people we might get these fictitious participant characteristics and myocardial infarction data:

	Cinnamon gum	**Menthol gum**
Number of people	100	100
Female	64%	45%
Age, mean	48 years	59 years
Smoker	8%	15%
Myocardial infarctions	2	8

TABLE 1

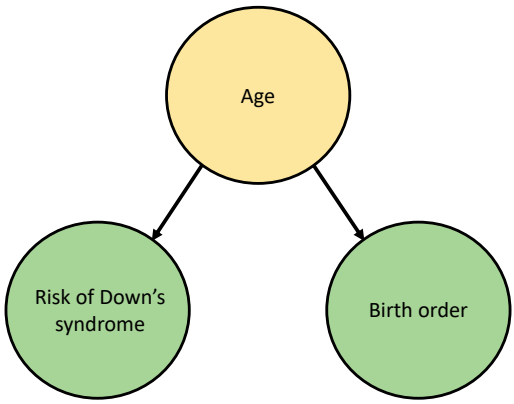
Example of patient characteristics

From the data in Table 1 above, it is evident that the cinnamon gum group is younger, has a higher proportion of females and a lower proportion of smokers. Higher age, male sex and smoking are all risk factors for myocardial infarctions and it should therefore be expected that the menthol gum group, on the basis of a higher prevalence of these risk factors, will display a higher disease occurrence of myocardial infarction. Thus, because the risk factors of age, sex and smoking are not evenly distributed across comparison groups, they *confound* the results. If the researcher was not aware of the importance of age, sex and smoking and measured them in the study, he or she might have instead attributed the difference in myocardial infarctions to the cinnamon gum. An example of confounding from Rothman's textbook is the observation that higher birth-order was suspected to increase the risk of Down's syndrome in children.(1) That is, a first-born child was suggested to have a lower risk of Down's syndrome than, say, the fourth-born. Early studies of

birth-order and risk of Down's syndrome were confounded, because they did not take the age of the mother into account and higher birth-order correlates strongly with the mother's age. In later studies of birth-order and risk of Down's syndrome which did take the age of the mother into account, the connection between birth-order and Down's syndrome disappeared completely. A confounder can be any factor that is a true cause, or the proxy of a cause, of an outcome and which is unevenly distributed across the exposure categories and which is not merely a mediating factor in the causal chain between exposure and outcome, see figure 2.

FIGURE 2

Example of confounding. The confounding factor of age of the mother increases the likelihood of both higher birth order and the risk of Down's syndrome. Analyzing the connection between Down's syndrome and birth order, without taking the age of the mother into account, will yield a confounded result.



In the birth-order example above, children with a higher birth-order were more likely to have older mothers; the confounding variable of age was thus not evenly distributed across the exposure category of birth-order. Randomization lets researchers compare the experience of an exposed group to the experience of another group which only differs from the exposed with respect to the absence of exposure. To iterate Rothman's statement: "*To measure a causal effect, we have to contrast the experience of exposed people with what would have happened in the absence of exposure.*" Randomization ensures that the characteristics of the comparison groups are similar in every way, including any potential known and unknown confounding factors, which means that any difference in outcome is not due to differences in characteristics across the exposure categories. The major downside of RCT's are their cost. Because they

are expensive, they rarely last longer than a few years. This makes it difficult to study outcomes that are rare or that occur long after the exposure. Interventional trials must also comply with ethical regulations, which prohibit the investigation of exposures that it would be unethical to knowingly subject trial participants to. For logical reasons, interventional studies are unable to study exposures that are not assignable to the study participants, such as education level, income or body mass index (BMI). Observational studies do not suffer from these limitations, but have limits of their own.

Dealing with confounding in cohort studies

In observational cohort studies, the exposure is not randomly assigned to study participants and patient characteristics are rarely similar across exposure categories. For example, people who smoke are different from people who do not smoke across several measurable dimensions such as age, level of education and history of medical conditions. Analogously, people with low blood pressure are different from those with high blood pressure. These differences in characteristics threaten to introduce confounding into observational studies and researchers must address this threat.

Restriction, or exclusion, is one way of reducing confounding in observational studies.(3) Since confounding can only occur when a potential confounding factor is unevenly distributed across exposure categories, simply restricting patients who smoke from participating in a study will ensure that smoking is not a confounder for that particular study. After restriction, the number of smokers (zero) will be evenly distributed across the exposure categories. Restriction has the downside of decreasing the number of people who are eligible for inclusion in the trial, which may cause problems both in the statistical analysis and for the *external validity* of the study. A study's external validity is a measure of how generalizable its results are to patients in the real world. If a study does not comprise any smokers, it follows logically that its conclusions may not apply to smokers. If investigators restrict inclusion in a study too strictly and across too many variables, it may be difficult to explain whom the results of the study apply to.

Stratification is another way of investigating the confounding effects of a variable. If smoking is suspected to be a confounder in a study, the researchers can calculate the *risk ratio* (see "Measuring disease" below) for exposed and unexposed participants for both smokers and non-smokers. If the risk ratios are the same for both smokers and non-smokers in both exposed and unexposed participants, then smoking is not a confounding factor, whereas the opposite is true if the risk ratios are different. Stratification by inherently categorical variables such as sex or smoking is a straightforward process, whereas continuous variables, such as age or blood pressure, must be categorized into suitable intervals before stratification. Stratification can be thought of as a kind of post-hoc restriction, with the advantage that it maintains overall sample size. Stratification can be performed on several variables at once, but this is rarely done because the sample size in the analyses quickly dwindles as further strata are added.(1, 3)

Adjustment for potential confounders through statistical, multivariate regression models is also commonplace in observational studies. In a multivariate regression model, the dependent variable is the outcome and the independent variables comprise the exposure and factors that have been determined to be potential confounders. The multivariate regression model takes all included independent variables, frequently called *covariates*, into account and provides an estimate of their independent effects on the outcome. Regression models allow for easier controlling for multiple potential confounders at once than stratification, but are methodologically more opaque and harder to understand theoretically than stratification (see also "Methods" below).(1) Identification and proper adjustment for potential confounders requires knowledge both of known risk factors for an outcome and some of the pitfalls of multivariate regression analyses. The latter issue can be handled with the help of directed acyclic graphs (DAGs), which can be constructed using tools such as DAGitty to determine which potential confounders to include in a model.(4-6) A simple DAG, drawn with DAGitty, is shown below. The model code of more elaborate DAGs from Study III can be viewed in the Appendix and copied into the "Model code" window at http://www.dagitty.net/dags.html to view the DAGs.

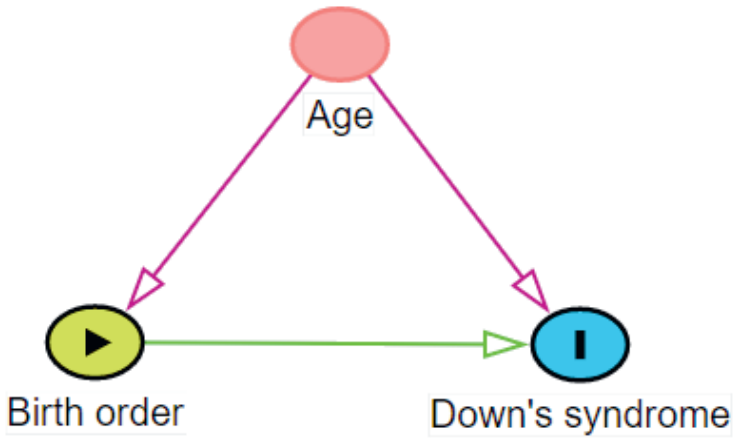


FIGURE 3

Directed acyclic graph (DAG) with birth order as the exposure (green) and Down's syndrome as the outcome (blue). The relationship between exposure and outcome (green arrow) is the one the researchers intends to study. The user specifies how a variable, such as age, affects the exposure and the outcome. Potential confounders that should be adjusted for are red and biasing paths are purple arrows.

An important caveat of all methods that address confounding in observational studies is that they can only compensate for known and properly measured confounders. Unknown or inadequately measured confounders cannot be managed through restriction, stratification or adjustment in statistical models. The effect of unknown or unmeasured confounders on the results of a study is referred to as residual confounding. The possibility of residual confounding is an inherent limitation of observational studies.

Selection bias

Epidemiologists study samples from a population in order to draw conclusions about the population from which the sample came, see Figure 1. It is thus imperative that the sample is representative of the population which the researchers aspire to study. For example, an epidemiological study might wish to study how blood pressure affects the risk of stroke specifically in people older than 75 years. The researchers then recruit study participants via advertising in newspapers or in social media. This recruitment procedure is likely to introduce *selection bias*, because people who are more than 75 years old and have the capacity to read and react to ads in newspapers and social media are different from those who are above 75 and *do not* respond to such ads. The former group is likely to be

decidedly healthier than the latter, which illustrates the key component of selection bias. It occurs when the relationship between an exposure and an outcome differs between participants and non-participants of a study.(1) Because of how the participants of the study were selected, they are likely to be healthier and at an overall lower risk of stroke than non-participants. The study is therefore likely to result in a biased underestimate of the connection between blood pressure and stroke in older patients. The reader of an epidemiological study should be mindful of how the study population was arrived at and what patients were excluded or not eligible for inclusion.

Information bias: Misclassification and missing data

All natural science is contingent on measurements, and epidemiology is no exception. Epidemiologists need to translate theoretical concepts like *blood pressure* and *stroke* into practically measurable phenomena. Measurements of exposure and outcome are particularly important in epidemiology. In order to bridge the gap between theory and practice for the purpose of an epidemiological study, an exposure like *blood pressure* could be redefined from:

BP = cardiac output * peripheral arterial resistance

to:

BP = the reading on the sphygmomanometer.

Similarly, an outcome like *stroke* could be redefined from:

Stroke = an abrupt loss of cerebral function due to haemorrhage or cerebral artery occlusion

to:

Stroke = a registered diagnosis of stroke.

Measurements allow theoretical concepts to transition from the realm of ideas to the natural world as perceptible analyzable phenomena. This measurement process has its price, however, and few concepts complete the transition into the natural world unscathed.

Case in point, the reading on the sphygmomanometer rarely shows the exact, true blood pressure, and conditions like epileptic seizures are sometimes misdiagnosed as strokes. The difference between the truth and the measurement is a *misclassification*. Misclassification can be either *nondifferential* or *differential*.(1-3)

Nondifferential misclassification occurs when a measurement error is equally likely to occur across exposure categories. Consider, for example, an observational study that analyzes the number of strokes (outcome) in a year among patients with hypertension (the exposure) in one specific primary care center and compares it to the number of strokes in patients without hypertension. Hypertension could be defined as BP ≥140/90 mmHg according to medical records from the primary-care center. Stroke could be defined as a registered diagnosis of stroke in the same medical records. If BP for all patients in this primary care center was measured with a faulty sphygmomanometer that randomly indicated 5 mmHg above or below the true value, the result would be non-differential misclassification, because the erroneous measurement would occur in both categories of exposure. This kind of measurement error, which is equally likely for both categories of exposure, would bias the study results towards underestimation of the effect of the exposure. In this example, patients without hypertension, with a true BP in the 135 – 139 range, are at risk for being erroneously categorized as hypertensive through a random 5 mmHg addition from the faulty sphygmomanometer. Because they do not actually have hypertension, they are at a lower risk of stroke and any erroneous inclusion of them into the hypertension exposure category would dilute the risk of stroke for the hypertension exposure category. Similarly, patients who do have hypertension, and a true BP in the 140 – 144 mmHg range, are at risk of being misclassified as not hypertensive through a random 5 mmHg subtraction from the faulty sphygmomanometer. Because patients who truly have hypertension are at an increased risk of stroke, any erroneous inclusion of them into the non-hypertension exposure category will inflate the risk of stroke for the non-hypertension exposure category. The net result will be a reduced difference in the risk of stroke between the exposure groups.

Non-differential misclassification thus generally decreases a study's chances of detecting differences between categories of exposure.

By contrast, differential misclassification occurs when a measurement error is more likely to occur in one of the exposure categories. If, for example, the patients with hypertension from the example above would be more likely to erroneously receive a diagnosis of stroke than patients without hypertension, we would have a differential misclassification of the outcome. A higher rate of erroneous stroke diagnoses in patients with hypertension would inflate the risk of stroke for that exposure category. If it were the other way around, and patients without hypertension were more likely to receive erroneous stroke diagnoses, the difference between the categories would be diluted instead. Differential misclassification is thus more unpredictable than its non-differential counterpart and can either increase or decrease the apparent risk of an outcome for the affected exposure group.

Missing data for clinical variables such as blood pressure, blood lipids or BMI are common among patients in observational research based on registry data. Missing data can be categorized as *missing completely at random*, *missing at random* and *missing not at random*.(7, 8) When there are no differences in the characteristics of patients with valid data entries for a given variable on the one hand, and those with missing data for the same variable, on the other hand, then data are missing completely at random. Data *missing completely at random* are the result of stochastic events such as dropped blood-sample vials in a laboratory or loss of data due to a power outage. Data which are *missing at random* can be missing to a higher degree in patients with certain characteristics, but the probability of a value being missing depends only on other measured variables. For example, if smokers are more likely to have their height measured than non-smokers, then height data is missing at random among the non-smokers. When data are missing at random, the likelihood of it missing does not depend on the variable itself, only on other, observed variables. We would thus not expect non-smokers to be shorter or taller than smokers. Finally, for data which are *missing not at random*, there is a connection between

the variable and the likelihood that it is missing. For example, if physicians would be reluctant to ask people who smelled of smoke whether they were smokers or not, there would be a connection between being a smoker and smoking data being missing. Missing data limit the internal validity of a study and its frequency should be reported, especially for key variables. Researchers can address missing data in several ways, some of which are described in the "Methods" chapter.

Chance and stastistical inference

As mentioned previously, analytical, epidemiological studies aspire to find differences in the risk of an outcome between categories of exposure. They wish to link an exposure to an outcome. To do so, they must assess the likelihood that any observed difference between exposure categories is not merely a result of chance. This is achieved with statistical hypothesis testing, which starts with the formulation of a *null hypothesis*. The conservative null hypothesis postulates that there is no difference between two comparison groups, such as two exposure categories. The counterpart of the null hypothesis is the *alternative hypothesis*, which instead states that there is a difference between the groups of comparison. For example, we could compare the height of male and female characters in Star Wars. Our null hypothesis would state there is no difference in height between male and female characters, whereas the alternative hypothesis would state the opposite. The average height of male characters in Star Wars is 183 cm and that of female characters is 166 cm. The values 183 and 166 are obviously different, but is the difference statistically significant? To find out, we first need to establish a level of significance, also known as α (alpha). By convention, epidemiological studies often employ a significance level, or α, of 5%. We then run a statistical test (in this case a Wilcoxon rank-sum test), which compares the heights of males and females in Star Wars and yields a *P value*. The P value shows how likely it is to observe a difference in height of this magnitude (or greater), provided that the null hypothesis is true. The philosopher Nicholas Maxwell facetiously described the p value as *"a measure*

of how embarrassing the observed data are to the null hypothesis." In our statistical test, the P value is 0.00285, or ≈ 0.3%. Since 0.3% is decidedly less than the previously specified significance level 5%, we can say that the height difference between males and females in Star Wars is statistically significant and reject the sufficiently embarrassed null hypothesis. It should be noted that the finding of a statistically significant difference is not a definite proof of actual difference. The significance level is an arbitrary cut-off, below which the researcher has determined that the null hypothesis should be discarded. If the P value were 0.049, or 4.9%, the result would thus be considered statistically significant, but there would also be an almost 1 in 20 chance that the result was simply a chance finding. If a null hypothesis is rejected when it is in fact true, the researcher commits a *type 1 error*. In contrast, if the null hypothesis is not rejected when it is in fact false, the researcher commits a *type 2 error*. The researcher can decrease the risk of type 1 errors by decreasing the significance level, for example from 5% to 1%, but this also increases the risk of a type 2 error. Conversely, the risk of a type 2 error can be decreased by increasing the α, for example from 5% to 10%, which instead increases the risk of a type 1 error. The risk of a type 2 error can also be decreased by increasing the sample size of a study. More observations increase the *power* of a study to detect a difference between comparison groups. The process of gathering data from a sample of a larger population; using statistical tests to analyze the data; and then extrapolating from the findings from the sample data to draw conclusions about the population which the sample came from is known as *statistical inference*. See also Figure 1.

In the Star Wars example above, male characters were taller than female characters. An epidemiologist might say that there was an *association* between sex and height. The term association is used to describe a connection between variables that seem to change together, i.e. that correlate. Because the term does not imply causality, it is frequently used in observational epidemiology, which is often cautious about making causal claims due to the methodological limitations outlined in this chapter. Although causally linked variables do correlate, not all correlations are causal, see Figure 4 below.

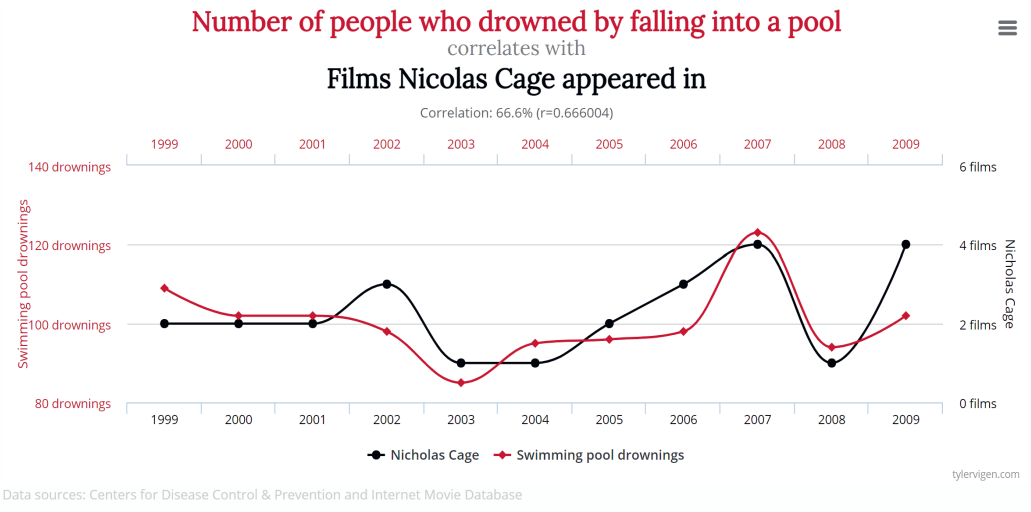


FIGURE 4

Spurious correlation between Nicolas Cage films and swimming pool drownings. Link to original: http://www.tylervigen.com/spurious-correlations Used in accordance with CC BY 4.0: https://creativecommons.org/licenses/by/4.0/

The reader of any epidemiological study should always bear in mind that there are three possible explanations for an association between an exposure and an outcome:

1. The finding is due to bias, such as confounding or misclassification
2. The finding is due to chance
3. The finding represents a true connection between exposure and outcome

Measuring disease

There are several ways to quantify disease in epidemiological studies. One way is to measure the number of times someone is afflicted by a disease, let's say a stroke, in a year. We can use fictitious data from the mythical city of Atlantis in the year 16 before the common era (BCE) as an example. A measure, which quantifies disease afflictions in a specific time span, is called *incidence.* Incidence can be described as a probability, *incidence proportion*, or as a rate, *incidence rate*. We can use the number of strokes suffered by the residents of Atlantis in one specific year, which counted 16 842 strokes, to explain the difference between incidence proportion and incidence rate.

TABLE 2

Comparison of incidence proportion and incidence rate

Incidence proportion		Incidence rate	
Population	8 871 000	Time at risk	8 733 000 person-years
Calculation: Incidence proportion	16 482 / 8 871 000 = 0.001898 ≈ **0.19 %**	Calculation: Incidence rate	16 842 / 8 733 000 person-years ≈ 0.001928/ person-years ≈ **1.93 per 1000 person-years**

The numbers above illustrate how the measure of incidence proportion (sometimes called *cumulative incidence*) is very much analogous to a probability or risk. Overall, 0.19% of the population in Atlantis were afflicted by stroke, which could be interpreted as a 0.19% risk of stroke per person, per year. It should be noted, however, that certain subpopulations will have either a larger risk (older people with other illnesses that predispose to stroke) or a smaller risk (younger, healthier people) of stroke than 0.19 % per year.

The incidence rate employs the unit of *person-time* in its denominator, in this case expressed as person-years. Person-time is the product of the number of people in a studied population multiplied by the time during which they were followed. The astute reader will have noticed the discrepancy in numbers between "Population" and "Time at risk" in Table 2 above. Why are these numbers not identical if the studied population numbered 8 871 000 people? Well, during the year 16 BCE, some of the residents of Atlantis moved from the city – they were *lost to follow-up* – while others died from causes other than stroke – were lost to *competing risks*. The people who moved and the people who died can no longer suffer a stroke in Atlantis and thus they do not contribute *person-time* to the denominator of the incidence rate after having moved or died. Consequently, the denominators differ because loss to follow-up and competing risk are being accounted for in the incidence rate measure. The nominator is identical (16 842) for both incidence proportion and incidence rate, because it represents the number of registered strokes in Atlantis. Because the denominator is smaller, the incidence rate measure is slightly larger than the incidence proportion (0.001928 vs 0.001898).

The incidence proportion thus slightly underestimates the risk of stroke because it does not take into account that there were people who could not develop the outcome of stroke, because they had been lost to follow-up or succumbed to competing risks.

The incidence rate of 0.001928 strokes/person-year is converted into the more manageable 1.93 strokes per 1000 person-years. This rate, or speed, means that for every 1000 person-years that pass, almost two (1.93) strokes will occur. The actual time needed, in calendar years, depends on the size of the population. For a population of one, one person-year unit will take one calendar year. For a population of twelve, however, one person-year will be completed in one calendar month. Every one of the twelve participants will then contribute one person-month, thus completing a person-year. The larger the population, the faster the accrual of person-time.

Incidence proportions and incidence rates thus provide measures of disease affliction for determinate time periods. For some diseases, it may also be meaningful to measure the number of people in a given population who suffer from a particular disease at a given moment. This measure is called *prevalence*. The prevalence of a disease is a proportion. It is calculated by dividing the number of people who have the disease at the moment of the study by the total number of people in the studied population. An example would be asking all fifty neighbors on your street today if they have symptoms of hay fever. If ten of them do, the prevalence would be (10/50) 0.2, or 20%. The prevalence of a disease is mainly affected by its incidence and by its duration. Near-sightedness (myopia) is both common and usually life-long. It therefore has a higher prevalence than the common cold, which although very common, is short-lasting (though rarely short-lasting enough). The common cold, in turn, has a higher prevalence than the aneurysmal, subarachnoid hemorrhage does. This is because the subarachnoid hemorrhage has a lower incidence than the common cold and because it is often fatal, which keeps its prevalence relatively low. Some diseases, such as hay fever and the common cold, also exhibit seasonal variation.

Measures of prevalence for chronic diseases such as hypertension, diabetes and obesity are important because they allow policy makers and healthcare professionals to estimate the burden of

disease in a population and adopt strategies to combat the diseases. Prevalence measures are commonplace in clinical research papers too. Nearly every clinical research paper features the equivalent of a "Table 1," which describes the background demographics of the study population at *baseline*, i.e. at the start of the study. Some of those demographics comprise the prevalence of diseases such as hypertension, cardiovascular disease and chronic, obstructive pulmonary disease. In societal as well as research contexts, prevalence measures provide information of the current disease burden of a specified population. All of the papers that this thesis is based on have their respective "Table 1," see the appendix for examples.

Comparisons between exposure groups

In analytical, epidemiological studies, the researcher is interested in how outcomes might vary between different groups of exposure. Epidemiologists from Atlantis might hypothesize that people with a diagnosis of hypertension will suffer more strokes than people without a diagnosis of hypertension. To compare the two categories of exposure, we can construct a table with disease measures. If 15% of the population of Atlantis has hypertension, we get Table 3 below.

TABLE 3

Disease measures for Atlanteans with or without hypertension

	Hypertension	**Without hypertension**
Number of people	1 330 650	7 540 350
Number of strokes	5 933	10 549
Incidence proportion	5 933 / 1 330 650 = 0.004458 ≈ 0.44%	10 549/7 540 350 = 0.00139 ≈ 0.14%
Incidence rate	5 933/ 1 135 290 person-years ≈ 5.23 per 1000 person-years	10 549/7 597 710 person-years ≈ 1.39 per 1000 person-years
Risk ratio	0.004458/0.00139 ≈ 3.21	0.00139/0.004458 ≈ 0.31
Rate ratio	5.23/1.39 ≈ 3.76	1.39/5.23 ≈ 0.26
Risk difference	= 0.004458 - 0.00139 ≈ 0.31%	= 0.00139 - 0.004458 ≈ - 0.31%

In the bottom rows of Table 3, three new measures are introduced: the *risk ratio*, *rate ratio* and *risk difference*. As mentioned previously, the incidence proportion can be thought of as a probability, a risk, of experiencing an outcome. In the example above, 0.44% of the population in Atlantis with hypertension suffered a stroke, while only 0.14% of its population without hypertension did so. The risk ratio, which is sometimes called relative risk, can be defined as the risk (incidence proportion) of the exposed population divided by the risk (incidence proportion) of the unexposed:

$$\textit{Risk ratio} = \textit{risk}^{\textit{exposed}}/\textit{risk}^{\textit{unexposed}}$$

The risk ratio expresses how much more probable it is for the residents of Atlantis with hypertension to suffer a stroke in the studied year, compared to those without hypertension. A risk ratio of 3.21 means that patients with hypertension have more than three times the risk of stroke, compared to patients without hypertension. The risk ratio for patients *without* hypertension, 0.31, is just the mirror image of the same numbers ($\text{risk}^{\text{unexposed}}/\ \text{risk}^{\text{exposed}}$), conveying that residents of Atlantis without hypertension have less than a third of the risk of stroke compared to patients with hypertension. The risk ratio and the rate ratio differ numerically, because the latter is a ratio of incidence rates, which takes time at risk into account.

$$\textit{Rate ratio} = \textit{incidence rate}^{\textit{exposed}}/\textit{incidence rate}^{\textit{unexposed}}$$

The rate ratio in our example is higher than the risk ratio. This means that the residents with hypertension contributed less person-time per person than did residents without hypertension. This may be due to loss of follow-up or to competing risks, such as a higher risk of death. Note that both the risk ratio and the rate ratio are measures of relative risk; that is, they express the relationship between the magnitudes of risk for two categories of exposure, but say nothing about the level of absolute risk. In our stroke example above, 1 in 250 residents of Atlantis with hypertension suffered a stroke, whereas only 1 in 714 residents without hypertension did. Risk ratios, due to their ratio nature, can be high even if the risk (incidence proportion)

in both the nominator and the denominator are infinitesimally small. Consequently, the relative risk measures, which comprise risk, rate and hazard ratios (see “Regression models” below), should not be presented on their own. They should be presented alongside absolute measures of risk, like the incidence proportion. The final row in the table shows an absolute measure of risk: the *risk difference*. It is defined:

$$\text{Risk difference} = \text{risk}^{\text{exposed}} - \text{risk}^{\text{unexposed}}$$

The risk difference thus subtracts the risk (incidence proportion) of the unexposed group from the exposed group. In this example, the risk difference (sometimes called absolute risk reduction) is 0.31%. Residents of Atlantis with hypertension have a 0.31% higher risk, per year, of having a stroke than residents without hypertension. A risk difference of 0.31% might sound a lot less intimidating than having a more than three times higher risk, but both measures are equally true. The risk difference measure also allows us to quantify how many residents of Atlantis that need to be cured of hypertension, so that they are no longer exposed, in order to avoid one stroke in one year. By inverting the risk difference, we get the *number needed to treat*:

$$\text{Number needed to treat} = 1/\text{risk difference}$$

Let us assume that the difference between the comparison groups is statistically significant. Since $1/0.31\% \approx 323$, this means that in order to prevent one stroke in one year in Atlantis, 323 people with hypertension need to not have it anymore. The proposition may seem absurd. How would anyone go about changing people from being exposed to hypertension to not being exposed to it? To essentially cure patients of hypertension? Such a Herculean feat would indeed fit well in the mythical city of Atlantis. Well, imagine if the exposure categories instead comprised not residents of Atlantis, but patients of today – patients with either well-controlled or dangerously high blood pressure. And imagine there were tools that could lower high blood pressure, tools that could lower the very force of blood.

1.2 Clinical hypertension

The force of blood

The tissues of our bodies need blood flow, perfusion, to function. In order to achieve flow across the blood vessels of our circulatory systems, which provide resistance to flow, pressure is needed. Blood flow can only be established across a pressure gradient and blood pressure thus decreases gradually from the aorta to the veins, see Figure 5. Blood pressure can be thought of as the force exerted by blood on the tissue walls that surround it. This force, the force of blood, is generated by the contraction of the ventricles (chambers) of the heart and withheld by the walls of the blood vessels. The actual blood pressure is the product of the flow from the heart and the resistance from the vessels of the circulatory system.(9) The flow from the heart is referred to as cardiac output, which itself depends on heart rate and the volume of blood ejected per heart beat (stroke volume). The blood pressure function thus reads:

Blood pressure = cardiac output * peripheral vascular resistance

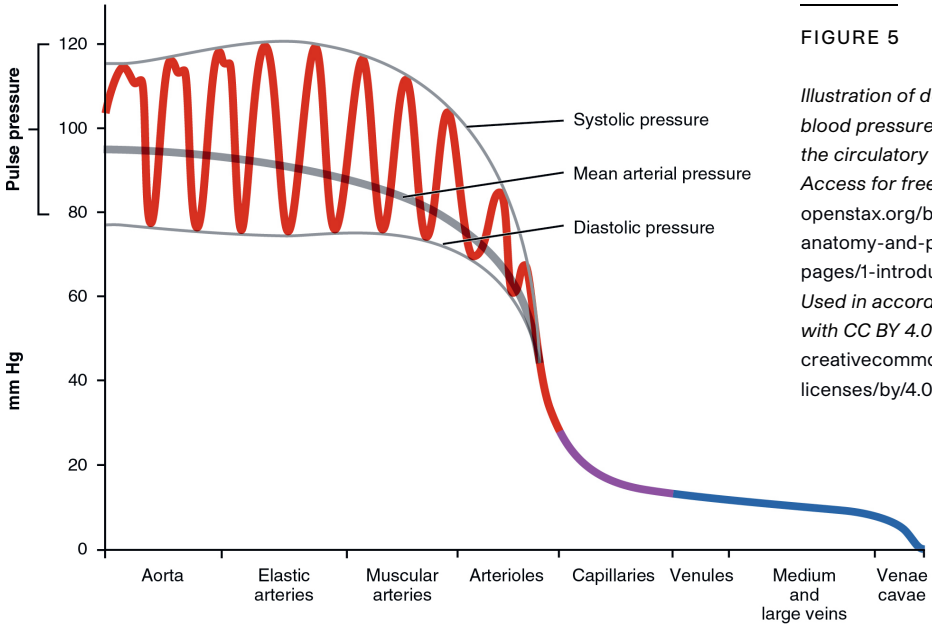


FIGURE 5

Illustration of decreasing blood pressure through the circulatory system. Access for free at https://openstax.org/books/anatomy-and-physiology/pages/1-introduction *Used in accordance with CC BY 4.0:* https://creativecommons.org/licenses/by/4.0/

This thesis concerns systemic blood pressure and arterial hypertension, but the principles of pressure are the same in the pulmonary circulation. As is evident by the figure below, blood pressure varies depending on location in the circulatory system. The pressures of most vessels, be it arteries, capillaries or venules, can be measured, and there are thus many different blood pressures. In the context of this thesis, however, "blood pressure" is used as a synonym for systemic, arterial blood pressure.

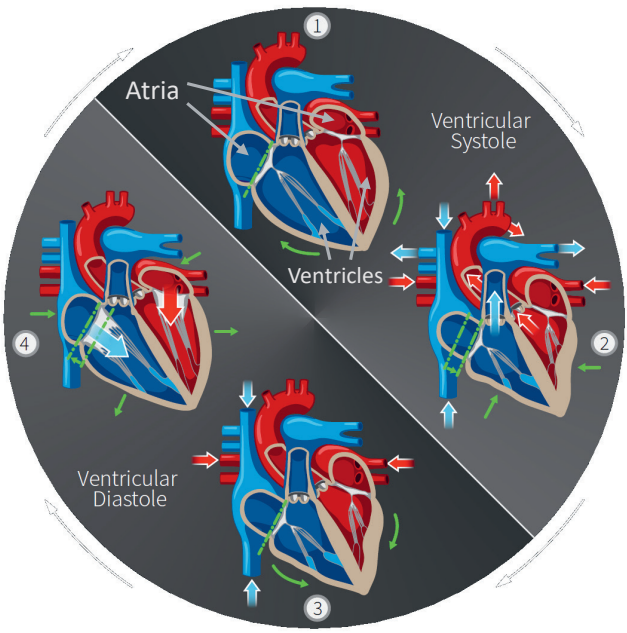
The figure above also shows different kinds of blood pressure: systolic, diastolic and mean arterial pressure. Pulse pressure is also shown. The systolic blood pressure (SBP) is the maximum pressure reached during *systole* (literally "contraction," in Greek), which is the forceful ejection of blood from the contracting ventricles. The diastolic blood pressure (DBP) is the lowest pressure reached during *diastole* (literally "distension" in Greek), which is the phase during which blood from the atria fill the relaxing ventricles of the heart, see Figure 6.

The mean arterial pressure (MAP) is the average pressure and can be expressed as:

$$MAP = DBP + (SBP-DBP)/3$$

FIGURE 6

Illustration of the cardiac cycle with systole and diastole. Adapted from the original, which can be accessed for free at https://www.hegasy.de/. *Used in accordance with CC BY-SA 4.0: https://creativecommons.org/licenses/by-sa/4.0/*



The DBP can be thought of as the baseline pressure. Under resting conditions, systole is shorter than diastole and constitutes a third of the cardiac cycle, which gives the 3 in the denominator in the equation above. The pulse pressure (PP) is the difference between SBP and DBP. It can be expressed as:

$$PP = SBP - DBP$$

The astute reader will have observed that MAP, consequently, can also be expressed as:

$$MAP = DBP + PP/3$$

Systolic and diastolic pressures are routinely measured in clinical practice (more on blood pressure measurement below), whereas pulse and mean arterial pressures are derived from SBP and DBP.

On average, SBP increases with age, save for the last decade of life. This contrasts with DBP, which increases until middle age and then declines,(10) see Figure 7.

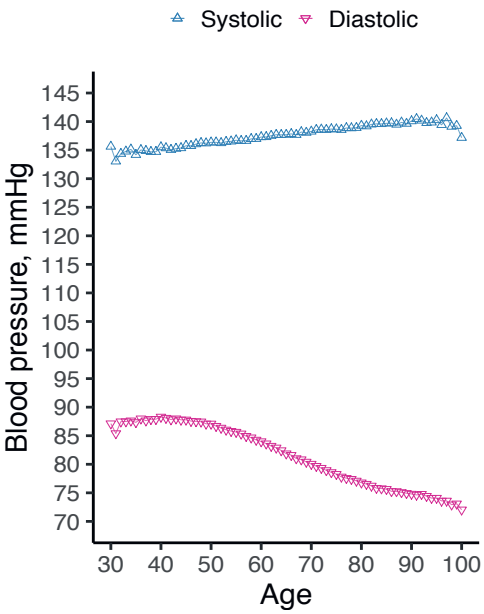


FIGURE 7

Blood pressure at different ages in patients with hypertension. Unpublished data from QregPV.

Regulation of blood pressure

Because blood pressure is the product of output from the heart and the resistance from the vessels of the circulatory system, it follows logically that the mechanisms that govern these systems must also be involved in hypertension and that understanding them is a part of understanding hypertension. Cardiac output depends on heart rate and stroke volume, the latter being dependent, in turn, on cardiac contractile strength and the volume of blood in the heart which is available for ejection from the ventricles into the arteries. Heart rate is mainly controlled via the sympathetic and parasympathetic nervous systems' influence on the sinoatrial node and via adrenaline and noradrenaline influence on β-adrenergic receptors of the heart. Stimulation of cardiac β-adrenergic receptors by adrenaline or noradrenaline increases heart rate as well as cardiac contractility and thus also, indirectly, stroke volume. Decreases in blood pressure are detected by stretch-sensitive baroreceptors in the aortic arch and the carotid arteries and lead to an increase in sympathetic nervous system tone, which increases the heart rate directly via the sinoatrial node and indirectly via adrenaline and noradrenaline release from the adrenal glands. These modulatory changes in tandem with a catecholamine-induced increase in cardiac contractility and peripheral arterial resistance raises blood pressure swiftly. In the case of a rise in blood pressure, the process is reversed and blood pressure is lowered through an increase in parasympathetic tone and a decrease in catecholamine release.(9)

The kidneys and the renin-angiotensin-aldosterone system (RAS) also play a central role in blood pressure regulation, as illustrated in Figure 8. They respond to decreases in blood flow by secreting renin, an enzyme which catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin-converting enzyme (ACE) then converts angiotensin I to angiotensin II, which increases blood pressure by increasing peripheral resistance through vasoconstriction and by stimulating aldosterone secretion from the adrenal cortex. Angiotensin II also increases thirst and fluid retention, the latter by stimulating the release of anti-diuretic hormone. Aldosterone

increases blood pressure by increasing sodium resorption from blood filtered by the kidney, which increases blood volume. Aldosterone also increases urinary potassium excretion. (11) In addition, the kidneys respond to blood pressure decrease by secreting erythropoietin, which raises blood pressure through increased vasoconstriction, which in turn is mediated by an inhibition of vasodilation mechanisms involving nitric oxide.(12) The compensatory, blood pressure-regulating mechanisms that originate in the kidneys react slower than the cardiac output-regulating mechanisms of the autonomic nervous system and the catecholamines and are more important for the long-term control of blood pressure.(13)

The blood vessels can also modulate local blood pressure themselves through the release of vasodilating nitric oxide or vasoconstricting endothelin from the innermost layer of the blood vessel, the endothelium.(14, 15)

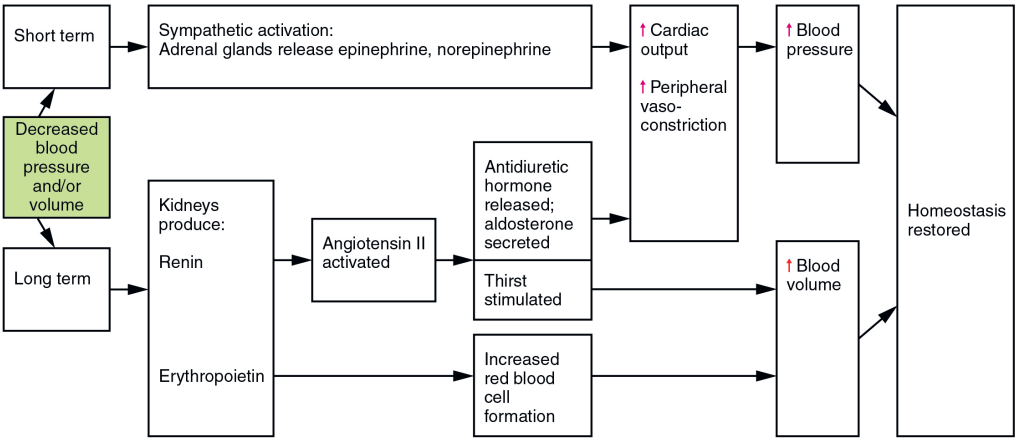


FIGURE 8

Illustration of normal, physiological response to blood pressure decrease. Access for free at https://openstax.org/books/anatomy-and-physiology/pages/20-4-homeostatic-regulation-of-the-vascular-system. *Used in accordance with CC BY 4.0: https://creativecommons.org/licenses/by/4.0/*

Measuring blood pressure

The very first blood pressure measurement was conducted by Stephen Hales in 1733.(16) The measurement procedure was of a decidedly invasive kind, whereby a brass tube was inserted into the left carotid artery of a horse, which would otherwise have been put down because of old age and poor health. The brass tube was in turn connected to a glass tube and the force of blood, as Hales called it, was measured ocularly as the height of the blood column, see Figure 9. The column of blood rose to 290 cm, which corresponds to 214 mmHg, a distinctly high blood pressure also by equine standards. The horse died from the exsanguination, an outcome which is fortunately exceedingly rare after BP measurement today.

FIGURE 9

Hales determines blood pressure in a horse. Credit: Wellcome Collection. Attribution 4.0 International (CC BY 4.0)

In the late 19th century, Scipione Riva-Rocci invented the sphygmomanometer (from *sphygmos*, pulse, and *manomètre*, pressure meter) and described how to non-invasively determine the SBP by palpation. Less than 10 years later, Nikolai Korotkoff published a paper describing how to use Riva-Rocci's sphygmomanometer to determine both SBP and DBP using the sounds that now carry his name, see Figure 10.(17) Although this auscultatory method supplies values for SBP and DBP that are lower and higher, respectively, than their true intra-arterial counterparts, it is still the gold standard for non-invasive determination of blood pressure. In the last decade, electronic, semiautomatic, oscillometric devices have become increasingly popular, especially for home use. They use an algorithm-based method to determine blood pressure from arterial pressure oscillations, which are detected by the cuff. Oscillometric devices are highly practical in noisy environments, because they do not rely on auscultation, but may give inaccurate measures in patients with

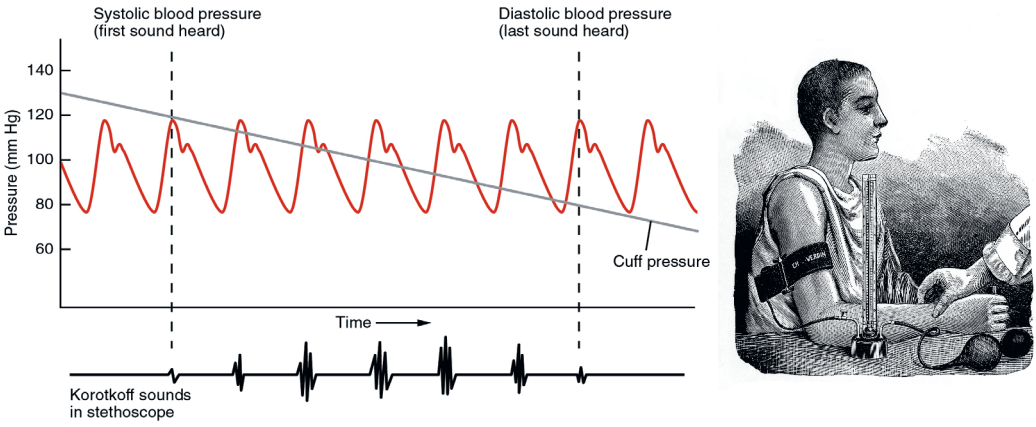


FIGURE 10

Illustration of Riva-Rocci's sphygmomanometer in use and the relation of the Korotkoff sounds to arterial blood pressure when BP is 120/80 mmHg. Credit: Wellcome Collection. Attribution 4.0 International (CC BY 4.0) and https://openstax.org/books/anatomy-and-physiology/pages/1-introduction, *respectively. Used in accordance with CC BY 4.0:* https://creativecommons.org/licenses/by/4.0/.

irregular pulse, such as in atrial fibrillation, or arteriosclerosis. Current guidelines recommend that BP be measured either by auscultatory or oscillometric sphygmomanometer and both methods are used in clinical practice.(18, 19).

Blood pressure is measured in many different settings and for a wide variety of reasons. In the emergency room (ER), clinicians fear the ominously low blood pressures of conditions like septic, anaphylactic and cardiogenic shock. This thesis, instead, elaborates on the perils of high blood pressure. The methods employed to properly identify and manage acute and dangerously low BP vis-à-vis chronic and dangerously high BP differ, where the measurement of the latter is rigorous and highly formalized to allow for accurate diagnosis and adequate reproducibility.

The paradigm shift

In the early 20th century, high blood pressure was considered a necessary and reflexive response which would drive perfusion through constricted arterioles. The idea of "essential hypertension" was born. The true importance of hypertension eluded the great Sir William Osler too, who likened the ageing circulatory system in humans to a rusty and clogged irrigation system, which needed high pressures.

In a 1912 address to his colleagues in the Glasgow Southern Medical Society, Osler described a case where a 40-year-old man suffered a sudden loss of speech, which gradually resolved over a week (i.e. most likely a stroke). The man's systolic blood pressure was 235 mmHg on examination and Osler concluded that his high blood pressure was *"not itself the disease, but a compensatory, salutary state."*(20) In similar fashion, Professor John Hay stated in 1931 that *"the greatest danger to a man with a high blood pressure lies in its discovery, because then some fool is certain to try and reduce it."*(21) The overall message of lectures on hypertension is decidedly different today, in large part thanks to the merits of meticulous actuaries of American insurance companies almost a hundred years ago. Insurance companies with life insurance policies have a natural economic incentive to use available data to predict mortality (i.e. expenses for the insurance companies), and in a 1925 report, it was concluded that *"mortality is lower than the average when systolic or diastolic pressure taken by itself is below the average, but no information is yet available regarding the effect of very low blood pressures"*.(22, 23) Not only did the actuaries discover the link between high blood pressure and cardiovascular disease and death nearly 100 years ago, they also possessed the prophetic perspicacity to identify a burning question which is still relevant in the blood pressure debate of today: At what blood pressure level is the risk of death or disease the lowest?

Evidence of the perils of high blood pressure accumulated from observational studies after the 1950s,(24) with important contributions coming from the seminal Framingham Heart Study, which also showed that systolic blood pressure had a stronger connection to cardiovascular disease than diastolic blood pressure.(25, 26) The 1960s saw the first randomized, controlled trial, the Veteran Affairs Cooperative study, with antihypertensive treatment as the intervention. The beneficial effects of treating diastolic pressures over 115 mmHg were staggering, with dramatic decreases in rates of myocardial infarctions, stroke, heart failure and death observed in the intervention group.(27) The follow-up trial, which treated diastolic blood pressure over 90 mmHg, found similar effects on stroke, heart

failure and death, but a weaker effect on coronary heart disease. (28) Despite these findings, hypertension did not become widely accepted as a significant risk factor for cardiovascular disease and death until 1977 when the first clinical guidelines on treatment of high blood pressure were published.(29) Late 1970s guidelines recommended treatment of patients younger than 50 years if BP was higher than 160/95 mmHg. In patients above age 50, the suggestion was not to pay too much attention to blood pressure levels below 200/110 mmHg. During the 1980s and 1990s, several large randomized, controlled trials showed beneficial effects of treating both systolic and diastolic hypertension.(30-37) This resulted in the adoption of a new BP treatment goal of <140/90 mmHg in the American guidelines of 1993.(32) In 2017, the American guidelines changed the very definition of hypertension from ≥140/90 mmHg to ≥130/80 mmHg on the basis of results from randomized, controlled trials with more ambitious BP targets in the intervention groups.(38-41) Although the 2018 European guidelines maintained the ≥140/90 mmHg definition of hypertension, the treatment goals of American and European guidelines are similar and both recommend a systolic blood pressure target of 130 mmHg for most patients with hypertension, see “Treatment of hypertension” below.(19)

The silent killer

Prevalence and clinical manifestations

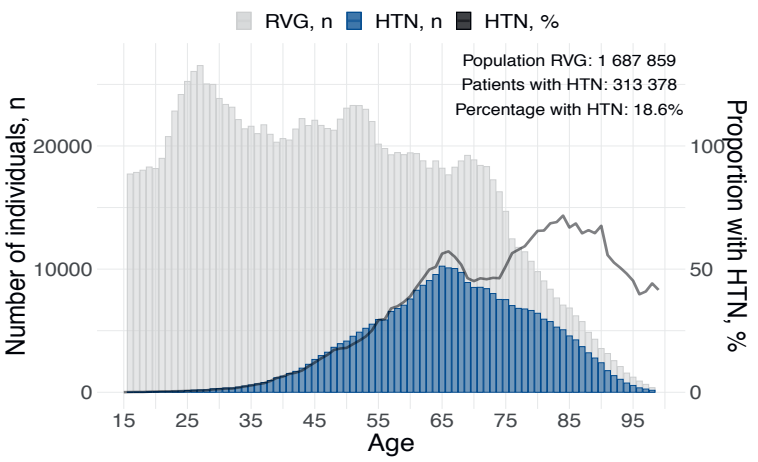
Hypertension is generally an asymptomatic condition. In fact, it causes symptoms so rarely that neither European nor American guidelines even mention any symptoms of it.(19, 38) Unspecific symptoms, particularly headache, may however occur.(42) On the other hand, many patients can have extremely high blood pressure and feel perfectly fine. For many patients with asymptomatic, undiagnosed hypertension, the first symptom of the condition may unfortunately be the aphasia of a stroke or the constricting chest pain of a myocardial infarction.

Hypertension's lack of symptoms makes it particularly insidious, almost like a secret agent of illness. It is the 007 of disease, if you will. What it lacks in symptoms, however, it makes up for in overall lethality, and hypertension is known as a silent killer. Sadly, it is so prolific in its detrimental craft that it was ranked the leading preventable cause of premature disease and death in 2015.(43) A diagnosis of high blood pressure is not in itself as dangerous to the individual as a diagnosis of, say, heart failure or cancer. The global lethality of hypertension instead comes from its ubiquity. In 2015, the global number of adults with hypertension was estimated to be 1.13 billion, or 15% of the world's then total population of 7.35 billion. (44) The sheer number of patients with hypertension combined with its causal role in stroke, coronary heart disease, heart failure, aortic dissection, peripheral arterial disease and renal failure is what makes it dangerous. (42, 45, 46) In the Region of Västra Götaland, Sweden, the prevalence of diagnosed hypertension was 18.6% in 2017, see Figure 11.

As mentioned previously (Figure 7), systolic blood pressure increases with age, which makes the prevalence of hypertension increase with age too. After 65 years of age, it is more common to have a diagnosis of hypertension than not to have it.

FIGURE 11

Number of residents in the Region of Västra Götaland by ages 15 – 99 (grey bars, RVG). Patients with a hypertension diagnosis, by age (blue bars, HTN). The line plot shows the prevalence of hypertension by age on the second y-axis to the right. Unpublished data from QregPV.



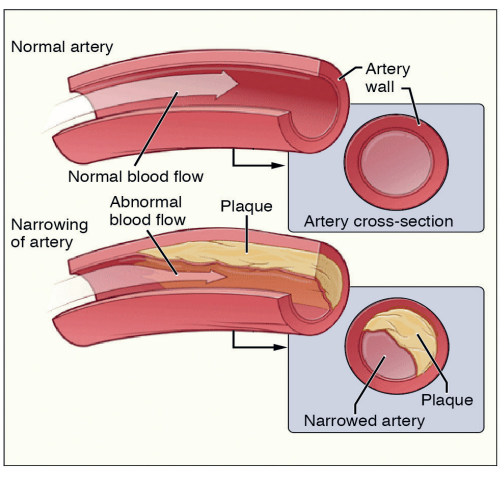
Pathophysiology

In primary hypertension, which is the type of hypertension that more than 90% of patients have, the condition is a result of dysfunction in several of the mechanisms involved in blood pressure regulation, which then cause a net increase in cardiac output and/or vaso-constriction. It has been suggested that a progressive increase in sodium retention, due to decreasing kidney function, is an important factor in primary hypertension.(13, 14) Salt can thus play a role in hypertension. Indeed, higher salt intake increases blood pressure, while lower intake lowers it.(47, 48) Rare monogenic disorders like 11-β-hydroxylase deficiency and Liddle syndrome also manifest with hypertension caused by excessive retention of sodium, which leads to a subsequent increase in blood volume, stroke volume and BP. In contrast, the salt-wasting syndromes of Bartter and Gitelman confer resistance to hypertension.(11)

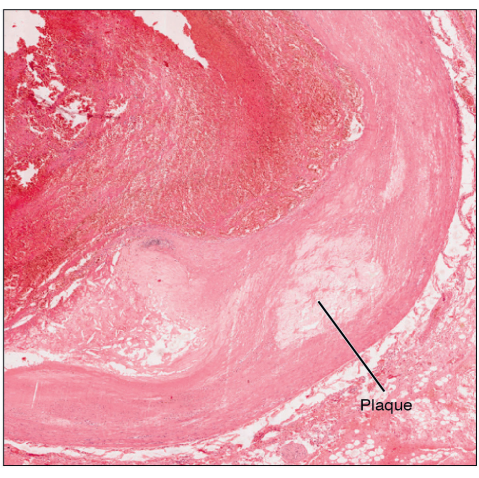
In most cases of primary hypertension, however, the effects of increased peripheral resistance likely outweigh those of increased cardiac output. (9, 42) The renin-angiotensin-aldosterone system plays a particularly important role in clinical hypertension. It is highly activated in patients with secondary hypertension due to renal artery stenosis, which causes decreased blood flow to one or both kidneys, and its activation increases BP via previously described mechanisms.

FIGURE 12

Atherosclerosis. Panel a) shows arterial narrowing due to atherosclerosis in longitudinal and cross-sectional view. Panel b) shows a photomicrograph of a cross-sectional plaque in artery wall. Access for free at https://openstax.org/books/anatomy-and-physiology/pages/20-2-blood-flow-blood-pressure-and-resistance. *Used in accordance with CC BY 4.0:* https://creativecommons.org/licenses/by/4.0/



(a)



(b)

The system is also upregulated in many patients with primary hypertension and it constitutes the main target of pharmaceutical treatment with ACE-inhibitors, angiotensin-receptor-blockers and mineral/aldosterone-receptor antagonists.(49)

Furthermore, angiotensin II is involved in the atherosclerotic process through its contributions to endothelial dysfunction, see Figure 12. Blood pressure-induced vascular remodeling and atherosclerotic changes may then exacerbate hypertension further through narrowing of arteriolar vessels and increase in peripheral resistance, which may create a vicious cycle.(14, 15, 50) The blood vessel distension caused by hypertension also leads to an increase in arterial stiffness, which is an independent predictor of cardiovascular disease.(51, 52) Data from a Mendelian randomization study support the hypothesis that a genetic predisposition for higher blood pressure is causally connected to a higher rate of BP increase with age.(53) This thus implicates that the higher blood pressure you have, the faster it increases with age.

In addition to salt consumption, lifestyle factors such as alcohol consumption, diet, calorie intake, BMI and physical exercise also affect blood pressure.(19, 54-57)

Approximately one tenth of patients with high blood pressure have a singular, identifiable cause for their diagnosis; they have secondary hypertension. The most common aetiology of secondary hypertension is renal disease, either renovascular (including the aforementioned renal artery stenosis) or renal parenchymal disease, such as renal failure. Obstructive sleep apnea is another common cause of secondary hypertension. Endocrine disorders, particularly hyperaldosteronism, should also be considered in the investigation of patients in whom secondary hypertension is suspected. There are exogenous causes of secondary hypertension as well. These include excessive licorice ingestion; substance abuse comprising central stimulants like amphetamine or cocaine; use of oral contraceptives; and use of drugs that may increase blood pressure.(19)

Primary hypertension is still sometimes referred to by the misnomer of “essential hypertension”. A term which I hope the reader will

agree should be resoundingly relegated to the history books after consideration of the material presented in the section “The paradigm shift” above.

Treatment

There is general agreement that the degree of ambition of antihypertensive treatment should scale with a patient’s absolute risk of cardiovascular disease, because patients with hypertension and a high risk of cardiovascular disease are more likely to reap short-term benefits of antihypertensive therapy.(58) Treatment of patients with high cardiovascular risk will thus prevent more strokes and myocardial infarctions, than treatment of patients with low risk. Several risk scores are available to establish the risk for an individual patient, based on the occurrence of risk factors or manifestations of cardiovascular disease. The 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend the use of the SCORE system to estimate cardiovascular risk, which estimates the risk of fatal cardiovascular disease within 10 years, see Figure 13.(19) The risk categories are: low (<1% risk of fatal CVD within 10 years); moderate (1 – 4%); high (5 – 10%); and very high (>10%). Put simply, the guidelines recommend pharmacological BP lowering treatment in all patients with BP ≥140/90. The only caveat being that patients with low cardiovascular risk should first attempt to lower BP through lifestyle modifications, such as decreased salt intake, physical exercise or weight loss before starting antihypertensive drug treatment.

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

FIGURE 13

Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities. CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions. BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation.[1]

The 2018 ESC/ESH Guidelines provide different drug treatment strategies for patients with hypertension based on coexisting conditions, such as coronary heart disease, heart failure or atrial fibrillation.(19) The core drug treatment strategy for patients with hypertension is shown in Figure 14. The cornerstone of antihypertensive treatment for all patients with hypertension is a RAS-blocker, such as an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For patients with uncomplicated hypertension, calcium-channel blockers and thiazide-like diuretics are also

1 *Bryan Williams, Giuseppe Mancia, Wilko Spiering et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 2018; 39 (33): 3021-3104 doi:10.1093/eurheartj/ehy339. Reprinted by permission of Oxford University Press © European Society of Cardiology.*

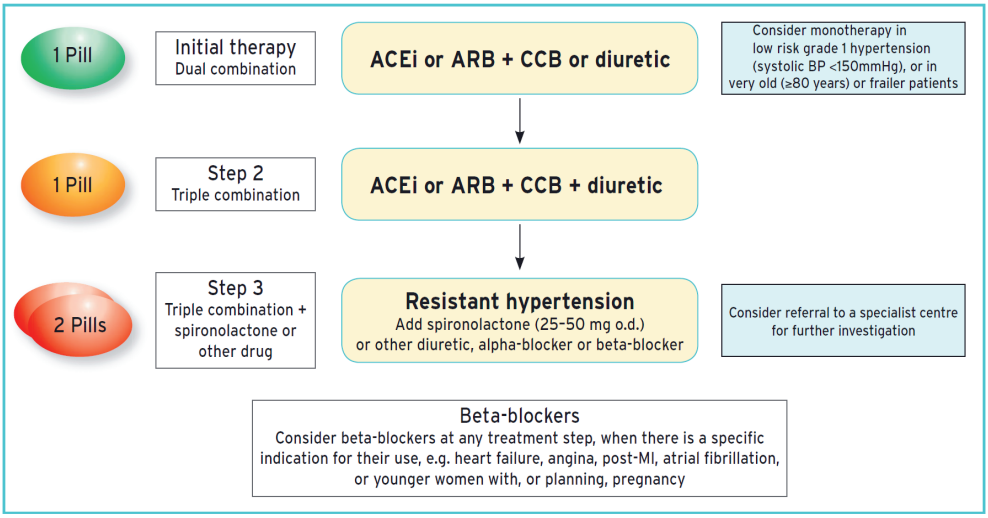


FIGURE 14

Core drug treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral artery disease.[2]

considered first-hand choices. In all but the very oldest patients, initiation of antihypertensive treatment with two drugs at once, preferably in a combination pill, is recommended to promote medication adherence. If the desired blood pressure target range is not attained with the initial therapy, further drugs are added in accordance with the drug algorithm.

The blood pressure target ranges for hypertension in isolation and in combination with concomitant diseases are listed in Table 4.

2 *Bryan Williams, Giuseppe Mancia, Wilko Spiering et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 2018; 39 (33): 3021-3104 doi:10.1093/eurheartj/ehy339. Reprinted by permission of Oxford University Press © European Society of Cardiology.*

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
18 - 65 years	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	**Target to <140 to 130** *if tolerated*	**Target to 130** *or lower if tolerated* Not <120	**Target to 130** *or lower if tolerated* Not <120	70–79
65 - 79 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
≥80 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

TABLE 4

CAD = coronary artery disease; CKD = chronic kidney disease (includes diabetic and non-diabetic CKD); DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.

[a]Refers to patients with previous stroke and does not refer to blood pressure targets immediately after acute stroke.

[b]Treatment decisions and blood pressure *targets may need to be modified in older patients who are frail and independent.*[3]

The J-curve phenomenon

The section "The paradigm shift" above has already shown that higher blood pressure levels are dangerous and increase the risk of cardiovascular disease and death. A blood pressure of zero obviously also increases the risk of death (quite drastically so), since all the organs of our bodies depend on perfusion to function. The J-curve illustrates how risk changes with the magnitude of a variable when both lower and higher values are associated with higher levels of risk than an intermediate value.(59, 60) The curve in Figure 15

3 *Bryan Williams, Giuseppe Mancia, Wilko Spiering et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 2018; 39 (33): 3021-3104 doi:10.1093/eurheartj/ehy339. Reprinted by permission of Oxford University Press © European Society of Cardiology.*

illustrates how risk (y-axis) changes in a J-shaped pattern when a variable (x-axis) such as blood pressure increases. The J-curve relationship between risk of death and variable magnitude is not unique to the domain of blood pressure, but can be identified for a plethora of variables where both scarcity and excess can be harmful. Consumption of water or food may serve as examples and so may biological quantities such as body-mass index, blood glucose or blood potassium levels.(61) This J-curve phenomenon begs the question: At what blood pressure level is risk of death or disease the lowest? The relationship between blood pressure and risk depends both on the type of cardiovascular outcome and the risk level of the patients studied.(45, 58) This thesis focuses on patients with hypertension in primary care, whose treatment is often primary preventive, and on the relationship between BP and stroke.

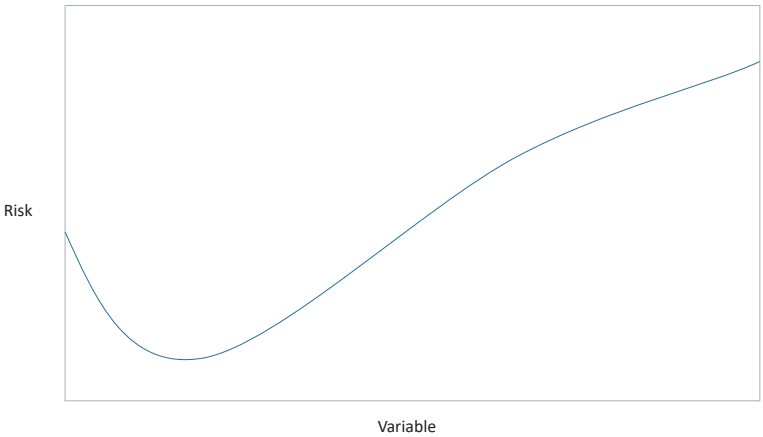


FIGURE 15

J-shaped curve showing risk of an outcome, such as death, plotted against the magnitude of a variable, such as blood pressure.

Primary prevention

Most patients with hypertension in Sweden are managed in primary care and a majority of them have not suffered any manifestations of cardiovascular disease, such as stroke, myocardial infarction or heart failure. All antihypertensive treatment in patients who do not have manifest cardiovascular disease is considered primary preventive. Although American and European guidelines define hypertension differently (≥130/80 vs ≥140/90 mmHg), both of them

recommend pharmacological, primary preventive, blood pressure-lowering treatment of patients with BP ≥140/90 mmHg and neither recommends pharmacological primary preventive treatment of patients with BP in the 130 – 139/80 – 89 mmHg range. (19, 38) These recommendations are in part based on a large RCT, which did not demonstrate a statistically significant decrease in the composite outcome of stroke, myocardial infarction or cardiovascular death when the SBP of the intervention group was lowered to 128 mmHg, compared to the control group's 134 mmHg.(62) Some meta-analyses have also questioned the overall benefit of lowering BP in patients with low baseline cardiovascular risk and SBP below 140 mmHg, while another suggested that lowering BP was beneficial when baseline SBP was below 130 mmHg.(63-65) Recently, preliminary results from a meta-analysis of individual patient data from 48 trials comprising 348 854 patients by the Blood Pressure Lowering Treatment Trialists' Collaboration, presented at the European Society of Cardiology Congress of 2020, estimated that lowering SBP by 5 mmHg decreases the relative risk of a major cardiovascular event (HR 0.90, 95% CI 0.88 – 0.92), irrespective of a patient's baseline cardiovascular risk level and blood pressure.(66) In addition, a 2019 observational, Mendelian randomization study, which compared the effects of genetic predisposition for lower SBP to that of higher SBP, found that a lifetime exposure to 2.9 mmHg lower SBP was significantly associated with lower risk of coronary heart disease.(67) The results from these two studies were not available when the latest American and European hypertension guidelines were released, but they suggest that modest decreases in blood pressure, even for patients with SBP 130 – 139 mmHg, for a long time may contribute to primary prevention of cardiovascular disease. This means that the risk nadir of the J curve for patients with hypertension, but without manifest cardiovascular disease, likely lies below SBP 130 mmHg. Regardless, it should be mentioned that since cardiovascular risk increases with increasing BP, the global disease-preventive effect of addressing the large number and proportion of patients with hypertension who do not attain BP <140/90 mmHg would be far

greater than treating a primary preventive population with SBP in the 130 – 139 mmHg range.(43)

Secondary prevention of stroke and myocardial infarction

It is widely accepted that patients with a history of stroke or transient ischemic attack (TIA) should be treated to a BP <140/90 mmHg to reduce the risk of recurrent stroke.(19, 38) This recommendation is largely based on data from two large randomized, controlled trials of patients with previous stroke or TIA, which both displayed lower incidence of stroke in the treatment groups compared to controls.(68, 69) Whether further BP lowering beyond <140/90 mmHg prevents stroke recurrence is less clear. In a secondary analysis of one of the aforementioned trials, which investigated associations between achieved SBP level during the trial and incidence of stroke, the lowest incidence of both ischemic and hemorrhagic stroke was observed in the lowest, 112 mmHg category. In this analysis there was no evidence of a J-curve.(70) Data from trials dating back to the 1960s which have comprised other populations, i.e. patients without previous stroke or TIA, have also shown that BP lowering may be particularly beneficial for preventing stroke.(27, 28, 33-36) Large observational studies have also suggested that SBP levels down to at least 115 mmHg are associated with lower risk of cardiovascular disease, including stroke.(45, 71) In contrast, results from a randomized controlled trial of patients with previous lacunar stroke, which compared incidence of stroke for an intervention group with an achieved SBP of 127 mmHg to a control group with an achieved mean SBP of 138 mmHg, showed no significant difference between the comparison groups. The investigators noted that, although not significantly different, the incidence of stroke was lower in the intervention group (22.5 per 1000 patient-years vs 27.7 1000 patient-years, HR 0.81, 95% CI 0.64 – 1.03) and that the risk of the secondary outcome of haemorrhagic stroke was significantly lower (HR 0.37, 95% CI 0.15 – 0.95) in the intervention group. The rate of adverse events was also similar across the comparison groups.(40) A 2017 meta-analysis of secondary stroke prevention

trials recommended SBP reduction to <130 mmHg to reduce the risk of stroke recurrence.(72)

As a consequence of the conflicting evidence for the benefit of lowering BP to <130/80 mmHg in secondary prevention of stroke, both American and European guidelines state that this lower BP target is not explicitly recommended, but that it may be considered in patients who tolerate it.(19, 38)

Hypertension is a major, preventable risk factor for myocardial infarction too.(45, 73) Although there are no RCTs which have exclusively comprised patients with hypertension and manifest coronary heart disease, there is ample evidence from RCT's, meta-analyses and observational studies that patients with hypertension and varying levels of cardiovascular risk benefit from blood pressure lowering treatment.(46, 58, 64, 66, 74) Currently, both American and European hypertension guidelines recommend a SBP target of <130 mmHg in patients with hypertension and coronary heart disease.

Knowledge gaps

Blood pressure in acute ischemic stroke

A diagnosis of hypertension is a well-established risk factor for ischemic stroke and blood pressure-lowering treatment thus reduces the risk of a first or recurrent ischemic stroke.(33, 34, 64, 68, 69) The management and predictive value of blood pressure in the setting of acute ischemic stroke, however, is more uncertain.(19) A large prevalence study, comprising over 275 000 patients with acute ischemic stroke, showed that more than two thirds of patients with acute ischemic stroke exhibit a SBP of more than 140 mmHg and one fifth have over 180 mmHg. (75) Blood pressure then typically decreases spontaneously and normalizes in a few days, with most of the decline occurring in the first days after the stroke.(76, 77) It has been suggested that the initially high blood pressure could be either beneficial, by causing improved perfusion of ischemic parenchyma, or detrimental, by causing edema or hemorrhage.

These circumstances beg the following questions:

- Should high blood pressure in the setting of acute ischemic stroke be treated?
- Do early blood pressure levels in acute ischemic stroke carry any prognostic information with respect to outcomes such as mortality and neurological function?

The first question was addressed by the Scandinavian Candesartan Acute Stroke Trial (SCAST), which randomized 2029 patients admitted with acute stroke (ischemic and hemorrhagic) and SBP >140 mmHg to either candesartan or placebo for seven days. Candesartan decreased mean SBP, but there was no difference (HR 1.09, 95% CI 0.84–1.41) in the primary composite outcome of vascular death and myocardial infarction during the six months of follow-up, compared to placebo. Instead, a trend towards worse functional outcome, as measured by modified Rankin Scale (mRS), for the candesartan group was noted (OR 1.17, 95% CI 1.00–1.38).(78) An even larger RCT in 2014 was similarly unable to demonstrate any benefit of pharmacologically lowering blood pressure in acute ischemic stroke.(79) Thus, there is no evidence that actively reducing BP in patients with acute ischemic stroke has any positive effects on outcomes of mortality and neurological function. Consequently, neither American nor European guidelines recommend routine lowering of BP in acute ischemic stroke.(19, 38) It should be mentioned, however, that there is a subgroup of patients with ischemic stroke for whom acute BP reduction seems beneficial: those who receive thrombolysis. Observational studies suggest that BP below 180/105 mmHg, for at least the first 24 h following thrombolysis, is associated with a lower risk of intracerebral hemorrhage.(80, 81)

As for the prognostic value of BP in acute ischemic stroke, several observational studies and secondary analyses from RCTs have investigated the association between different measures of BP and short- and long-term mortality and neurological outcomes. Some of these cohort studies did not find any associations between admission BP in acute stroke and mortality or mRS.(82, 83) A secondary analysis from a large RCT of nearly 18 000 patients

with acute ischemic stroke found a J-curve relationship in patients between short-term mortality, where SBP 150 mmHg was associated with the lowest risk and any SBP higher *or* lower was associated with higher risk (OR ~1.1 per 10 mmHg from 150). They found no association between admission SBP and long-term mortality and neurological function, however.(84) Other observational studies have also described a J-curve relationship between admission SBP and mortality.(85, 86)

Another variable with possible prognostic value in acute ischemic stroke is spontaneous change in BP after admission: the ΔBP. Several studies have shown an association between decrease from admission BP and less severe stroke and better neurological function.(87, 88) This contrasts with the findings from SCAST, in which pharmacologically mediated BP decrease was associated with a trend towards worse functional outcome.(78)

In summary, the prognostic value of BP level on the arrival to the ER and ΔBP for predicting mortality and neurological function, especially in the long term, remains unclear for patients with acute ischemic stroke.

Blood pressure in older patients

Antihypertensive treatment in older patients has been controversial for much of the 20th century. As mentioned, late 1970s medical literature recommended to not treat older patients with hypertension if BP was below 200/110 mmHg.(30) This recommendation was conclusively refuted by two landmark RCTs presented in 1991, which included older patients with SBP >160 and >180 mmHg respectively and showed that antihypertensive treatment effectively reduced the incidence of stroke, myocardial infarction and death.(33, 34) In these trials, "older" was defined as ≥60 years and 70 – 84 years, respectively. Later RCTs have provided further support that treatment to SBP both <160 mmHg and <150 mmHg is beneficial in older patients, including those over 80 years.(89, 90) Whether even more ambitious BP targets are suitable is still subject to debate. Current American and European guidelines disagree on the SBP treatment target for older (≥65 years) patients. The former recommend <130

mmHg, whereas the latter recommend 130 – 139 mmHg while also stating that SBP less than 130 mmHg should be avoided.(19, 38) Both guidelines lean on the prespecified subgroup analysis of patients older than 75 years from the SPRINT RCT, which showed lower risk of cardiovascular disease and death in the intervention group with SBP 123.4 mmHg compared to the control group with SBP 134.8 mmHg (HR 0.66, 95% CI 0.51 – 0.85), but its results are interpreted differently.(39, 74, 91) Observational data from primary care patients in the United Kingdom also support that attained SBP <130 mmHg may be associated with a lower risk of myocardial infarction, but also a higher risk of death.(92)

There is thus disagreement on whether SBP levels below 130 mmHg are beneficial for older patients.

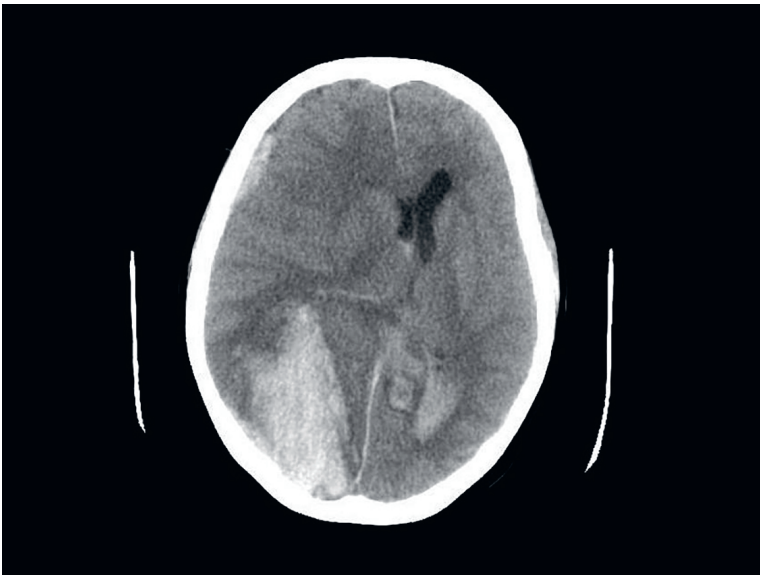
Blood pressure and risk of hemorrhagic stroke in patients with atrial fibrillation and oral anticoagulants

Hypertension is an important risk factor for atrial fibrillation (AF) and many patients with hypertension develop AF. When they do, according to the CHA_2DS_2-VASc algorithm, they require treatment with oral anticoagulants (OAC) to reduce the risk of ischemic, cardio-embolic stroke.(19, 93) This means that many patients with AF have both hypertension and OAC, which both are independent risk factors for hemorrhagic stroke, see Figure 16.(94) The ideal blood pressure level for this specific patient category has not been addressed by any RCT. Current guidelines recommend (class IIa) that a target SBP of 130 mmHg or lower should be considered for this patient group, with evidence (level B) coming from observational studies and secondary analyses of RCTs.

A secondary analysis from the RE-LY (dabigatran) trial dichotomized patients by history of hypertension at trial entry.(95) The authors did not report the outcome of hemorrhagic stroke specifically, but patients with hypertension had a higher rate of intracranial hemorrhage, albeit without a statistically significant difference between the groups (HR 1.26, 95% CI 0.91 – 2.36).

FIGURE 16

Computer tomography of large, right-sided, posterior intracerebral hemorrhage in a patient with warfarin. Courtesy of Dr Jeremy Jones, Radiopaedia.org, rID: 6153



The secondary analysis from the Aristotle (apixaban) trial dichotomized patients in three different ways: by history of hypertension at trial entry; by blood pressure at trial baseline; and by blood pressure during the trial.(96) Results showed higher incidence rates of hemorrhagic stroke in patients with a history of hypertension before the trial and in patients with SBP ≥140 mmHg at the trial baseline, but the difference was not statistically significant from the respective comparison categories. Patients with elevated blood pressure (SBP ≥140 mmHg and/or DBP ≥90 mmHg) during the trial did, however, display a significantly increased (HR 1.85, 95% CI 1.26 – 2.72) risk of hemorrhagic stroke. The secondary analysis from the Rocket-AF (rivaroxaban) trial showed a higher event rate of hemorrhagic stroke for patients SBP ≥160 mmHg.(97) Patients with hypertension prior to baseline and SBP ≥140 mmHg also had a significantly higher risk of hemorrhagic stroke (HR 3.04, 95% CI 1.06 – 8.71), compared to patients with no prior history of hypertension.

An observational study of patients with antithrombotic therapy (44% OAC) showed an association between higher SBP during follow-up, but not at baseline, and an increased risk of intracranial hemorrhage (HR 1.45 per 10 mmHg increase, 95% CI 1.08 – 1.92).(98) Another cohort study from 2017 linked uncontrolled hypertension,

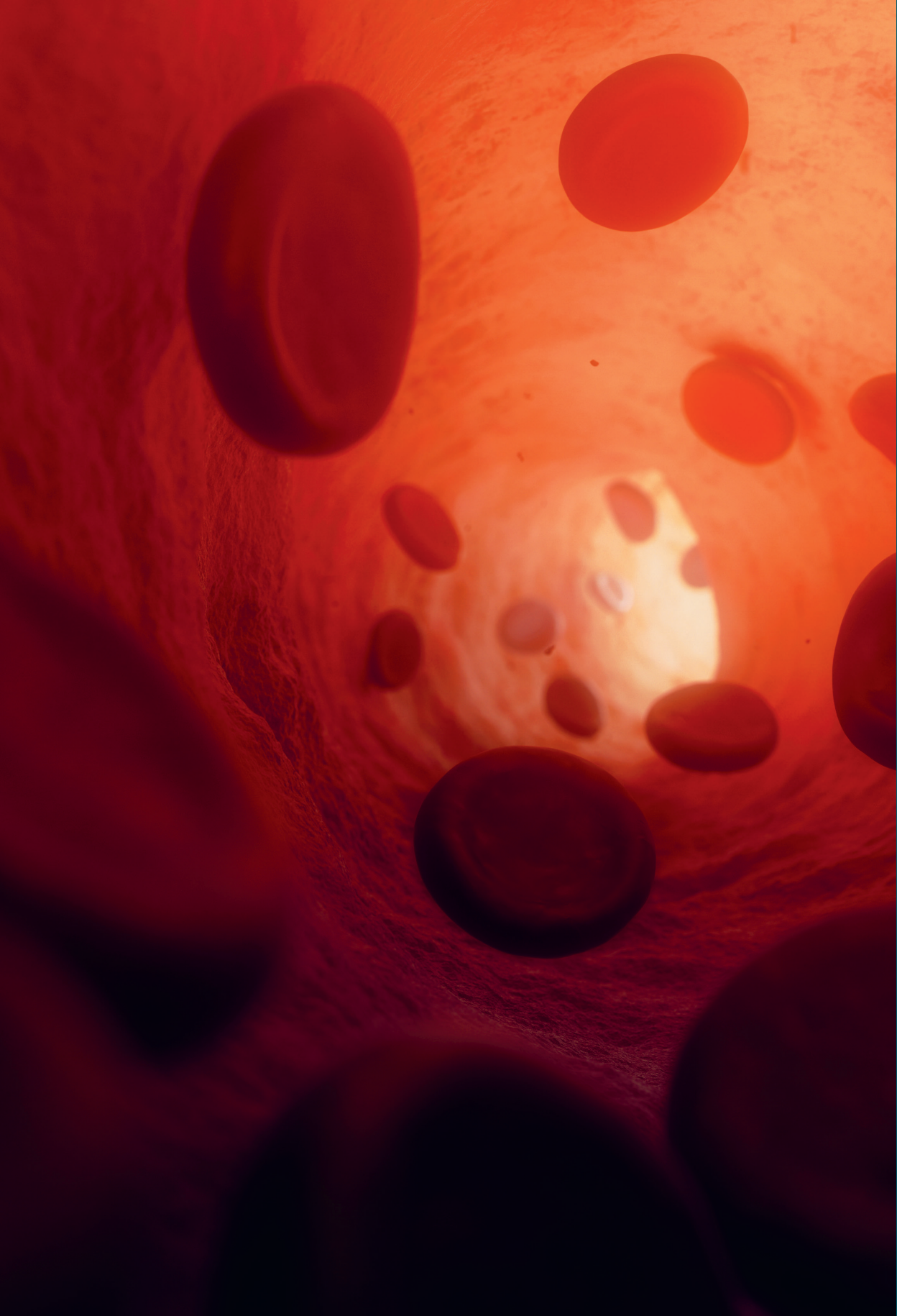
defined as SBP ≥150 mmHg, in patients with AF (55% with OAC) to an increased risk (HR 4.46, 95% CI 1.78-9.75) of hemorrhagic stroke. (99)

The analysis of the relationship between blood pressure level and risk of hemorrhagic stroke seems to be complicated by the low incidence of the latter. With an incidence rate of 2 – 3 hemorrhagic strokes per 1000 person-years, statistical power becomes an issue. The above mentioned studies of patients with AF, OAC and hypertension have all found higher incidence rates of hemorrhagic stroke in patients with higher SBP, but these differences have not been uniformly statistically significant. Taken together, they may point to a higher risk of hemorrhagic stroke in patients with a SBP higher than 140 or perhaps 150 mmHg.

Nevertheless, it remains unclear whether higher SBP can be tied with certainty to an increased risk of hemorrhagic stroke in patients with AF and OAC and if that risk varies over different SBP levels. The predictive value of SBP at baseline, i.e. prior to initiation of OAC therapy, in these patients also remains unclear.

Trends in blood pressure, blood lipids and smoking in primary care

High blood pressure, high blood cholesterol and tobacco smoking are major risk factors for cardiovascular disease.(43) Improved control of blood pressure and blood lipids and smoking cessation decrease the risk of cardiovascular disease in patients with hypertension.(58, 73, 100, 101) Control of these important cardiovascular risk factors have broadly improved in population-based samples in high-income countries during the last decades.(44, 102-106) Population-based samples are however just that: samples. Most patients with hypertension are managed in primary care, but representative data on trends in blood pressure, blood lipids and smoking from Swedish primary care for the last decade are scarce.



Chapter 2

Aim

"Trying is the first step towards failure."

– Homer Simpson

Aim

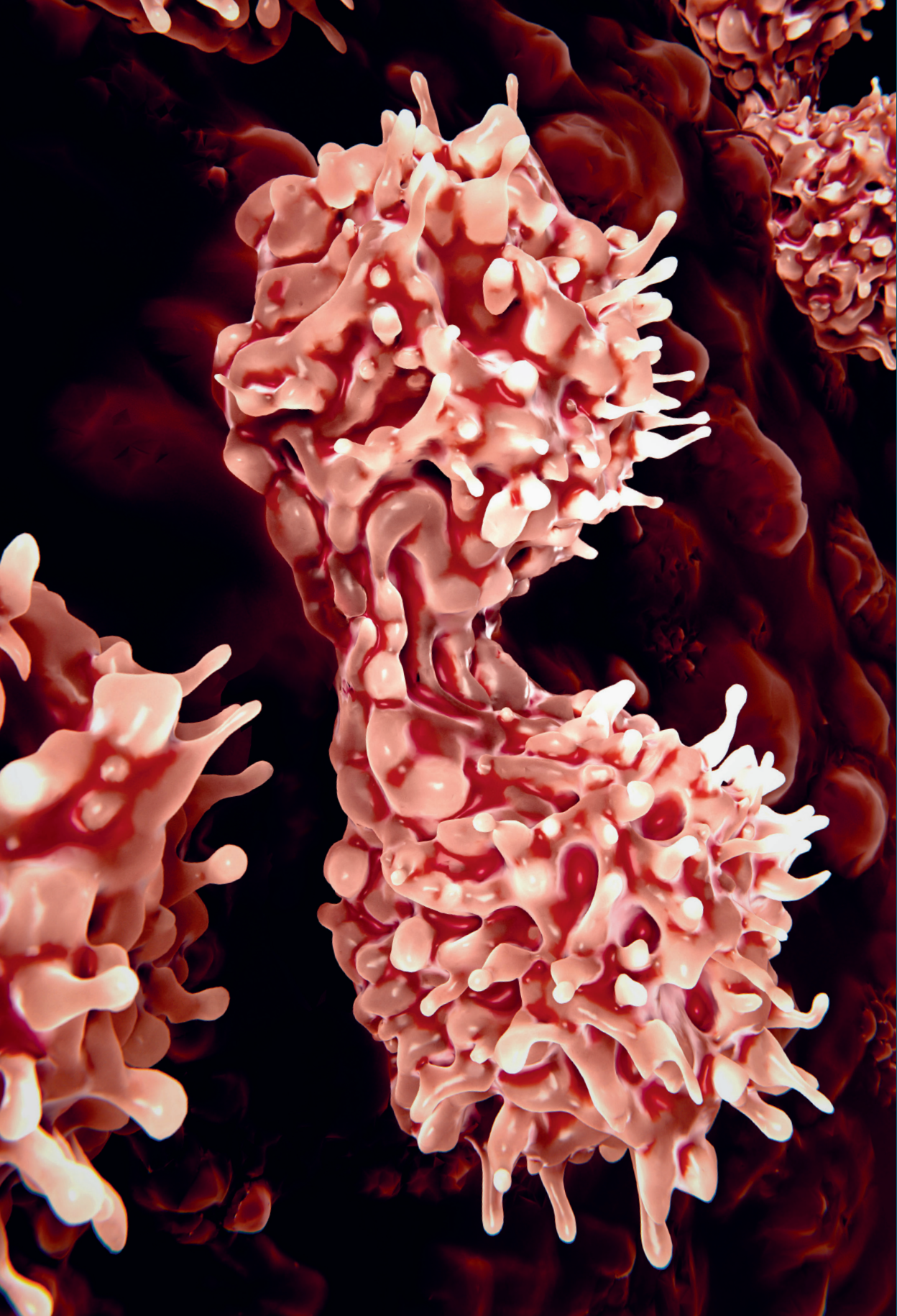
The overarching aim of this thesis is to investigate the prevalence, temporal trends and associations to cardiovascular outcomes of blood pressure levels in patients in Västra Götaland. The specific research aims of the studies that constitute the foundation of this thesis are listed below:

I. To determine the prognostic value of the admission blood pressure level and early changes in blood pressure in predicting mortality, stroke severity and functional outcome in patients with acute ischemic stroke

II. To investigate the association between blood pressure levels lower than current treatment recommendations and risk of myocardial infarction or stroke in patients without previous cardiovascular disease, with special emphasis on older patients

III. To investigate the risk of haemorrhagic stroke at different levels of systolic blood pressure in patients with hypertension, atrial fibrillation and oral anticoagulants

IV. To describe changes in systolic blood pressure levels in patients with hypertension in primary care in the Region of Västra Götaland from 2010 – 2017 and how well blood pressure, blood lipids and smoking are controlled in this population



Chapter 3

Methods

3

"All models are wrong,
but some are useful."

– George Box

3.1 Introduction to methods

The personal identity number and data linkage

All permanent residents of Sweden have personal identity numbers, which are used by all healthcare providers and by Swedish authorities, such as the National Board of Health and Welfare, Statistics Sweden and the National Tax Agency, to identify individuals.(107) The use of a shared identifier across healthcare and national and regional registers offers excellent opportunities for observational research, because clinical and register data can be linked. This thesis is based on observational studies which all have originated in data from clinical practice, to which national and regional register data have been linked, see Figure 17.

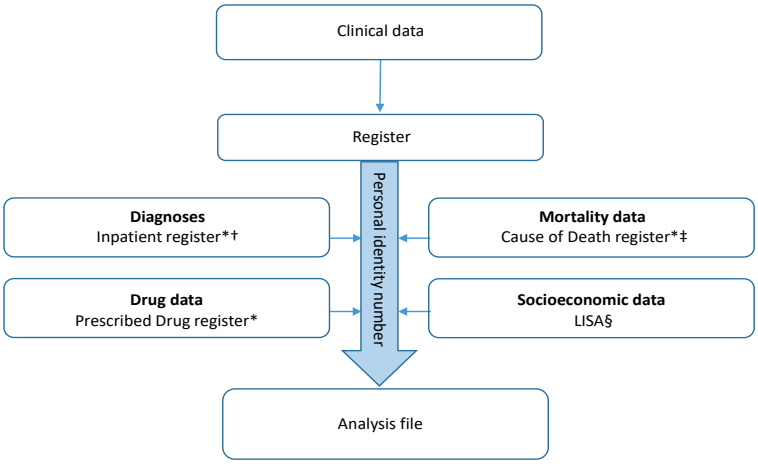


FIGURE 17

General data flow in Studies I – IV. Clinical data enter into a register and are linked to data from national and regional registers via the personal identity number.
**Not applicable for Study I*
†Studies II and IV also used diagnosis data from the regional register Vega
‡Mortality data in Study I came from the Total Population Register
§Only Studies II and IV

National and regional registers

The National Patient Register holds nation-wide diagnosis data, according to the 10th revision of the International Classification of Diseases (ICD-10), from hospital discharges since 1987 and from hospital-based outpatient appointments since 2001, but does not have diagnostic data from primary care. Both primary and contributing diagnoses are included from hospital-based care and the register shows high validity for some diagnoses, like stroke, atrial fibrillation and myocardial infarction, but lower validity for others, like hypertension.(108, 109) The Cause of Death Register holds data on practically all deaths in Sweden since 1961 and 96% of all deaths

also has a specific cause of death registered. The validity for causes of death is highest for deaths due to malignancies and cardiovascular disease.(110-113) The Prescribed Drug Register was established in 2005. It holds data on prescribed and dispensed drugs in outpatient care such as drug name, amount, dosage and prescriber workplace and profession. The register does not cover prescription-free drugs; drugs used in hospital wards; and certain drugs used in hospital-based outpatient care, such as chemotherapeutic or immunomodulatory infusions given in oncology or rheumatology care. It also does not cover drugs that have been prescribed, but not dispensed. The drugs covered in the register account for more than 80% of the total drug volume in Sweden. For cardiovascular drugs, the coverage is more than 95%.(114) The National Patient Register, the Cause of Death Register and The Prescribed Drug Register are managed by the National Board of Health and Welfare (Socialstyrelsen).

The Total Population Register was started in 1968 and holds information on personal data of the population of Sweden, such as birth, family members, marital status, emigration and death. Most data in the Total Population Register are reported to it by professionals such as physicians, midwives and officials, which leads to overall high data quality. Virtually all deaths (>99%) in Sweden are reported to the register within 30 days of the date of death.(115) The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) contains data on socioeconomic variables like education, civil status, income and country of birth since 1990. (116, 117) LISA and the Total Population Register are managed by Statistics Sweden (Statistiska Centralbyrån).

Vega is the regional administrative healthcare database of Västra Götaland. Since the year 2000, it comprises data on diagnoses, procedures, residence and health care visit-related information, such as data on type of health-care professional and type of health-care provider visited. Data quality has improved since 2005, when a new reimbursement system incentivized improved diagnosis reporting. The register covers all health care – private and public – in the Region of Västra Götaland. Data on diagnoses and procedures in hospital-based care are forwarded from Vega to the National Patient Register.(118)

Dealing with missing data

As mentioned in “Methodology in epidemiological studies”, missing data is a common issue in observational epidemiology and a potential source of information bias. The studies in this thesis also have missing data, more for some variables than for others, and have addressed missing data differently.

Studies I and IV used complete case analysis, in which only participants with no data missing data for analyzed variables are included into models or calculations. This method is simple to grasp conceptually, but has two major disadvantages: 1) it leads to loss of statistical power and 2) it may introduce bias if data are not missing completely at random.

Studies II and III used multiple imputation by chained equation to generate substitute values, which replace missing data points. Imputation solves the problem of statistical power loss completely, because the imputation process completes the data set. Imputation is also adequate if data are either missing completely at random or missing at random. If, however, imputation is used to generate data that are missing not at random, bias can result. There is, unfortunately, no way to determine whether missing data are missing completely at random, missing at random or missing not at random. Regardless, multiple imputation by chained equation is considered the preferred method of dealing with missing data.(2, 8, 119)

Regression models

This thesis employs regression models to adjust for potential confounders. Regression models are used to calculate how a variable, such as height, affects another one, such as weight. We can return to the galaxy far, far away for an example. A linear regression model can be used to calculate how a change in height affects the weight for characters in Star Wars. In this model, height is the independent variable, the predictor, and weight is the dependent, the outcome, because we are calculating how the latter depends on the former. The independent variables in the model are often referred to as *covariates.* The model yields a coefficient of 0.62 for height, which means that weight increases by 0.62 kg for every 1 cm of height

increase. There may, however, be other variables that also affect weight, such as gender. If gender is also included in the model, which is now a multivariate, linear regression model, we get coefficients for both height and gender which are 0.59 and 22.4, respectively. When several covariates are included, the coefficients represent change in the dependent variable per unit of change in the independent variable, when all other covariates are kept constant. Since height is a continuous variable, the increase of 0.59 kg is per cm, when gender is kept constant. Gender, however, is a categorical variable and the 22.4 in this example is the weight increase associated with being male, compared to female, when height is kept constant. Because gender is a covariate in the model, the analysis of the effect of height on weight is now *adjusted* for gender. Note that the coefficient for height decreased slightly when gender was included into the model.

Three of the papers in this thesis use the Cox proportional-hazards model, which is a regression model that incorporates time, in addition to the covariates and the dependent variable.(120) Unlike the coefficients from a linear regression model, the coefficients from a Cox regression are rarely presented. Instead, the exponentiated coefficients, called *hazard ratios*, are presented. The hazard ratio (HR) is a relative risk measure for binary outcomes, which can be calculated in epidemiological studies when follow-up time differs between participants. For example, the dynamic cohort of QregPV comprises patients in Västra Götaland with hypertension since 2010. If we want to analyze the association between patients' first blood pressure level in QregPV and stroke, the time span between the blood pressure measurement and the stroke is the *time to event*. As in the linear regression example above, we can include additional covariates, such as age or history of stroke. The final model yields hazard ratios for the outcome for all included covariates. The hazard ratio can be thought of as the average relative risk of the outcome during follow-up.(121) The Cox regression model assumes the hazard ratio between comparison groups is constant over time, i.e. that the hazard is proportional. The proportional hazards assumption should be tested for the covariates that are included in the model. This can

be accomplished with statistical tests or plotting and visual inspection of the scaled Schoenfeld residuals.(122) Because Cox regression allows for adjustment for several covariates and takes time to event into account, it has become the de facto standard model for survival analysis in observational epidemiology.

Ethics

All studies in the thesis were approved by the Regional Ethical Review Board of Gothenburg:

- Study I is covered by the approval with registration number 036-06
- Studies II and IV are covered by the approval with registration number 1062-15
- Study III is covered by the approval with registration number 577-17

3.2 Study I – Blood pressure in acute ischemic stroke

Data sources and study population

This paper is based on data collected in a quality register of the stroke ward of the medical department at Sahlgrenska University Hospital. Patients with stroke who received thrombolytic therapy or underwent thrombectomy were not admitted to the stroke ward of the medical department, instead they were treated at the stroke ward of the neurological department. From 2005 to 2009, the register prospectively and consecutively included all patients admitted to the ward with acute stroke or transitory ischemic attack. It comprises data on comorbidity on register inclusion; data on clinical variables collected during the period of admission at ward; and outcome data such as mortality and level of neurological function at different points in time after inclusion.

Comorbidities were established through interviews – aided by standardized forms – of included patients or their next of kin. Baseline comorbidities were also indirectly inferred through the patients' drug treatment, e.g. use of antihypertensive or antidiabetic drugs was interpreted as baseline diagnoses of hypertension and diabetes, respectively. Measurements of clinical variables were performed by healthcare professionals as part of clinical practice. Systolic and diastolic blood pressures were measured in the supine position and defined as the levels of pressure where Korotkoff sounds appeared and disappeared, respectively. Blood pressures were measured on arrival to the ER and on admission to the ward, with the latter measurement occurring no later than twelve hours after the first. Acute stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS).(123) The modified Rankin Scale (mRS) was used to measure neurological function at follow-up visits or, for patients unable to travel, via telephone after three and twelve months.(124, 125). Mortality data were acquired from the Total Population Register, which is managed by Statistics Sweden and which holds information on all registered deaths.(115) All collected data was entered into the register by research nurses.

In study I, the study population comprised all patients in the stroke register with acute ischemic stroke.

Statistical analysis

We defined BP on arrival to the ER and ΔBP (which was calculated as BP^{ER}– BP^{ward} = ΔBP) during the first day as exposure variables. Outcome variables comprised NIHSS; mortality at one, three and twelve months; and mRS at three and twelve months. Baseline characteristics of the study population were presented with mean ± standard deviation (SD) for continuous variables and with percentages of valid entries for categorical variables. The day of arrival to the ER was defined as the index date and all patients were followed for one year or until death, whichever occurred first.

We used a multivariate, linear regression model to analyze the association between NIHSS score and the BP variables. NIHSS, in its ordinal scale, was the dependent variable and BP, as a continuous variable, was the independent variable. We identified age, sex and history of ischemic stroke as potential confounders and included them as covariates in the analysis.

In the analysis of mortality, a Cox proportional-hazards model was used.(120) Survival in days was the time variable; death at one, three or twelve months were dependent variables and BP was the independent variable. Age, sex, NIHSS score, heart failure, diabetes mellitus, and history of ischemic stroke were included as covariates in the model to reduce the effect of potential confounding. Based on the covariates in the Cox regression, we also plotted an adjusted survival curve to depict the difference in survival between patients with an increase or decrease in systolic blood pressure (SBP).

The ordinal scale (0 – 6) variable mRS was dichotomized: 0 – 2 on the scale was considered a good outcome and 3 – 5 was considered a poor outcome. Patients with mRS of 6 were excluded from the analysis of neurological function, because mRS of 6 equals death, and the outcome of mortality was analyzed separately. The dichotomized mRS variable was used as the dependent variable in a binary, logistic regression model and the BP variables were set as the independent variable. This model also comprised age, sex, NIHSS score, heart failure, diabetes mellitus, and history of ischemic stroke as covariates. A P value below 0.05 was considered statistically significant. All analyses in study I were performed with SPSS Statistics, version 24 (IBM Corporation, Armonk, New York, United States).

3.3 Study II – Blood pressure levels and risk of stroke or myocardial infartion in older patients without previous cardiovascular disease

Data sources and study population

Both Study II and IV are based on data from QregPV, which is a quality assurance register for primary care. The register comprises patients with hypertension, diabetes mellitus, coronary heart disease, chronic obstructive pulmonary disease and asthma. It was founded as a tool for providing feedback to primary-care providers on the trends of a select group of risk factors: smoking status, body-mass index, blood pressure, blood cholesterol, glycated haemoglobin, waist circumference and spirometry. The trends of these risk factors can be viewed in aggregate for all primary-care centers or at the level of an individual primary-care center, which allows for feedback on risk-factor control to specific primary-care centers. All primary-care centers in the Region of Västra Götaland have provided QregPV with data since 2010. In 2017, the Region of Västra Götaland had 1.7 million residents. Risk-factor data are collected from the electronic health records of the primary centers on a monthly basis with a data extraction tool, which collects data only from patients with the diagnoses of interest. Diagnoses are defined according to ICD-10: I10 – I15 for hypertension; I20 – I25 for coronary heart disease; E10 – E14 for diabetes mellitus; J44 for chronic obstructive pulmonary disease; and J45 for asthma. Current data from QregPV can be viewed on its homepage.(126) Clinical data in QregPV was linked to data from the National Patient Register, the Cause of Death Register, the Prescribed Drug Register, the Longitudinal Integrated Database for Health Insurance and Labour Market Studies and Vega, see Figure 17.

In Study II, we included patients aged 40 – 90 years with treated hypertension. We used restriction to limit the effect of potential confounding from previous manifest cardiovascular disease and cancer. The relationship between blood pressure and cardiovascular disease in patients with diabetes has been studied elsewhere and we therefore excluded patients with diabetes from this study.(127) Restriction was achieved through exclusion, based on ICD-10 codes in the National Patient Register or Vega, of patients with cancer (C00 – 97), diabetes (E10, E11, E13, E14) and previous stroke (I61, I63, I64) or myocardial infarction (I21), prior to the start of the study. Patients with SBP <110 mmHg and BMI <18.5 were also excluded to reduce

confounding, because very low SBP or BMI are independent predictors of illness and mortality.(128-130)

Statistical analysis

In Study II, SBP was the exposure and acute, non-fatal stroke *or* myocardial infarction constituted the composite outcome. We chose to use the SBP measured at least one year after an established diagnosis of hypertension as the exposure. This ensured a reasonable amount of time for antihypertensive treatment before study start. The date of this SBP measurement was defined as the index date. Patients were stratified into two age groups: 40 – 75 years and 76 – 90 years. We then assigned patients to one of four categories of SBP: 110–129 mmHg, 130–139 mmHg, 140–149 mmHg and 150 mmHg or higher. The primary outcome was defined as the occurrence of an ICD-10 diagnosis of either non-fatal stroke *or* acute myocardial infarction in the National Patient Register or Vega after the index date (I61, I63, I64 and I21, respectively). We chose the composite of non-fatal stroke *or* myocardial infarction in the interest of measurement accuracy, since the validity of these diagnoses is high in the National Patient Register.(108, 109) We also included all-cause mortality as a secondary outcome. Mortality was defined as a registered death in the Cause of Death Register after the index date. We followed patients from the index date until a first event of the primary outcome, death or December 31st, 2015. Because of high frequencies of missing values for blood lipids and smoking, we performed 10 cycles of multiple imputation by chained equation to generate substitute data.(119)

Unadjusted outcome data were presented with number of events and incidence rates. Cumulative incidence of the primary outcome for the different SBP categories was also calculated with the Kaplan-Meier estimate.(131) A multivariate Cox proportional-hazards model was used to calculate adjusted hazard ratios for the outcomes. The SBP categories were the independent variables in the regression and the 130 – 139 mmHg category was defined as the reference category. A P value below 0.05 was considered statistically significant. Statistical analyses in Study II were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

3.4 Study III – Blood pressure levels and risk of haemorrhagic stroke in patients with atrial fibrillation and oral anticoagulants

Data sources and study population

Study III is based on data from the Swedish Primary Care Cardiovascular Database of Skaraborg (SPCCD-SKA). It has been described in detail elsewhere.(132) SPCCD-SKA is a database that comprises data from 73 885 patients ≥30 years with hypertension or hypertension-related diseases, based on ICD-10 codes (hypertension I10 – 15; coronary heart disease I20 – 25; atrial fibrillation and flutter I48; heart failure I50; cerebrovascular disease I60 – 69; peripheral artery disease I70 – 74; diabetes mellitus E10 – 11; or chronic renal failure N18). The database covers two thirds of the primary-care centers in Skaraborg, which constitutes the eastern part of the Region of Västra Götaland and has about 260 000 residents. A purpose-built software was used to extract clinical data from the electronic health records of the participating primary-care centers. These clinical data comprised age, sex, height, weight, blood pressure, blood lipids, creatinine, glycated haemoglobin, smoking status, and ICD-10 diagnoses registered in primary care. Clinical data in SPCCD-SKA was then linked via the personal identity number to data from the National Patient Register, the Cause of Death Register and the Prescribed Drug Register, see Figure 17.

In Study III the study population comprised all patients in SPCCD-SKA with atrial fibrillation or flutter, hypertension, oral anticoagulant (OAC) treatment and recorded measurements of systolic blood pressure. Atrial fibrillation was defined as the presence of an ICD-10 diagnosis of I48 in SPCCD-SKA or the National Patient Register, while hypertension was defined as the presence of any ICD-10 diagnosis in the I10 – 14 range. Treatment with OAC was defined as a dispensed prescription of warfarin [Anatomic Therapeutic Chemical classification system (ATC) B01AA03], dabigatran (ATC B01AE07), rivaroxaban, apixaban or edoxaban (all three with ATC B01AF).

Statistical analysis

In Study III, baseline SBP was the exposure and haemorrhagic stroke was the outcome. We defined the index date as the day a prescription of OAC was dispensed for the first time in a patient with hypertension and atrial fibrillation. The exposure variable, baseline SBP,

was defined as the SBP measured closest in time (up to two years) prior to start of OAC therapy. The primary outcome of haemorrhagic stroke was defined as the occurrence of an ICD-10 diagnosis of I60 – I61 in the National Patient Register after the index date. Patients were followed from the index date until a haemorrhagic stroke, cessation of OAC therapy or December 31st 2016 occurred. To prevent misclassifying patients with aborted OAC as being treated with OAC, we censored patients who did not collect another prescription of OAC within 180 days of the latest dispensing. In addition to haemorrhagic stroke, we also explored secondary outcomes comprising any stroke, ischaemic stroke, any haemorrhage, gastrointestinal haemorrhage and all-cause mortality. The diagnoses in the secondary outcomes were defined by ICD-10, see below for details. Mortality was defined as a registered death after the index date, according to the Cause of Death Register. Body mass index, blood cholesterol and smoking status had high frequencies of missing values, which were imputed with multiple imputation by chained equation. Missing data were separately imputed for males and females after 100 imputation cycles for each sex.(119) Baseline characteristics of the study population were presented with mean and standard deviation for continuous variables and with count and/or percentage for categorical variables.

Unadjusted outcome data were presented with number of events and incidence rates. We used a Cox proportional-hazards model with SBP as the independent variable and haemorrhagic stroke as the dependent variable to calculate hazard ratios for the primary outcome. Systolic blood pressure as a continuous variable, with 130 mmHg as the reference, was used in the primary analysis to preserve statistical power.(133, 134) An analysis with SBP as a categorical variable, with 130 – 139 mmHg as the reference, was also performed. Potential confounders were identified with directed acyclic graphs constructed with DAGitty.(4, 6) In our directed acyclic graph, age, sex, high alcohol consumption, use of platelet-inhibition, blood cholesterol, and history of cerebrovascular disease or diabetes were determined to be potential confounders in our model and we thus included them as covariates in the Cox regression.

We then plotted the hazard ratio of haemorrhagic stroke as a restricted cubic spline with five knots. A P value below 0.05 was considered statistically significant. All analyses were made with SAS Version 9.4 (SAS Institute, Cary, North Carolina, USA).

ICD-10 diagnoses of secondary outcomes

- Any stroke (I60 – I61, I63),
- Ischemic stroke (I63)
- Any haemorrhage (I31.2, I60 – I62, S06.4 – S06.6, I85, I98.3, K22.8, K25 – K29, K62.5, K66.1, K92.0 – K92.2, N83.6, N83.7, N85.7, N93.9, R31.9, H11.3, H31.3, H35.6, H43.1, H45.0, J94.2, M25.0, R04, R58, D629, D683, D698, D699, DR029, DR033)
- Gastrointestinal haemorrhage (I85, K22.8, K25 – K29, K62.5, K66.1 and K92.0 – K92.2)

3.5 Study IV – Trends in blood pressure, blood lipids and smoking in primary care in Västra Götaland

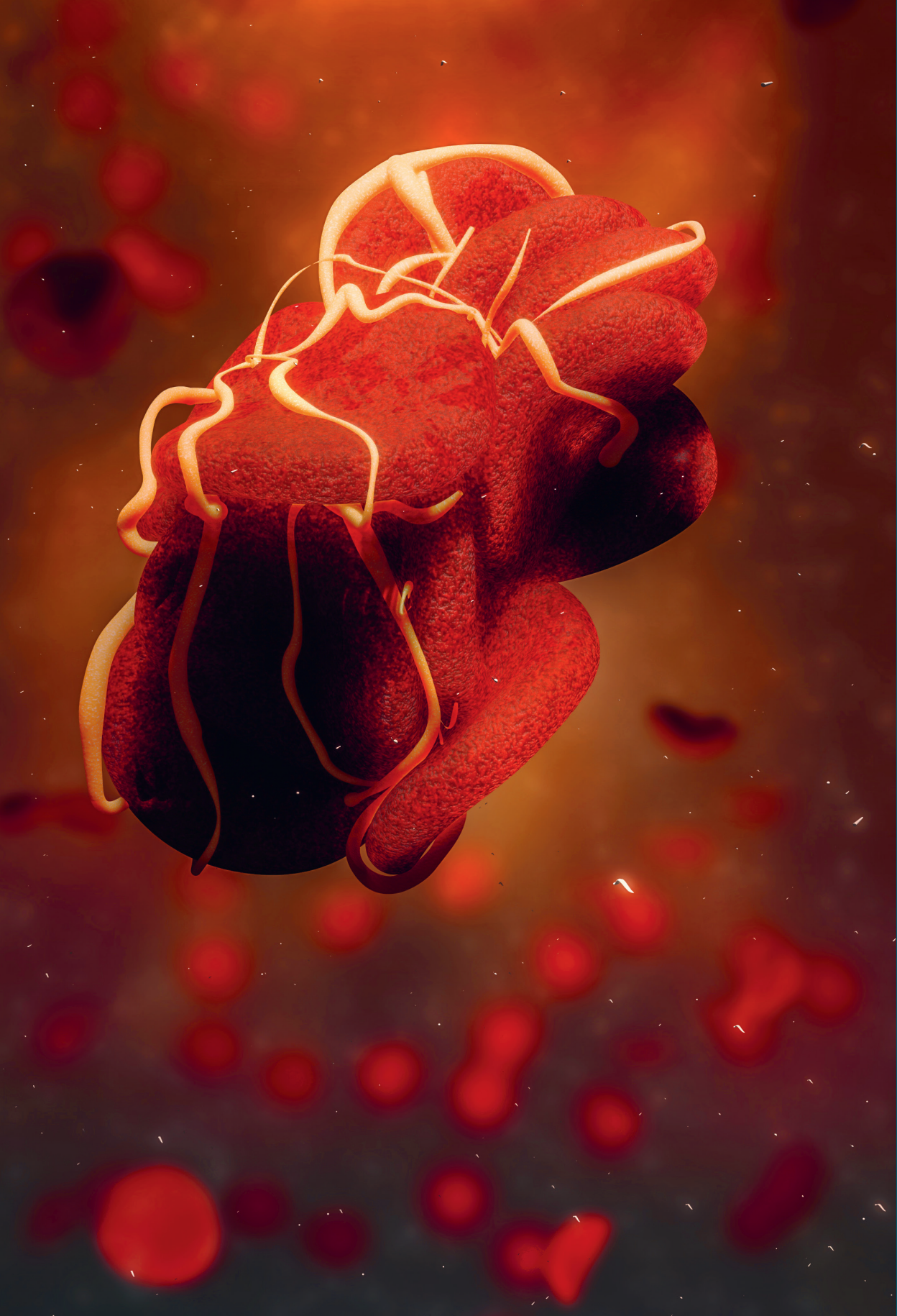
Study population

Study IV also used data from QregPV and the registers linked to it, although from a longer time span than Study II did. QregPV is described in the section on Study II above. The primary purpose of Study IV was to describe longitudinal trends in blood pressure control, blood cholesterol control and smoking habits from 2010 to 2017 in patients in QregPV with isolated hypertension, which was defined as ICD-10 codes I10 – I15. Patients with coronary heart disease (I20 – I25) or diabetes mellitus (ICD E10 – E14) were excluded from this analysis. The paper also described patient characteristics at inclusion into QregPV for all three diagnoses of hypertension, coronary heart disease and diabetes mellitus. Data on blood pressure, blood cholesterol and smoking habits were collected as part of routine clinical practice. If multiple measurements of a variable were available in the same year, the last registered was used. Measurement of blood pressure was performed according to guidelines during hypertension-related clinical visit, however, blood pressure values in the QregPV also comprises measurements at clinical visits not related to hypertension. We also described changes in use of antihypertensive drug classes and statins from 2010 – 2017. Drug classes were defined by ATC codes: thiazide diuretics (C03A, C03B, C03EA, C09BA, C09DA); calcium-channel blockers (C07FB02, C08CA, C09BB, C09DB); beta-blockers (C07); angiotensin-receptor blockers (C09C, C09D); angiotensin-converting-enzyme inhibitors (C09A, C09B); mineral-receptor antagonists (C03DA); and statins (C10AA, C10AX, C10BA). A dispensed prescription of a drug class in a calendar year was defined as use of that drug class in the same year. We defined BP <140/90 mmHg as the target blood pressure, since that was the broadly recommended BP target in 2017. (135) The target for LDL-cholesterol was defined as <2.6 mmol/l, which was also in line with current recommendations.(136) We defined target smoking status as non-smoking.

Statistical analysis

In Study IV, all analyses were descriptive. Continuous variables were presented with mean or median with standard deviation

or interquartile range as, depending on variable distribution. We presented categorical variables with count and percentage. We calculated 95% confidence intervals (95% CI) for the mean SBP and LDL-C and for the proportions of patients who reached target BP, target LDL-C and for the proportion of smokers from 2010 to 2017. We calculated proportions of BP control, LDL-C control and smoking based on valid data entries. When calculating the annual proportions of patients with ≥1, ≥2 or 3 controlled risk factors, we only used data from patients with all three risk factors recorded for the year in question. All analyses were performed with R, version 4.0.3 in RStudio, version 1.4.(137, 138)



4

Chapter 4

Results

"Without data, you're just another person with an opinion."

– W. Edwards Deming

4.1 Study I – Blood pressure in acute ischemic stroke

We identified 799 patients with acute ischemic stroke in the stroke-ward register. The mean age was 78.4 ±8.0 years and 52% were female. Hypertension was the most frequent comorbidity (57%). In total, 157 patients died during twelve months of follow-up. There was no significant association between BP level on arrival to the ER and mortality. There was, however, a significant association between ΔBP and mortality at one, three and twelve months of follow-up (hazard ratio, ΔSBP and mortality at twelve months: 0.989, 95% CI 0.982 – 0.996). A larger decrease in BP thus predicted a decreased risk of mortality. The difference in mortality between patients with a decrease in SBP and an increase in SBP is illustrated in Figure 18.

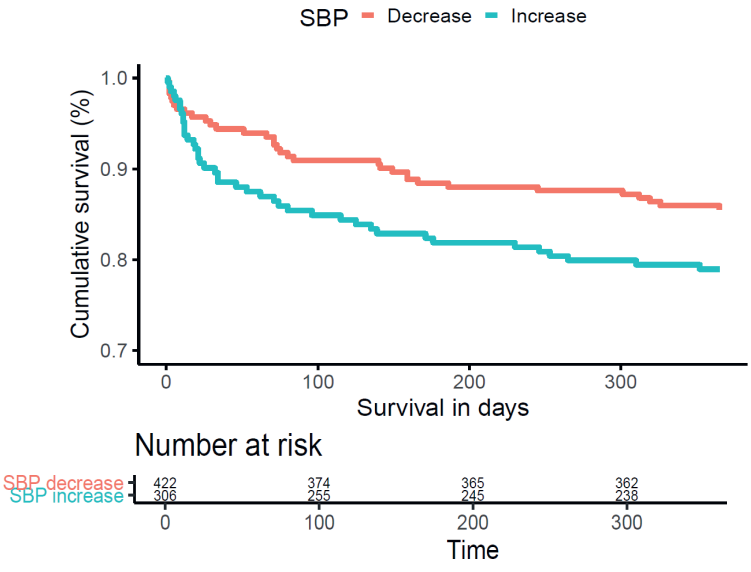


FIGURE 18

Plot of adjusted survival curve depicting the difference in survival between patients with an increase or decrease in systolic blood pressure (SBP). P value for difference 0.04. SBP denotes systolic blood pressure. Model adjusted for age, sex, severity of stroke, heart failure, diabetes mellitus, SBP, and history of ischemic stroke (IS). Note that the y axis is truncated and begins at 0.7, i.e. 70 %. Slightly adapted from the original.[4]

In contrast, there was no association between ΔBP change and neurological function at follow-up. Instead, there was a significant association between BP on arrival to the ER and better long-term neurological function, as measured by mRS (odds ratio, SBP and mRS at 12 months: 0.989, 95% CI 0.982 – 0.996).

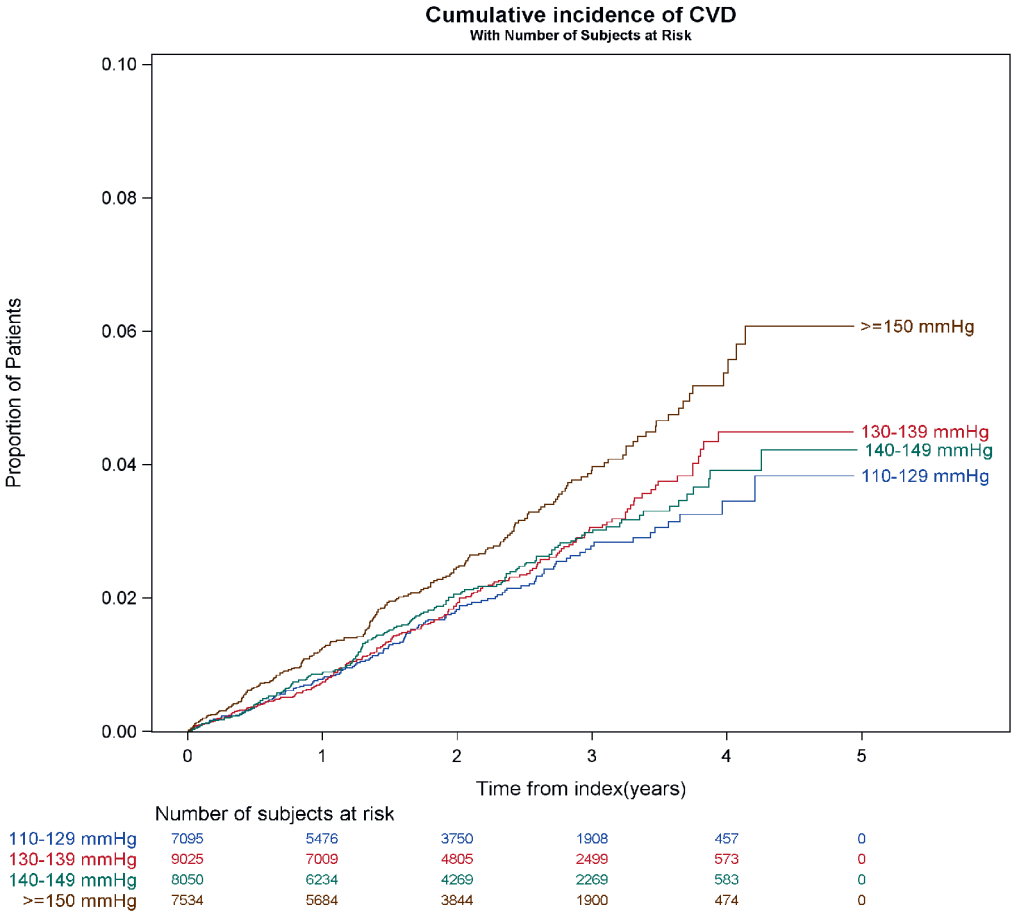
4 *Bager J-E, Hjalmarsson C, Manhem K, Andersson B. Acute blood pressure levels and long-term outcome in ischemic stroke. Brain and Behavior. 2018;8(6):e00992.* https://doi.org/10.1002/brb3.992.

4.2 Study II – Blood pressure levels and risk of stroke or myocardial infartion in older patients without previous cardiovascular disease

We identified 31 704 patients aged 40 – 90 years with treated hypertension without previous cardiovascular disease, of which 5041 were 76 – 90 years old. The patients in the lowest SBP category, 110 – 129 mmHg, had a higher frequency of coronary heart disease, atrial fibrillation and heart failure at baseline than all the other SBP categories.

FIGURE 19

Kaplan–Meier estimate displaying cumulative incidence of stroke or myocardial infarction (CVD) over time for the different SBP groups in patients aged 40–90 years. Note that the y-axis is enlarged to show the 0 – 10% range.[5]



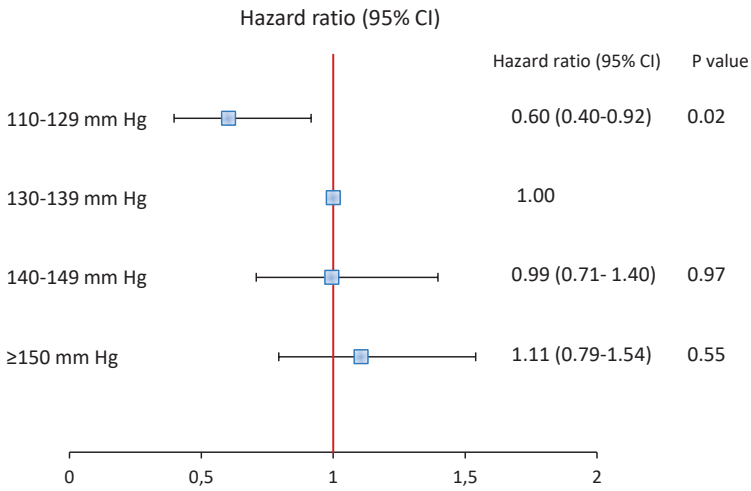
5 *Johan-Emil Bager, Per Hjerpe, Manhem K, et al. Treatment of hypertension in old patients without previous cardiovascular disease. Journal of Hypertension 2019;37(11):2269-2279.* https://doi.org/10.1097/hjh.0000000000002163. *Reprinted by permission of Wolters Kluwers Health, Inc ©.*

Overall, patients with SBP 110 – 129 mmHg had the lowest incidence rate of the combined primary outcome of non-fatal stroke or myocardial infarction, see Figure 19.

However, in the multivariate Cox regression model, there was no statistically significant difference between the 110 – 129 mmHg category and the reference 130 – 139 mmHg category in the overall study population (age 40 – 90 years) or among the younger patients (40 – 75 years). In contrast, there was a statistically significant association between the 110 – 129 mmHg category and lower risk (hazard ratio 0.60, 95% CI 0.40 – 0.92) of stroke or myocardial infarction in the prespecified subgroup analysis of older patients (76 – 90 years), see Figure 20. In these older patients, the unadjusted risk difference between the SBP 110 – 129 mmHg group and the reference group was 1.8%

FIGURE 20

Hazard ratios for the combined outcome of non-fatal stroke or myocardial infarction in different SBP groups in patients aged 76–90 years when compared to the reference 130 – 139 mmHg category. CI denotes confidence interval.[6]



There was no statistically significant difference in risk of mortality between any SBP category and the reference 130 – 139 mmHg category in any age group.

6 *Johan-Emil Bager, Per Hjerpe, Manhem K, et al. Treatment of hypertension in old patients without previous cardiovascular disease. Journal of Hypertension 2019;37(11):2269-2279.* https://doi.org/10.1097/hjh.0000000000002163. *Reprinted by permission of Wolters Kluwers Health, Inc ©.*

4.3 Study III – Blood pressure levels and risk of haemorrhagic stroke in patients with atrial fibrillation and oral anticoagulants

We identified 3 972 patients with atrial fibrillation, hypertension and recently initiated oral anticoagulant treatment in SPCCD-SKA and followed them for a total of 17 264 person-years (4.3 years per patient, on average). Their mean age was 77.0 ±8.5 years and 47.8% were female. Previous stroke was more frequent in patients with higher blood pressure levels at baseline. For patients with lower blood pressure at baseline, coronary heart disease and heart failure was more common. An overwhelming majority, 87.8%, were treated with warfarin and 34.2% were also treated with platelet-inhibition at baseline.

Forty patients suffered haemorrhagic strokes during follow-up. The incidence rate of haemorrhagic stroke was lowest (1.2 per 1000 person-years) in the <130 mmHg category and the ≥180 mmHg category, but in the latter we only registered one event. The highest incidence rate (5.8 per 1000 person-years) was observed in the 160 – 179 mmHg category. The unadjusted cumulative incidence of haemorrhagic stroke was 0.7% for patients with SBP in the 130 – 139 mmHg range and 1.4% for those in the 140 – 179 mmHg range. In the primary multivariate Cox regression analysis with SBP as a continuous variable, the range of 145 – 180 mmHg was associated with a more than doubled risk of haemorrhagic stroke compared to SBP 130 mmHg. In the categorical analysis of SBP, the 160 – 179 range was also associated with a higher risk of hemorrhagic stroke compared to the reference 130 – 139 mmHg category (hazard ratio 3.53, 95% CI 1.35 – 9.23). Both the primary continuous analysis and the categorical analysis of SBP are shown in Figure 21. In the secondary analyses of SBP as a continuous variable, we observed a statistically significant association between any stroke and SBP in the 155 – 170 mmHg range. We also noted a significant association between SBP <105 mmHg and an increased risk of death.

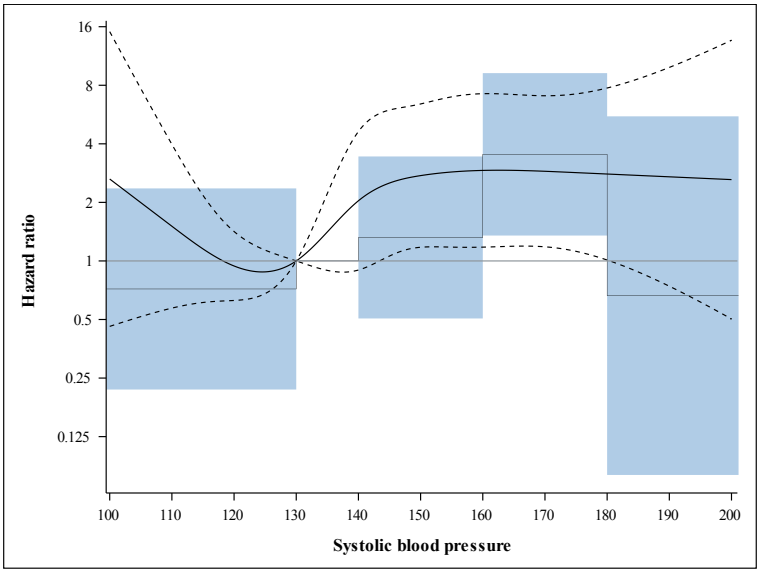


FIGURE 21

This figure shows two analyses of systolic blood pressure (SBP): The thick, solid line shows the hazard ratio of haemorrhagic stroke at different levels of SBP when SBP is analyzed as a continuous variable. The dashed lines show the confidence intervals for this analysis of SBP. 130 mmHg is the reference. The thin black line, instead, shows the hazard ratio for the five different blood pressure categories (<130, 130 – 139, 140 – 159, 160 – 179 and ≥180 mmHg). The dark boxes show the confidence intervals of the hazard ratio for the categorical analysis of SBP vertically and the width of the SBP categories horizontally. The 130 – 139 mmHg is the reference. The model was adjusted for age, sex, high alcohol intake, platelet-inhibition, cholesterol, baseline cerebrovascular disease and diabetes.[7]

7 *Johan-Emil Bager, Per Hjerpe, Linus Schiöler, et al. Blood pressure levels and risk of haemorrhagic stroke in patients with atrial fibrillation and oral anticoagulants: results from The Swedish Primary Care Cardiovascular Database of Skaraborg. Electronically published online ahead of print. https://doi.org/10.1097/hjh.0000000000002838. Reprinted by permission of Wolters Kluwers Health, Inc ©.*

4.4 Study IV – Trends in blood pressure, blood lipids and smoking in primary care in Västra Götaland

After exclusion of patients with coronary heart disease and/or diabetes, 259 753 patients with isolated hypertension and longitudinal risk factor data were identified in QregPV. Mean age increased from 67.7 years in 2010 to 68.7 years in 2017 and the proportion of women decreased from 58.3% to 56.5%, see Table 5. From 2010 to 2014, SBP decreased from 140.5 mmHg to 137.1 mmHg and then increased slightly to 137.6 mmHg in 2017, see Table 5. The initial difference in SBP between men and women disappeared during follow-up, see Figure 22. LDL-C stayed more or less the same from 2010 to 2017. The proportion of patients who attained BP lower than 140/90 mmHg and LDL-C lower than 2.6 mmol/L increased from 38.9% and 19.7% to 49.1% and 21.1%, respectively, during follow-up. The proportion of smokers decreased from 15.7% to 12.3%, see Figure 23. The relative frequency of missing data was highest for LDL-C and smoking. The proportions of missing data in 2010 were 64.0% and 89.2%, respectively for these two risk factors, and the proportions decreased to 53.8% and 59.2%, respectively, in 2017. See Table 5. The relative frequency of patients with controlled BP, controlled LDL-C and who were non-smokers increased from 8.1% in 2010 to 10.0% in 2017.

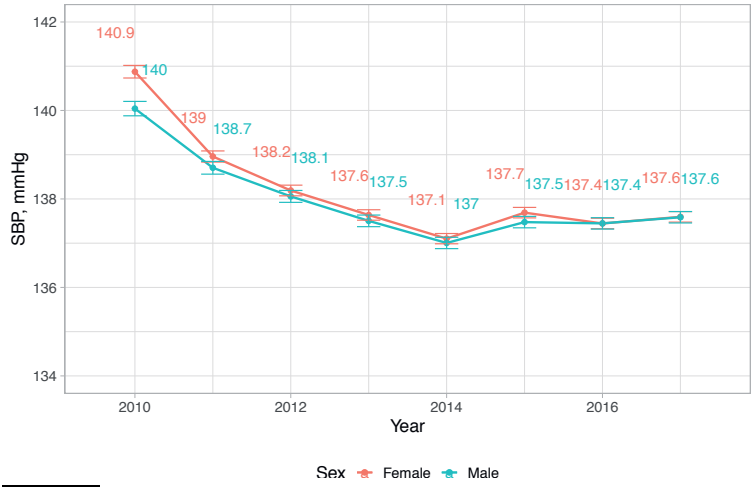


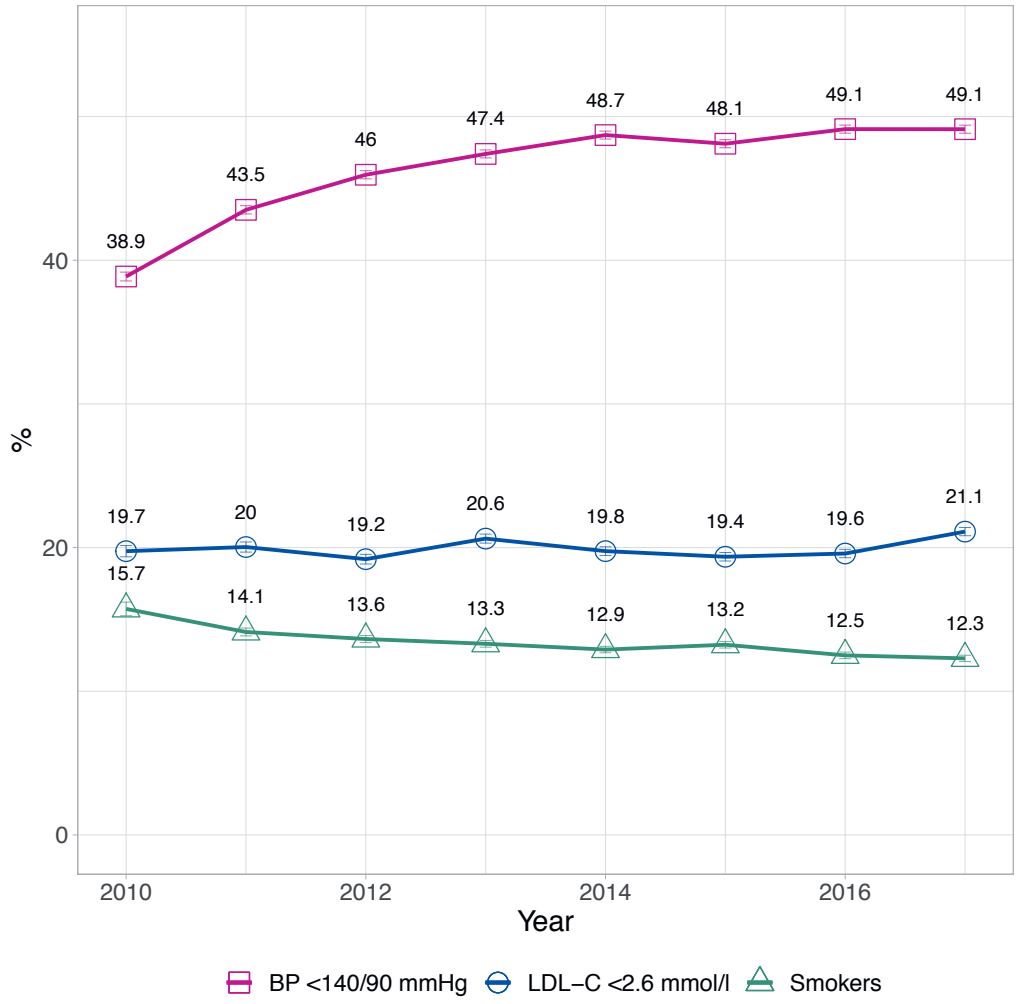
FIGURE 22

Mean systolic blood pressure (SBP) in patients with isolated hypertension by year and sex. The bars indicate 95% confidence intervals.

	2010	2011	2012	2013	2014	2015	2016	2017
Patients with recorded variables, n	109663	123421	128853	133798	136358	136303	140891	145903
Age, years (SD)	67.7 (12.6)	67.7 (12.7)	67.9 (12.6)	68.0 (12.6)	68.3 (12.6)	68.5 (12.6)	68.6 (12.6)	68.7 (12.7)
Female sex, n (%)	63888 (58.3%)	71417 (57.9%)	74085 (57.5%)	76568 (57.2%)	77899 (57.1%)	77575 (56.9%)	79751 (56.6%)	82428 (56.5%)
SBP, mmHg (SD)	140.5 (17.0)	138.9 (16.3)	138.1 (15.8)	137.6 (15.8)	137.1 (15.6)	137.6 (15.7)	137.4 (15.6)	137.6 (15.7)
SBP measurements, n (%)	97248 (88.7%)	112930 (91.5%)	119250 (92.5%)	123949 (92.6%)	125491 (92%)	123907 (90.9%)	122927 (87.2%)	123418 (84.6%)
LDL-C, mmol/l (SD)	3.38 (0.940)	3.39 (0.955)	3.40 (0.952)	3.35 (0.951)	3.40 (0.971)	3.43 (0.986)	3.44 (0.997)	3.38 (0.988)
LDL-C measurements, n (%)	39441 (36%)	49607 (40.2%)	52614 (40.8%)	63757 (47.7%)	66392 (48.7%)	68231 (50.1%)	71348 (50.6%)	78464 (53.8%)
Smoker, n (%)	3592 (15.7)	8749 (14.1)	10015 (13.6)	10764 (13.3)	11075 (12.9)	11101 (13.2)	10008 (12.5)	10615 (12.3)
Smoking data, n(%)	22835 (20.8%)	61941 (50.2%)	73455 (57%)	80913 (60.5%)	85857 (63%)	83858 (61.5%)	80088 (56.8%)	86389 (59.2%)
≥1 risk factor controlled, n(%)	9502 (92.3%)	29637 (93.9%)	36159 (94.1%)	45690 (94.6%)	48666 (94.8%)	48257 (94.6%)	46252 (95%)	49275 (95.3%)
≥2 risk factors controlled, n(%)	4724 (45.9%)	15677 (49.6%)	19467 (50.6%)	25463 (52.7%)	27375 (53.3%)	26942 (52.8%)	26386 (54.2%)	28436 (55%)
3 risk factors controlled, n(%)	835 (8.1%)	2776 (8.8%)	3412 (8.9%)	4769 (9.9%)	4906 (9.6%)	4806 (9.4%)	4613 (9.5%)	5186 (10%)
Complete risk factor data, n (%)	10292 (9.4%)	31576 (25.6%)	38435 (29.8%)	48312 (36.1%)	51319 (37.6%)	51030 (37.4%)	48672 (34.5%)	51725 (35.5%)
Antihypertensive use, n (%)	102105 (93.1%)	114123 (92.5%)	119470 (92.7%)	124601 (93.1%)	127705 (93.7%)	128056 (93.9%)	132294 (93.9%)	136917 (93.8%)
Antihypertensive drugs, number per patient (SD)	1.89 (1.08)	1.85 (1.08)	1.85 (1.07)	1.86 (1.07)	1.86 (1.06)	1.86 (1.04)	1.85 (1.05)	1.85 (1.04)
Statin use, n (%)	30841 (28.1%)	33436 (27.1%)	34741 (27.0%)	36564 (27.3%)	37666 (27.6%)	38206 (28.0%)	40307 (28.6%)	42234 (28.9%)

TABLE 5

Longitudinal risk factor and drug use data of patients with isolated hypertension in QregPV 2010 – 2017. Variables are presented with mean (standard deviation) or count (%). SBP denotes systolic blood pressure; LDL-C, low-density lipoprotein cholesterol.

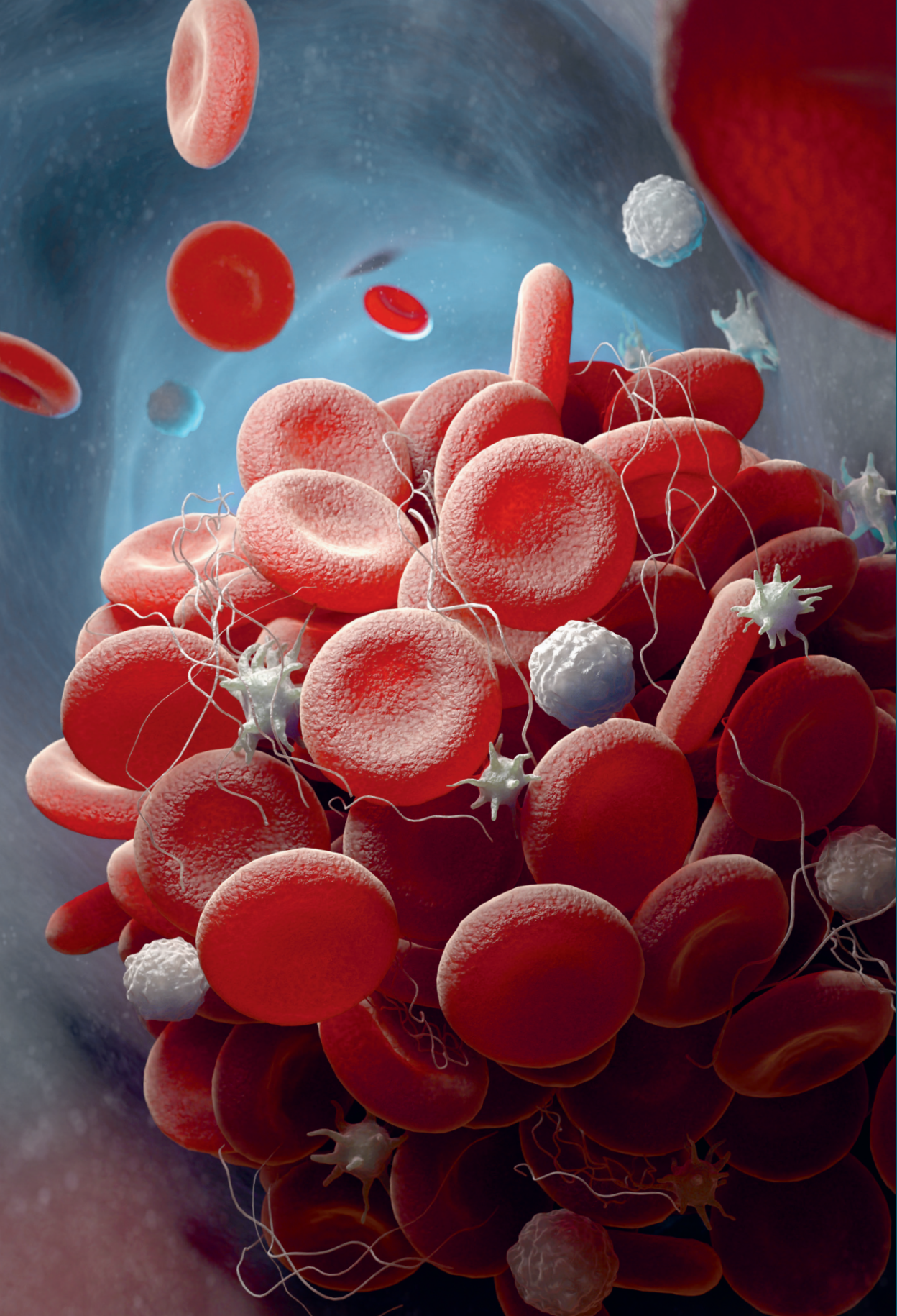


If target BP had included systolic and diastolic blood pressures of 140 and 90 mmHg, respectively (i.e., a target of ≤140/90 mmHg), there would instead be an increase in well-controlled BP from 56.2% in 2010 to 63.1% in 2017.

The average number of antihypertensive drugs per patient changed little during follow-up and was 1.85 in 2017. Statin use remained essentially unchanged during the same time span and was 28.9% in 2017.

FIGURE 23

Proportion of patients with isolated hypertension with controlled blood pressure (BP), low-density lipoprotein cholesterol (LDL-C) and who are smokers from 2010 to 2017. Bars inside symbols represent 95% confidence intervals.



Chapter 5

Discussion

"Data do not understand causes and effects; humans do."

– Judea Pearl

5.1 Key results and interpretation

Study I – Blood pressure levels in acute ischemic stroke

Study I featured 799 older patients (mean age 78.4 years) with acute ischemic stroke who were not eligible for thrombolysis or thrombectomy. In the study, we analyzed the association between BP or ΔBP and several outcomes. The main finding was an association between blood pressure decrease and lower risk of death (HR 0.989, 95% CI 0.982 – 0.996 and P-value 0.003 for a 1 mmHg drop in SBP and mortality at 12 months). This means that patients with a decrease in SBP, when comparing SBP on arrival to the ER to SBP on admission to the ward, have a lower risk of death at 12 months. The HR of 0.989 is barely lower than 1, but since ΔSBP is a continuous variable, it reflects the hazard ratio per 1 mmHg decrease. The risk of death thus decreases by 1% for every mmHg of SBP decrease, which means that a decrease of 10 mmHg would yield a HR of 0.895 (0.989^10 = 0.895), or roughly a 10% decrease in risk of death.

Stroke is a powerful trigger of BP increase, which explains the high prevalence of high blood pressure in acute ischemic stroke.(75) The hypertensive reaction does not, however, have a clear correlation to the amount of ischemic cerebral tissue, and may instead be a result of dysfunction in BP control mechanisms, like the parasympathetic nervous system.(139, 140) Blood pressure usually starts to decrease within hours of stroke onset, in part owing to reperfusion of previously ischemic brain parenchyma.(76, 77, 140) If blood pressure decrease correlates with reperfusion of ischemic brain tissue, it may be the case that patients with BP decreases have less brain ischemia, than those without BP decreases. This might explain some of the prognostic value of ΔBP. If successful cerebral reperfusion was the lone driving force behind BP decrease, we would have expected ΔBP to be a significant predictor of long-term neurological function as well, but there was no such association in our analysis. Another possibility is that the capacity to respond to stroke with a strong BP increase and subsequent decrease is a marker of adequate heart function. Analogously, a lack of this capacity may be part of the explanation as to why lower BP is often associated with increased mortality in observational studies.(130, 141)

Regardless of the mechanisms behind the association between ΔBP and mortality, we have learned from randomized trials that pharmacologically induced BP decrease is not beneficial in most patients with acute ischemic stroke.(78, 142) It therefore seems reasonable to assume that BP decrease in acute ischemic stroke can be an effect of one or more beneficial phenomena, perhaps including brain tissue reperfusion, that lead to a better prognosis. Blood pressure decrease in acute ischemic stroke does not, however, itself cause a lower risk of death.

Study II – Blood pressure levels and risk of stroke or myocardial infartion in older patients without previous cardiovascular disease

Study II comprised 31 704 patients with hypertension, but without previous cardiovascular disease, of which 5 041 were older (76 – 90 years). The mean follow-up time was two years. In this study, the primary outcome was a composite of non-fatal stroke or myocardial infarction. We analyzed the risk of the primary outcome for different SBP categories, with 130 – 139 mmHg category as the reference. There was no significant difference in risk of the primary outcome for any SBP category in the overall study population. In the pre-specified subgroup analysis of older patients, however, those with SBP in the 110 – 129 mmHg range had a lower risk of the primary outcome (HR 0.60, 95% CI 0.40 – 0.92, P-value 0.02), compared to patients with SBP in the 130 – 139 mmHg range. Older patients with SBP in the 110 – 129 mmHg thus had a 40% lower relative risk of suffering a non-fatal stroke or myocardial infarction, than those with SBP in the 130 – 139 mmHg range. The unadjusted risk difference between these SBP categories was 1.8%, which means that about 56 patients would need to move from the 130 – 139 mmHg category to the 110 – 129 mmHg category for two years to prevent one non-fatal stroke or myocardial infarction.

The results from our study differ from those of two large RCTs, which both showed neutral effects of achieving a lower BP in older patients. The investigators of the former trial acknowledged that the lack of a difference between the comparison groups was

unexpected, whereas those of the latter deemed their trial underpowered to detect a difference.(143, 144) Instead, our results are in agreement with findings from the pre-specified subgroup analysis of older patients in the SPRINT trial, which showed a lower risk of cardiovascular disease and death in the intervention group with SBP 123.4 mmHg compared to the control group with SBP 134.8 mmHg. Our data are also in line with a large British observational study which also found an association between SBP <130 mmHg and lower risk of myocardial infarction.(74, 92) Meta-analyses with individual-participant data also lend general support to the notion that lower blood pressure decreases the risk of cardiovascular disease, irrespective of cardiovascular risk level and baseline blood pressure.(58, 66)

Our findings thus support the <130 mmHg SBP target for older, non-institutionalized patients which is recommended in the American hypertension guidelines.(38) It should also be mentioned that no hitherto conducted randomized, controlled trial has shown any evidence that lowering blood pressure is in itself harmful.

Study III – Blood pressure levels and risk of haemorrhagic stroke in patients with atrial fibrillation and oral anticoagulants

Study III analyzed the risk of haemorrhagic stroke at different levels of baseline SBP in 3 972 patients with hypertension, atrial fibrillation and treatment with oral anticoagulants. There were 40 haemorrhagic strokes during a mean follow-up of 4.3 years per patient. In the primary analysis, which featured SBP as a continuous variable, a systolic blood pressure in the 145 – 180 mmHg range was associated with a risk of haemorrhagic stroke that was more than twice that at the reference SBP of 130 mmHg. See Figure 21. The unadjusted cumulative incidence of haemorrhagic stroke was 0.7% for patients with SBP in the 130 – 139 mmHg range and 1.4% for those in the 140 – 179 mmHg range. This yields a risk difference of 0.7%, which means that about 143 patients would need to transition from the 140 – 179 mmHg range to the 130 – 139 mmHg range for 4.3 years to prevent one haemorrhagic stroke.

Both components of haemorrhagic stroke – subarachnoid haemorrhage and intracerebral haemorrhage – are the result of rupture of cerebral arteries. It would seem reasonable that the occurrence and extent of such haemorrhages are related to both the strain on the vascular wall caused by the force of blood and to the coagulation capacity of the blood itself. Indeed, hypertension and anticoagulant therapy are major risk factors for haemorrhagic stroke. The major aetiological factor of the subarachnoid haemorrhage is an anatomical deviation in the form of an aneurysm with a defective vessel wall, which has an inherently lower capacity to resist pressure. In intracerebral haemorrhage, hypertension both sets the stage, by contributing to arterial degeneration over years and decades, and performs the starring role by subsequently rupturing a cerebral artery. (42, 94)

European hypertension and AF guidelines both recommend lowering of SBP to less than 130 mmHg for patients with AF and OAC.(19, 93) The evidence for this recommendation come from secondary analyses of RCTs and observational studies, which have found higher incidence rates of haemorrhagic stroke in patients with either a diagnosis of hypertension or higher SBP, although these differences have not been uniformly, statistically significant. (95-99, 145) Regardless, previous studies seem to display a trend which indicates a higher risk of haemorrhagic stroke in patients with a SBP higher than 140 or perhaps 150 mmHg. Haemorrhagic stroke is a difficult outcome to study due to its low incidence. The overall incidence rate of haemorrhagic stroke in our study was 2.3 per 1000 patient-years, which can be compared to the more than four times higher incidence rate of ischemic stroke of 12.6 per 1000 patient-years in this study. The incidence rate of haemorrhagic stroke in our work was similar to that in the NOAC trials, despite most of our patients being treated with warfarin.(146-149) In our study, we leveraged the advantages of observational data from primary care, which comprised long follow-up and relatively numerous participants, and found an increased risk of haemorrhagic stroke in the 145 – 180 mmHg range of SBP. Our study also adds that baseline BP, not just follow-up or intra-trial BP, has prognostic

importance for patients with hypertension, AF and OAC. We believe these results suggest that patients with SBP in the 145 – 180 mmHg range, who are eligible for OAC, may benefit from additional anti-hypertensive treatment.

The findings in our study – a more than doubled risk of haemorrhagic stroke in the SBP 145 to 185 mmHg range – thus support the blood pressure recommendations for patients with OAC in current European guidelines for AF and arterial hypertension.(19, 93)

Study IV – Trends in blood pressure, blood lipids and smoking in patients with hypertension in Västra Götaland 2010 – 2017

Study IV described risk factor trends in 259 753 primary-care patients with isolated hypertension, i.e. without ischemic heart disease and diabetes mellitus. The main findings were improved control of BP and decreased smoking, whereas control of LDL-C changed little. The proportion of patients with BP <140/90 and LDL-C <2.6 mmol/L and who were non-smokers increased from 8.1% in 2010 to 10.0% in 2017. Consequently, nine out of ten patients with isolated hypertension in Västra Götaland exhibited insufficient control of one or more important, modifiable, cardiovascular risk factors in 2017.

Data from both population-based studies and primary care have described trends of decreasing SBP, improving BP control and decreased smoking in the industrialized world during the last decades.(44, 102-106, 150) Our primary-care results from QregPV are in agreement with those studies, with the possible caveat that the trend of SBP decrease may be attenuating, which American data too may suggest.(106) Antihypertensive treatment (~1.8 drugs per patient) was stable throughout follow-up and comparable to previous Swedish primary-care data.(151) It was also lower in our material than in the intervention group (~2.8 drugs per patient) of the SPRINT trial, which suffered fewer cardiovascular events than the control group (~1.8 drugs per patient).(39)

Levels of LDL-C, LDL-C control and statin use stayed more or less the same during follow-up in our material, this contrasts to cholesterol trends from population-based surveys.(104-106) Statin

use was, however, similar to that in patients with antihypertensive treatment in a European primary-care survey.(152)

In 2017, there was considerable room for improvement in control of modifiable risk factors for patients with isolated hypertension in Västra Götaland. Only one in five had LDL-C <2.6 mmol/l and half of them had insufficient BP control. Less than a third of patients used statins and the average number of antihypertensive drugs did not change. Increasing the use of statins and antihypertensive treatment should, along with promoting other evidence-based lifestyle modifications, decrease the risk of cardiovascular disease and death in patients with hypertension.

5.2 Limitations and strengths

General limitations

The observational studies that this thesis is based upon all rely on the accuracy of three fundamental presuppositions:

1. Clinical variables, especially exposures, are measured correctly
2. Diagnoses, especially outcomes, are measured correctly
3. Valid data entries are representative of missing data entries

When these presuppositions fail, bias results. Errors or differences in measuring clinical variables and establishing diagnoses across time or primary-care centers may cause misclassification and subsequent bias. Especially when exposures are not measured in the same way across exposure categories. All studies in this thesis focus heavily on blood pressure values and the reader should question whether the theoretical concept of blood pressure is reasonably represented by the practical definitions used for it in the papers. Has the theoretical concept of blood pressure made it safely from the realm of ideas into the natural world and our analyses? For example, a variable like blood pressure can be measured for many reasons, using different sphygmomanometers, by different personnel categories and, perhaps most importantly, in different circumstances. The SPRINT trial sparked discussions because they measured BP in a different way, compared to previous trials. It was debated whether the theoretical concept of BP as an exposure was adequately represented by the measurement technique used in SPRINT.(39, 153) Study I serves as another example of how BP can be affected by external factors. In the patients with acute ischemic stroke in Study I, BP was measured under circumstances of extreme physiological stress, which tend to cause high BP. The BP values in Study I are thus not comparable to those in the other Studies. They also serve as a reminder that BP is very much a dynamic variable. This observation subsequently begs the question under which circumstances BP values in Studies II – IV were measured and whether they are comparable to the BP values in American and European hypertension guidelines, which have been referenced throughout this thesis. As the perhaps not entirely unbiased author, I would point out that all BP values in all

studies have been measured clinically and in the service of our patients. They have been used by nurses and physicians to monitor patients for signs of deterioration, to determine diagnoses and to shape treatment decisions. They are not perfect, but they are real.

The diagnoses in study II – IV are based on ICD-10 diagnoses from both primary and hospital-based care. Diagnostic data has been used to delineate study participants, to describe baseline comorbidities, to adjust for confounding and, most importantly, to measure outcomes. As a clinician, I know that diagnoses can be both missed and made in error. Shortness of breath, for instance, is sometimes the result of acute heart failure and sometimes of pneumonia. And sometimes of pulmonary embolism. The road through symptoms, laboratory tests and radiological results can be long, winding and bewildering and does not always lead to a diagnosis. It is reasonable that some diagnoses are more precise than others. For instance, the accuracy of hypertension and diabetes mellitus diagnoses – both based on numerical, measurable thresholds – in primary care is higher than that for ischemic heart disease.(147) Diagnostic data on stroke and myocardial infarction from hospital-based care, which were outcomes in Study II and III, are also highly accurate.(108, 109) While other diagnoses, like mental disorders related to alcohol use (F10 in ICD-10), which we used as a covariate in the regression analyses in Study III, are likely to be far less accurate. Outcome data on mortality, the primary outcome of Study I and a secondary outcome in Study II and III, in Sweden is virtually completely accurate.(76)

Missing data is a common issue in observational studies, particularly those based on routine clinical data. For example, the large proportion of missing data entries on LDL-C and smoking in Study IV may introduce information bias. If, for example, patients with missing LDL-C and smoking data differ in LDL-C values and smoking rate from those with valid data, then results from the latter are not representative of the former. In Study II and III we used multiple imputation by chained equation to generate substitute data. This method assumes that the probability of a variable being missing can be predicted based only on the values of other non-missing variables.

In addition to the limitations associated with the three fundamental presuppositions above, a few more caveats should be mentioned. In Studies II – IV we equated the collection of a drug prescription with drug treatment. However, patients who collect drug prescriptions may take the drug according to the prescription. But they may also take it, but not according to the prescription. Also, they might not take the drug at all, even though they collected it. It is likely that equating the collection of a drug prescription to drug treatment leads to an overestimation of drug use. Because this overestimation is the same for all patients, regardless of exposure group, it leads to non-differential misclassification.

In studies I – III we performed multivariate regression analyses to adjust for potential confounding factors. However, residual confounding due to unidentified or improperly measured confounders is still possible.

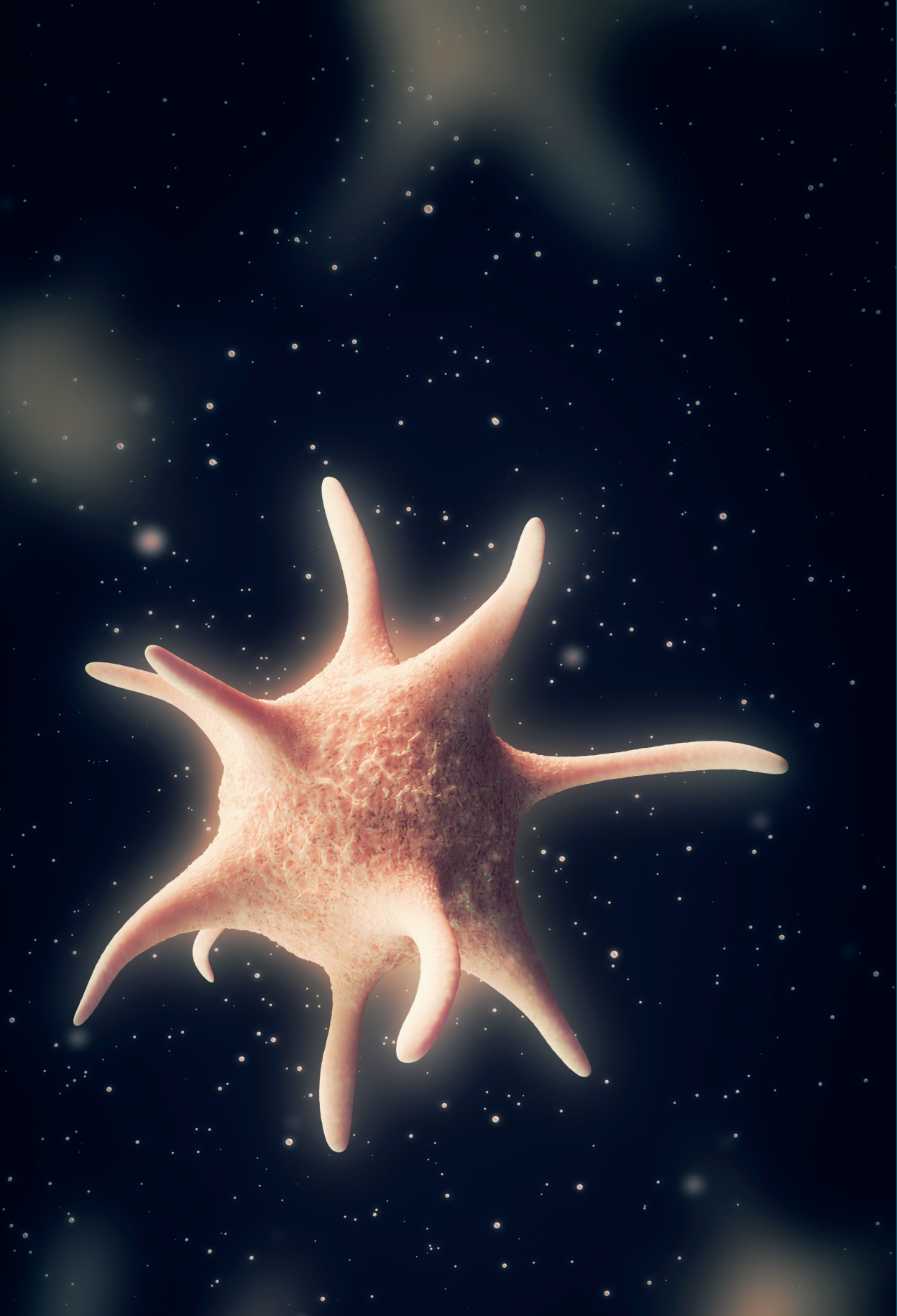
Finally, all observational cohort studies share the inherent limitation that they cannot prove a causal relation between an exposure and an outcome. This applies to the studies in this thesis as well.

General strengths

All studies are based on clinical data from registries. One major strength of all studies is the unbiased inclusion method. Patients have not been actively selected for inclusion, rather they have qualified for entry into the respective registries based on diagnoses determined by healthcare professionals.

Data in Study II and IV came primarily from QregPV, which has several strengths. The most prominent of which is the large sample size. QregPV comprises data of all patients with hypertension from all primary-care centers in an entire region of Sweden. This means that data from QregPV have high external validity. Because data in QregPV come from the second most populous region in Sweden, Västra Götaland (population ~1.7 million), they are not only representative of that region, but likely also of Sweden as a whole. Other strengths are its longitudinal data from 2010 to 2017 and the possibility to use the personal identity number to acquire additional data from other national and regional registers.

Study III has strengths similar to those in Study II and IV. SPCCD-SKA, like QregPV, comprises primary-care patient data and although coverage is lower in SPCCD than in QregPV, an impressive two thirds of all primary-care centers in Skaraborg (population ~260 000) are represented in SPCCD-SKA. SPCCD-SKA has even more longitudinal data than QregPV: from 2001 to 2016.



Chapter 6

Conclusions

6

“Life can only be understood backwards, but it must be lived forwards”

– Søren Kierkegaard

The overarching aim of this thesis was to investigate the prevalence, temporal trends and associations to cardiovascular outcomes of blood pressure levels in patients in Västra Götaland. These are the condensed conclusions of the four studies which constitute the foundation of this thesis:

I. Early blood pressure change predicts mortality in patients with acute ischemic stroke.

II. Systolic blood pressure in the 110 – 129 mmHg range is associated with a lower risk of stroke or myocardial infarction, compared to 130 – 139 mmHg, in older patients without manifest cardiovascular disease.

III. Systolic blood pressure in the 145 – 180 mmHg range is associated with a higher risk of haemorrhagic stroke, compared to 130 mmHg, in patients with hypertension, atrial fibrillation and oral anticoagulants.

IV. Systolic blood pressure decreased in patients with isolated hypertension in primary care in Västra Götaland from 2010 – 2017. Despite improved control of blood pressure, blood lipids and smoking, 90% of patients were still exposed to at least one uncontrolled, modifiable risk factor for cardiovascular disease in 2017.

Closing remarks and future perspectives

Blood pressure is a not a dichotomous phenomenon, but rather an intravascular force that exerts pressure on the blood vessel walls and which can increase or decrease along a continuous scale. We should therefore expect that the effects of modifying blood pressure also change along a continuous rather than binary scale. William

Kannel, a former director of the renowned Framingham Heart Study (who incidentally also coined the term "risk factor") wrote that: *"Hypertension is better characterized as a pathologic-physiologic state than as a 'disease.' Its cardiovascular consequences are proportional to the height of the blood pressure, making it impossible to define a critical value that can be labeled 'hypertension'."*(154) If this were true, we should expect the relative (but not absolute) risk to decrease in similar magnitude along with BP decreases in all patients, regardless of their cardiovascular risk or baseline BP level. Indeed, this hypothesis seems to be supported by several types of studies.(71) A Mendelian randomization study has shown that small differences in BP are associated with large relative risk reductions over long periods of time and meta-analyses of individual participant data from RCTs have shown that a reduction of BP has the same effect on the relative risk reduction of cardiovascular disease irrespective of a patient's risk of cardiovascular disease.(53, 58, 66)

Consequently, it would seem that patients with a higher absolute risk of CVD (which should also entail a shorter expected remaining life span) would have greater incentive to desire treatment, because of the treatment's large chance of short-term benefit. On the other hand, patients with a lower risk of CVD (which should entail a longer expected remaining life span) might also have incentive for treatment, because of its large chance of long-term benefit. Put differently, for a young and healthy patient, a small decrease in blood pressure for a very long time might be as important as a larger decrease for a short time in an older patient with manifest cardiovascular disease. Ultimately, I believe that patients should be thoroughly informed about the difference in absolute and relative risks so that they can participate in making treatment decisions.

From a community standpoint, hypertension remains an unnecessarily widespread agent of cardiovascular disease and death.(43, 45) We possess a wide arsenal of pharmacological countermeasures with which to combat it, yet half of all patients with hypertension still do not attain a BP <140/90 mmHg, much less <130/80 mmHg. Thus currently the major challenge is not to determine at what BP level the risk nadir is situated in the J-shaped curve; rather,

it is to find ways to address the blood pressure burden in the legions of patients with hypertension who do not attain <140/90 mmHg. Patients with hypertension in Västra Götaland used 1.8 antihypertensive drugs per person, whereas the SPRINT trial has shown that 2.8 drugs per person is safe.(39) Consequently, there seems to be room for at least one more antihypertensive drug for every patient with hypertension in Västra Götaland, and likely all of Sweden. Lifestyle modifications, which may comprise a healthy diet; regular exercise; smoking cessation; and weight control, may be alternatives for patients wary of additional drug therapy. Statin treatment is also underutilized and should be used to a greater extent to reduce long-term risk of cardiovascular disease in patients with hypertension.(67, 136, 155)

Going forward, observational data from registries like QregPV and SPCCD can be used to monitor changes in cardiovascular risk factors over time, to inform policy makers and to identify factors associated with treatment success and clinical outcomes. Higher data quality is desirable for purposes of increasing the internal validity of future studies from QregPV and similar registries. Structural incentives that promote measurements of variables, especially those that display high proportions of missing data, may improve data quality.

Chapter 7

Tack

”If I have seen further
it is by standing on the
shoulders of Giants.”

– Sir Isaac Newton

Citatet av Sir Isaac Newton från 1676 på föregående sida fångar kärnfullt hur all kunskap idag bygger på kunskap från igår. Med en obruten kedja av tal och text transporterar mänskligheten sin allra mest dyrbara vara – kunskap – genom generationerna och använder den för att se och nå ett litet stycke till. Idag, mer än någonsin tidigare, finns våra föregångares kunskaper tillgängliga för oss att lära av. Det talade språket och den skrivna texten har fått sällskap av inspelade röster och rörliga bilder och därmed står närmast oräkneliga färdigheter, kunskaper och erfarenheter från tidigare generationers jättar redo att förflyttas från analoga och digitala kunskapslager till det nyfikna sinne som är öppet för att ta emot dem. Allt lärande är i någon mån också en övning i blygsamhet. Det är först när man börjar bekanta sig med ett kunskapsområde som man förstår hur lite man vet om det – en liten mängd kunskap öppnar upp insikten om hur avgrundsdjup okunskapen i samma ämne är. Jag har haft nöjet och förmånen att både avtäcka, och förhoppningsvis i någon mån fylla, mina kunskapsluckor av personer med begåvning och färdighet som överstiger min egen. Dessa personer vill jag rikta några tacksamhetens ord till.

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